Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Crohn's disease and ulcerative colitis are the principal types of inflammatory bowel disease. It is important to note that not only does Crohn's disease affect the small intestine and large intestine, it can also affect the mouth, esophagus, stomach and the anus whereas ulcerative colitis primarily affects the colon and the rectum.

**CLASSIFICATION**
The chief types of inflammatory bowel disease are Crohn's disease and ulcerative colitis (UC). Inflammatory bowel diseases fall into the class of autoimmune diseases, in which the body's own immune system attacks elements of the digestive system.

Accounting for fewer cases are other forms of IBD, which are not always classified as typical IBD:
- Microscopic colitis subdivided into collagenous colitis and lymphocytic colitis
- Diversion colitis
- Behçet's disease
- Indeterminate colitis

No disease specific markers are currently known in the blood, enabling the reliable separation of Crohn's disease and ulcerative colitis patients. The way doctors can tell the difference between Crohn's disease and UC is the location and nature of the inflammatory changes. Crohn's can affect any part of the gastrointestinal tract, from mouth to anus (skip lesions), although a majority of the cases start in the terminal ileum. Ulcerative colitis, in contrast, is restricted to the colon and the rectum. Microscopically, ulcerative colitis is restricted to the mucosa (epithelial lining of the gut), while Crohn's disease affects the full thickness of the bowel wall ("transmural lesions"). Lastly, Crohn's disease and ulcerative colitis present with extra-intestinal manifestations (such as liver problems, arthritis, skin manifestations and eye problems) in different proportions.

**SIGNS AND SYMPTOMS**

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defecation</td>
<td>Often-porridge-like, sometimes steatorrhea</td>
<td>Often-mucus-like and with blood</td>
</tr>
<tr>
<td>Tenesmus</td>
<td>Less common</td>
<td>More common</td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Indicates severe disease</td>
</tr>
<tr>
<td>Fistulae</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Often</td>
<td>More seldom</td>
</tr>
</tbody>
</table>

In spite of Crohn's disease and Ulcerative Colitis being very different diseases, both may present with any of the following symptoms: abdominal pain, vomiting, diarrhea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis and weight loss. Anemia is the most prevalent extraintestinal complication of inflammatory bowel disease. Associated complaints or
Diseases include arthritis, pyoderma gangrenosum, primary sclerosing cholangitis, and non-thyroidal illness syndrome (NTIS). Associations with deep vein thrombosis (DVT) and bronchiolitis obliterans organizing pneumonia (BOOP) have also been reported. Diagnosis is generally by assessment of inflammatory markers in stool followed by colonoscopy with biopsy of pathological lesions.

### Diagnostic findings

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum involvement</td>
<td>Commonly</td>
<td>Seldom</td>
</tr>
<tr>
<td>Colon involvement</td>
<td>Usually</td>
<td>Always</td>
</tr>
<tr>
<td>Rectum involvement</td>
<td>Seldom</td>
<td>Usually</td>
</tr>
<tr>
<td>Involvement around the anus</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Bile duct involvement</td>
<td>No increase in rate of primary sclerosing cholangitis</td>
<td>Higher rate</td>
</tr>
<tr>
<td>Distribution of disease</td>
<td>Patchy areas of inflammation (skip lesions)</td>
<td>Continuous area of inflammation</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Deep geographic and serpiginous (snake-like) ulcers</td>
<td>Continuous ulcer</td>
</tr>
<tr>
<td>Depth of inflammation</td>
<td>May be transmural, deep into tissues</td>
<td>Shallow, mucosal</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Common</td>
<td>Seldom</td>
</tr>
<tr>
<td>Granulomas on biopsy</td>
<td>May have non-necrotizing non-peri-intestinal crypt granulomas</td>
<td>Non-peri-intestinal crypt granulomas not seen</td>
</tr>
</tbody>
</table>

### CAUSES

#### Pathophysiology

<table>
<thead>
<tr>
<th></th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine response</td>
<td>Associated with T_h_17</td>
<td>Vaguely associated with T_h_2</td>
</tr>
</tbody>
</table>

IBD is a complex disease which arises as a result of the interaction of environmental and genetic factors leading to immunological responses and inflammation in the intestine.

- **Diet**
  A diet high in protein, particular animal protein, may be associated with increased risk of inflammatory bowel disease and relapses

- **Microbiota**
The enteral bacteria can be altered by environmental factors, such as concentrated milk fats (a common ingredient of processed foods and confectionery) or oral medications such as antibiotics and oral iron preparations.

■ **Breach of intestinal barrier**
Loss of integrity of the intestinal epithelium plays a key pathogenic role in IBD. Changes in the composition of the intestinal microbiota are an important environmental factor in the development of IBD. Detrimental changes in the intestinal microbiota induce an inappropriate (uncontrolled) immune response that results in damage to the intestinal epithelium.

■ **Genetics**
The genetic contribution is poorly understood and seems to arise from the small contribution of dozens of genes. 163 IBD susceptibility loci were confirmed, which means that 163 alleles that can increase the susceptibility to the disease have been found.

**DIAGNOSIS**
The diagnosis is usually confirmed by biopsies on colonoscopy. Fecal calprotectin is useful as an initial investigation, which may suggest the possibility of IBD.

**DIFFERENTIAL DIAGNOSIS**
Other diseases may cause an increased excretion of fecal calprotectin, such as infectious diarrhea, untreated coeliac disease, necrotizing enterocolitis, intestinal cystic fibrosis and neoplastic pediatric tumor cells.
Conditions with similar symptoms as Crohn's disease includes intestinal tuberculosis, Behçet's disease, ulcerative colitis, nonsteroidal anti-inflammatory drug enteropathy, irritable bowel syndrome and coeliac disease.
Conditions with similar symptoms as ulcerative colitis includes acute self-limiting colitis, amebic colitis, schistosomiasis, Crohn's disease, colon cancer, irritable bowel syndrome, intestinal tuberculosis and nonsteroidal anti-inflammatory drug enteropathy.

**TREATMENT**

<table>
<thead>
<tr>
<th>Management</th>
<th><strong>Crohn's disease</strong></th>
<th><strong>Ulcerative colitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalazine</td>
<td>Less useful</td>
<td>More useful</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Effective in long-term</td>
<td>Generally not useful</td>
</tr>
<tr>
<td>Surgery</td>
<td>Often returns</td>
<td>Usually cured by</td>
</tr>
<tr>
<td></td>
<td>Following removal of affected part</td>
<td>Removal of colon</td>
</tr>
</tbody>
</table>

Mesalazine is more useful in ulcerative colitis than in Crohn's disease. Generally, depending on the level of severity, IBD may require immunosuppression to control the symptoms, with drugs such as prednisone, TNF inhibitors, azathioprine (Imuran), methotrexate, or 6-mercaptopurine. Steroids, such as the glucocorticoid prednisone, are frequently used to control disease flares.
Surgery
CD and UC are chronic inflammatory diseases, and are not medically curable, so surgery is required. Ulcerative colitis can in most cases be cured by Proctocolectomy. Surgery cannot cure Crohn's disease but may be needed to treat complications such as abscesses, strictures or fistulae. Severe cases may require surgery, such as bowel resection, strictureplasty or a temporary or permanent colostomy or ileostomy. In Crohn's disease, surgery involves removing the worst inflamed segments of the intestine and connecting the healthy regions.

Medical therapies
The choice of which drugs to use and by which route to administer them (oral, rectal, injection, infusion) depends on factors including the type, distribution, and severity of the patient's disease, as well as other historical and biochemical prognostic factors, and patient preferences. For example, mesalazine is more useful in ulcerative colitis than in Crohn's disease. Generally, depending on the level of severity, IBD may require immunosuppression to control the symptoms, with drugs such as prednisone, TNF inhibitors, azathioprine (Imuran), methotrexate, or 6-mercaptopurine. Steroids, such as the glucocorticoid prednisone, are frequently used to control disease flares and were once acceptable as a maintenance drug. Biological therapy for inflammatory bowel disease, especially the TNF inhibitors, are used in people with more severe or resistant Crohn's disease and sometimes in ulcerative colitis.

Nutritional and dietetic therapies
Anaemia is commonly present in both ulcerative colitis and Crohn's disease. Enteral nutrition has been found to be efficient to improve hemoglobin level in patients with inflammatory bowel disease, especially combined with erythropoietin.

Microbiome
Fecal microbiota transplant is a relatively new treatment option for IBD.

Alternative medicine
The best supportive evidence was found for herbal therapy, with Plantago ovata and curcumin in UC maintenance therapy, wormwood in CD, mind/body therapy and self-intervention in UC, and acupuncture in UC and CD.

Novel approaches
Stem cell therapy is undergoing research as a possible treatment for IBD.
## 2. JAUNDICE

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yellowish coloration of skin and whites of the eyes, pruritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes</td>
<td>High bilirubin levels</td>
</tr>
<tr>
<td>Diagnostic method</td>
<td>Blood bilirubin, liver panel</td>
</tr>
<tr>
<td>Differential diagnosis</td>
<td>Carotenemia, taking rifampin</td>
</tr>
<tr>
<td>Treatment</td>
<td>Based on the underlying cause</td>
</tr>
</tbody>
</table>

**Jaundice**, also known as *icterus*, is a yellowish or greenish pigmentation of the skin and whites of the eyes due to high bilirubin levels. It is commonly associated with itchiness. The feces may be pale and the urine dark. Jaundice in babies occurs in over half in the first week following birth and in most is not a problem. If bilirubin levels in babies are very high for too long, a type of brain damage, known as kernicterus, may occur. Causes of jaundice vary from non-serious to potentially fatal. Levels of bilirubin in blood are normally below 1.0 mg/dL (17 µmol/L) and levels over 2–3 mg/dL (34-51 µmol/L) typically results in jaundice. High bilirubin is divided into two types: unconjugated (indirect) and conjugated (direct). Conjugated bilirubin can be confirmed by finding bilirubin in the urine. Other conditions that can cause yellowish skin but are not jaundice include carotenemia from eating large amounts of certain foods and medications like rifampin. High unconjugated bilirubin may be due to excess red blood cell breakdown, large bruises, genetic conditions such as Gilbert's syndrome, not eating for a prolonged period of time, newborn jaundice, or thyroid problems. High conjugated bilirubin may be due to liver diseases such as cirrhosis or hepatitis, infections, medications, or blockage of the bile duct. In the developed world, the cause is more often blockage of the bile duct or medications while in the developing world, it is more often infections such as viral hepatitis, leptospirosis, schistosomiasis, or malaria. Blockage of the bile duct may occur due to gallstones, cancer, or pancreatitis. Medical imaging such as ultrasound is useful for detecting bile duct blockage.

Treatment of jaundice is typically determined by the underlying cause. If a bile duct blockage is present, surgery is typically required; otherwise, management is medical. Medical management may involve treating infectious causes and stopping medication that could be contributing. Among newborns, depending on age and prematurity, a bilirubin greater than 4–21 mg/dL (68-360 µmol/L) may be treated with phototherapy or exchanged transfusion. The itchiness may be helped by draining the gallbladder or ursodeoxycholic acid. The word *jaundice* is from the French *jaunisse*, meaning "yellow disease".

### SIGNS AND SYMPTOMS

The main sign of jaundice is a yellowish discoloration of the white area of the eye and the skin. Urine is dark in colour. Slight increases in serum bilirubin are best detected by examining the sclerae, which have a particular affinity for bilirubin due to their high elastin content. The presence of scleral icterus indicates a serum bilirubin of at least 3 mg/dL. The conjunctiva of the eye are one of the first tissues to change color as bilirubin levels rise in jaundice. This is sometimes referred to as *scleral icterus*. The sclera themselves are not "icteric" (stained with bile...
pigment), however, but rather the conjunctival membranes that overlie them. The yellowing of the "white of the eye" is thus more properly termed *conjunctival icterus*. The term "icterus" itself is sometimes incorrectly used to refer to jaundice that is noted in the sclera of the eyes; its more common and more correct meaning is entirely synonymous with jaundice, however.

**COMPLICATIONS**

Hyperbilirubinemia, more precisely hyperbilirubinemia due to the unconjugated fraction, may cause bilirubin to accumulate in the gray matter of the central nervous system, potentially causing irreversible neurological damage leading to a condition known as kernicterus. Depending on the level of exposure, the effects range from clinically unnoticeable to severe brain damage and even death. Newborns are especially vulnerable to hyperbilirubinemia-induced neurological damage and therefore must be carefully monitored for alterations in their serum bilirubin levels.

**DIFFERENTIAL DIAGNOSIS**

**Types of jaundice**

Jaundice is classified into three categories, depending on which part of the physiological mechanism the pathology affects. The three categories are:

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hepatic/hemolytic</td>
<td>The pathology is occurring prior to the liver due to either:</td>
</tr>
<tr>
<td></td>
<td>A. Intrinsic defects in RB cells</td>
</tr>
<tr>
<td></td>
<td>B. Extrinsic causes external to RB cells</td>
</tr>
<tr>
<td>Hepatic/hepatocellular</td>
<td>The pathology is located within the liver caused due to disease of parenchymal cells of liver.</td>
</tr>
<tr>
<td>Post-Hepatic/cholestatic</td>
<td>The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage.</td>
</tr>
</tbody>
</table>

**Pre-hepatic**

*Pre-hepatic* jaundice is caused by anything that causes an increased rate of hemolysis (breakdown of red blood cells). Unconjugated bilirubin comes from the breakdown of the heme pigment found in red blood cells' hemoglobin. The increased breakdown of red blood cells leads to an increase in the amount of unconjugated bilirubin present in the blood and deposition of this unconjugated bilirubin into various tissues can lead to a jaundiced appearance. In tropical countries, severe malaria can cause jaundice in this manner. Certain genetic diseases, such as sickle cell anemia, spherocytosis, thalassemia, pyruvate kinase deficiency, and glucose 6-phosphate dehydrogenase deficiency can lead to increased red cell lysis and therefore hemolytic jaundice. Commonly, diseases of the kidney, such as hemolytic uremic syndrome, can also lead to coloration.

In jaundice secondary to hemolysis, the increased production of bilirubin leads to the increased production of urine-urobilinogen. Bilirubin is not usually found in the urine because unconjugated bilirubin is not water-soluble, so, the combination of increased urine-urobilinogen with no bilirubin (since, unconjugated) in urine is suggestive of hemolytic jaundice.
Laboratory findings include:
- Urine: no bilirubin present, urobilinogen > 2 units (i.e., hemolytic anemia causes increased heme metabolism; exception: infants where gut flora has not developed).
- Serum: increased unconjugated bilirubin.
- Kernicterus is associated with increased unconjugated bilirubin not carried by albumin. Newborns are especially vulnerable to this due to increased permeability of the blood brain barrier.

### Hepatocellular

_Hepatocellular_ (hepatic) jaundice can be caused by acute or chronic hepatitis, hepatotoxicity, cirrhosis, drug-induced hepatitis and alcoholic liver disease. Cell necrosis reduces the liver's ability to metabolize and excrete bilirubin leading to a buildup of unconjugated bilirubin in the blood. Other causes include primary biliary cirrhosis leading to an increase in plasma conjugated bilirubin because there is impairment of excretion of conjugated bilirubin into the bile. The blood contains an abnormally raised amount of conjugated bilirubin and bile salts, which are excreted in the urine. Jaundice seen in the newborn, known as _neonatal jaundice_, is common in newborns as hepatic machinery for the conjugation and excretion of bilirubin does not fully mature until approximately two weeks of age. Rat fever (leptospirosis) can also cause hepatic jaundice. In hepatic jaundice, there is invariably cholestasis. Defects in bilirubin metabolism also lead to jaundice, as in Gilbert's syndrome (a genetic disorder of bilirubin metabolism that can result in mild jaundice).

Laboratory findings depend on the cause of jaundice.
- Urine: Conjugated bilirubin present, urobilirubin > 2 units but variable (except in children). Kernicterus is a condition not associated with increased conjugated bilirubin.
- Plasma protein show characteristic changes.
- Plasma albumin level is low but plasma globulins are raised due to an increased formation of antibodies.

Bilirubin transport across the hepatocyte may be impaired at any point between the uptake of unconjugated bilirubin into the cell and transport of conjugated bilirubin into biliary canaliculi. In addition, swelling of cells and oedema due to inflammation cause mechanical obstruction of intrahepatic biliary tree. Hence in hepatocellular jaundice, concentration of both unconjugated and conjugated bilirubin rises in the blood. In hepatocellular disease, there is usually interference in all major steps of bilirubin metabolism—uptake, conjugation and excretion. Excretion is the rate-limiting step, however, and usually impaired to the greatest extent. As a result, conjugated hyperbilirubinaemia predominates.

The unconjugated bilirubin still enters the liver cells and becomes conjugated in the usual way. This conjugated bilirubin is then returned to the blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver. Thus, most of the bilirubin in the plasma becomes the conjugated type rather than the unconjugated type, and this conjugated bilirubin, which did not go to intestine to become urobilinogen, gives the urine the dark color.

### Post-hepatic

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile containing conjugated bilirubin in the biliary system. The most common causes...
are gallstones in the common bile duct, and pancreatic cancer in the head of the pancreas. Also, a group of parasites known as "liver flukes" can live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, cholangiocarcinoma, pancreatitis, cholestasis of pregnancy, and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome (gallstone impaction in the cystic duct or gallbladder neck, with the enlarged gallbladder squeezing on the common hepatic duct).

In complete obstruction of the bile duct, no urobinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that bilirubin gets converted to urobinogen by microorganisms, with the urobinogen later being partially reabsorbed from the intestine into the general circulation, and then excreted into the urine. In this case, presence of bilirubin (conjugated) in the urine without urobinogen suggests obstructive jaundice, either intra-hepatic or post-hepatic. The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal feces get their color from bile pigments. They can, however, occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice.

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus" because of the direct and indirect effects of pruritogens in bile such as bile salts. No single test can differentiate between various classifications of jaundice. A combination of liver function tests is essential to arrive at a diagnosis.

Diagnostic tests

<table>
<thead>
<tr>
<th>Function test</th>
<th>Pre-hepatic jaundice</th>
<th>Hepatic jaundice</th>
<th>Post-hepatic jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>Normal / increased</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Conjugated bilirubin</td>
<td>Normal</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Normal / increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Urobinogen</td>
<td>Normal / increased</td>
<td>Decreased</td>
<td>Decreased / negative</td>
</tr>
<tr>
<td>Urine color</td>
<td>Normal</td>
<td>Dark (urobinogen + conjugated bilirubin)</td>
<td>Dark (conjugated bilirubin)</td>
</tr>
<tr>
<td>Stool color</td>
<td>Normal</td>
<td>slightly pale</td>
<td>Pale</td>
</tr>
<tr>
<td>Alkaline phosphatase levels</td>
<td>Normal</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Alanine transferase and aspartate transferase levels</td>
<td>Normal</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Conjugated bilirubin in urine</td>
<td>Not present</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Neonatal jaundice

Neonatal jaundice is usually harmless: this condition is often seen in infants around the second day after birth, lasting until day 8 in normal births, or to around day 14 in premature births. Typical causes for neonatal jaundice include normal physiologic jaundice, jaundice due to formula supplementation, and hemolytic disorders that include hereditary spherocytosis, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, ABO/Rh blood type autoantibodies, or infantile pyknocytosis. Serum bilirubin normally drops to a low level without any intervention required. In cases where bilirubin rises higher, a brain-damaging condition known as kernicterus can occur, leading to significant disability. This condition has been rising in recent years due to less time spent outdoors. A Bili light is often the tool used for early treatment, which often consists of exposing the baby to intensive phototherapy. Sunbathing is effective treatment, and has the advantage of ultra-violet-B, which promotes Vitamin D production. Bilirubin count is lowered through bowel movements and urination, so frequent and effective feedings are especially important.

DIFFERENTIAL DIAGNOSIS

Yellow discoloration of the skin, especially on the palms and the soles, but not of the sclera or inside the mouth is due to carotenemia—a harmless condition.

PATHOPHYSIOLOGY

Jaundice itself is not a disease, but rather a sign of one of many possible underlying pathological processes that occur at some point along the normal physiological pathway of the metabolism of bilirubin in blood. When red blood cells have completed their life span of approximately 120 days, or when they are damaged, their membranes become fragile and prone to rupture. As each red blood cell traverses through the reticuloendothelial system, its cell membrane ruptures when its membrane is fragile enough to allow this. Cellular contents, including hemoglobin, are subsequently released into the blood. The hemoglobin is phagocytosed by macrophages, and split into its heme and globin portions. The globin portion, a protein, is degraded into amino acids and plays no role in jaundice. Two reactions then take place with the heme molecule. The first oxidation reaction is catalyzed by the microsomal enzyme heme oxygenase and results in biliverdin (green color pigment), iron and carbon monoxide. The next step is the reduction of biliverdin to a yellow color tetrapyroly pigment called bilirubin by cytosolic enzyme biliverdin reductase. This bilirubin is "unconjugated," "free" or "indirect" bilirubin. Approximately 4 mg of bilirubin per kg of blood is produced each day. The majority of this bilirubin comes from the breakdown of heme from expired red blood cells in the process just described. Approximately twenty percent comes from other heme sources, however, including ineffective erythropoiesis, and the breakdown of other heme-containing proteins, such as muscle myoglobin and cytochromes.

Hepatic events

The unconjugated bilirubin then travels to the liver through the bloodstream. Because this bilirubin is not soluble, however, it is transported through the blood bound to serum albumin. Once it arrives at the liver, it is conjugated with glucuronic acid (to form bilirubin diglucuronide,
or just "conjugated bilirubin") to become more water-soluble. The reaction is catalyzed by the enzyme UDP-glucuronyl transferase. This conjugated bilirubin is excreted from the liver into the biliary and cystic ducts as part of bile. Intestinal bacteria convert the bilirubin into urobilinogen. From here urobilinogen can take two pathways. It can either be further converted into stercobilinogen, which is then oxidized to stercobilin and passed out in the feces, or it can be reabsorbed by the intestinal cells, transported in the blood to the kidneys, and passed out in the urine as the oxidised product urobilin. Stercobilin and urobilin are the products responsible for the coloration of feces and urine, respectively.

**DIAGNOSIS**

Most patients presenting with jaundice will have various predictable patterns of liver panel abnormalities, though significant variation does exist. The typical liver panel will include blood levels of enzymes found primarily from the liver, such as the aminotransferases (ALT, AST), and alkaline phosphatase (ALP); bilirubin (which causes the jaundice); and protein levels, specifically, total protein and albumin. Other primary lab tests for liver function include gamma glutamyl transpeptidase (GGT) and prothrombin time (PT).

Some bone and heart disorders can lead to an increase in ALP and the aminotransferases, so the first step in differentiating these from liver problems is to compare the levels of GGT, which will only be elevated in liver-specific conditions. The second step is distinguishing from biliary (cholestatic) or liver (hepatic) causes of jaundice and altered laboratory results. The former typically indicates a surgical response, while the latter typically leans toward a medical response. ALP and GGT levels will typically rise with one pattern while aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rise in a separate pattern. If the ALP (10–45 IU/L) and GGT (18–85) levels rise proportionately about as high as the AST (12–38 IU/L) and ALT (10–45 IU/L) levels, this indicates a cholestatic problem. On the other hand, if the AST and ALT rise is significantly higher than the ALP and GGT rise, this indicates an hepatic problem. Finally, distinguishing between hepatic causes of jaundice, comparing levels of AST and ALT can prove useful. AST levels will typically be higher than ALT. This remains the case in most hepatic disorders except for hepatitis (viral or hepatotoxic). Alcoholic liver damage may see fairly normal ALT levels, with AST 10x higher than ALT. On the other hand, if ALT is higher than AST, this is indicative of hepatitis. Levels of ALT and AST are not well correlated to the extent of liver damage, although rapid drops in these levels from very high levels can indicate severe necrosis. Low levels of albumin tend to indicate a chronic condition, while it is normal in hepatitis and cholestasis.

**PREVENTION**

It is not possible to prevent all cases of jaundice because it is can be a wide range of conditions or circumstances. However, by taking certain precautions risk of developing jaundice can be minimized. These include:

- Ensure not to take alcohol if it is taken then not to exceed the recommended daily amount (RDA) for alcohol consumption.
- Maintain a healthy weight for height and build.
- Avoid high risk behaviors such as intravenous drugs.
- Avoid potentially contaminated food/water and maintain good hygiene.
- Avoid medications and toxins which can cause hemolysis or directly damage the liver.
- Avoid fat in diet
- Manage cholesterol level
- Physical exercise

**MANAGEMENT**

There’s no treatment for jaundice as such, but disease can be managed by managing symptoms and causes of jaundice.

Sometime use liver tonic.
1. HEPATITIS

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Infectious disease, gastroenterology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Yellowish skin, poor appetite, abdominal pain</td>
</tr>
<tr>
<td>Complications</td>
<td>Scarring of the liver, liver failure, liver cancer</td>
</tr>
<tr>
<td>Duration</td>
<td>Short term or long term</td>
</tr>
<tr>
<td>Causes</td>
<td>Viruses, alcohol, toxins, autoimmune</td>
</tr>
<tr>
<td>Prevention</td>
<td>Vaccination (for viral hepatitis)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Medication, liver transplant</td>
</tr>
</tbody>
</table>

INTRODUCTION

**Hepatitis** is inflammation of the liver tissue. Some people have no symptoms whereas others develop yellow discoloration of the skin and whites of the eyes, poor appetite, vomiting, tiredness, abdominal pain, or diarrhea. Hepatitis may be temporary (acute) or long term (chronic) depending on whether it lasts for less than or more than six months. Acute hepatitis can sometimes resolve on its own, progress to chronic hepatitis, or rarely result in acute liver failure. Over time the chronic form may progress to scarring of the liver, liver failure, or liver cancer.

The most common cause worldwide is viruses. Other causes include heavy alcohol use, certain medications, toxins, other infections, autoimmune diseases, and non-alcoholic steatohepatitis (NASH). There are five main types of viral hepatitis: type A, B, C, D, and E. Hepatitis A and E are mainly spread by contaminated food and water. Hepatitis B is mainly sexually transmitted, but may also be passed from mother to baby during pregnancy or childbirth. Both hepatitis B and hepatitis C are commonly spread through infected blood such as may occur during needle sharing by intravenous drug users. Hepatitis D can only infect people already infected with hepatitis B. Hepatitis A, B, and D are preventable with immunization. Medications may be used to treat chronic cases of viral hepatitis. There is no specific treatment for NASH; however, a healthy lifestyle, including physical activity, a healthy diet, and weight loss, is important. Autoimmune hepatitis may be treated with medications to suppress the immune system. A liver transplant may also be an option in certain cases.

SIGNS AND SYMPTOMS

- Acute hepatitis
- Fulminant hepatitis
- Chronic hepatitis

Hepatitis has a broad spectrum of presentations that range from a complete lack of symptoms to severe liver failure. The acute form of hepatitis, generally caused by viral infection, is characterized by constitutional symptoms that are typically self-limiting. Chronic hepatitis...
Acute hepatitis

Acute viral hepatitis follows a pattern of infection that involves three distinct phases:

1. The initial prodromal phase (preceding symptoms) involves non-specific and flu-like symptoms common to many acute viral infections. These include fatigue, nausea, vomiting, poor appetite, joint pain, and headaches. Fever, when present, is most common in cases of hepatitis A and E. Late in this phase, people can experience liver-specific symptoms, including choloruria (dark urine) and clay-colored stools.

2. Yellowing of the skin and whites of the eyes follow the prodrome after about 1–2 weeks and can last for up to 4 weeks. The non-specific symptoms seen in the prodromal typically resolve by this time, but people will develop an enlarged liver and right upper abdominal pain or discomfort. 10–20% of people will also experience an enlarged spleen, while some people will also experience a mild unintentional weight loss.

3. The recovery phase is characterized by resolution of the clinical symptoms of hepatitis with persistent elevations in liver lab values and potentially a persistently enlarged liver. All cases of hepatitis A and E are expected to fully resolve after 1–2 months. Most hepatitis B cases are also self-limiting and will resolve in 3–4 months. Few cases of hepatitis C will resolve completely.

Both drug-induced hepatitis and autoimmune hepatitis can present very similarly to acute viral hepatitis, with slight variations in symptoms depending on the cause. Cases of drug-induced hepatitis can manifest with systemic signs of an allergic reaction including rash, fever, serositis (inflammation of membranes lining certain organs), elevated eosinophils (a type of white blood cell), and suppression of bone marrow activity.

Fulminant hepatitis

Fulminant hepatitis, or massive hepatic cell death, is a rare and life-threatening complication of acute hepatitis that can occur in cases of hepatitis B, D, and E, in addition to drug-induced and autoimmune hepatitis. The complication more frequently occurs in instances of hepatitis B and D co-infection at a rate of 2–20% and in pregnant women with hepatitis E at rate of 15–20% of cases. In addition to the signs of acute hepatitis, people can also demonstrate signs of coagulopathy (abnormal coagulation studies with easy bruising and bleeding) and encephalopathy (confusion, disorientation, and sleepiness). Mortality due to fulminant hepatitis is typically the result of various complications including cerebral edema, gastrointestinal bleeding, sepsis, respiratory failure, or kidney failure.

Chronic hepatitis

Acute cases of hepatitis are seen to be resolved well within a six-month period. When hepatitis is continued for more than six months it is termed chronic hepatitis. Chronic hepatitis is often asymptomatic early in its course and is detected only by liver laboratory studies for screening purposes or to evaluate non-specific symptoms. As the inflammation progresses, patients can develop constitutional symptoms similar to acute hepatitis, including fatigue, nausea, vomiting, poor appetite, and joint pain. Jaundice can occur as well, but much later in the disease process and is typically a sign of advanced disease. Chronic hepatitis interferes with hormonal functions of the liver which can result in acne, hirsutism (abnormal hair growth), and amenorrhea (lack of menstrual period) in women. Extensive damage and scarring of the liver over time defines
cirrhosis, a condition in which the liver’s ability to function is permanently impeded. This results in jaundice, weight loss, coagulopathy, ascites (abdominal fluid collection), and peripheral edema (leg swelling). Cirrhosis can lead to other life-threatening complications such as hepatic encephalopathy, esophageal varices, hepatorenal syndrome, and liver cancer.

**CAUSES**

- **Infectious**
- **Metabolic**
- **Autoimmune**
- **Genetic**
- **Ischemic hepatitis**
- **Other**

Causes of hepatitis can be divided into the following major categories: infectious, metabolic, ischemic, autoimmune, genetic, and other. Infectious agents include viruses, bacteria, and parasites. Toxins, drugs, alcohol, and non-alcoholic fatty liver disease are metabolic causes of liver injury and inflammation. Autoimmune and genetic causes of hepatitis involve genetic predispositions and tend to affect characteristic populations.

### Infectious

#### i.) Viral hepatitis

Viral hepatitis is the most common type of hepatitis worldwide. Viral hepatitis is caused by five different viruses (hepatitis A, B, C, D, and E). Hepatitis A and hepatitis E behave similarly: they are both transmitted by the fecal–oral route, are more common in developing countries, and are self-limiting illnesses that do not lead to chronic hepatitis. Hepatitis B, hepatitis C, and hepatitis D are transmitted when blood or mucous membranes are exposed to infected blood and body fluids, such as semen and vaginal secretions. Viral particles have also been found in saliva and breastmilk. However, kissing, sharing utensils, and breastfeeding do not lead to transmission unless these fluids are introduced into open sores or cuts.

Hepatitis B and C can present either acutely or chronically. Hepatitis D is a defective virus that requires hepatitis B to replicate and is only found with hepatitis B co-infection. In adults, hepatitis B infection is most commonly self-limiting, with less than 5% progressing to chronic state, and 20 to 30% of those chronically infected developing cirrhosis or liver cancer. However, infection in infants and children frequently leads to chronic infection. Unlike hepatitis B, most cases of hepatitis C lead to chronic infection. Hepatitis C is the second most common cause of cirrhosis. Blood transfusions were a major factor in spreading hepatitis C virus.

#### ii.) Parasitic hepatitis

Parasites can also infect the liver and activate the immune response, resulting in symptoms of acute hepatitis with increased serum IgE (though chronic hepatitis is possible with chronic infections). Of the protozoans, Trypanosoma cruzi, Leishmania species, and the malaria-causing Plasmodium species all can cause liver inflammation. Another protozoan, Entamoeba histolytica, causes hepaticis with distinct liver abscesses.
Of the worms, the cestode Echinococcus granulosus, also known as the dog tapeworm, infects the liver and forms characteristic hepatic hydatid cysts. The liver flukes Fasciola hepatica and Clonorchis sinensis live in the bile ducts and cause progressive hepatitis and liver fibrosis.

iii.) Bacterial hepatitis
Bacterial infection of the liver commonly results in pyogenic liver abscesses, acute hepatitis, or granulomatous (or chronic) liver disease. Pyogenic abscesses commonly involve enteric bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and are composed of multiple bacteria up to 50% of the time. Acute hepatitis is caused by *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Bartonella henselae*, *Borrelia burgdorferi*, salmonella species, brucella species and campylobacter species. Chronic or granulomatous hepatitis is seen with infection from mycobacteria species, *Tropheryma whipplei*, *Treponema pallidum*, *Coxiella burnetii*, and rickettsia species.

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i.) Alcoholic hepatitis
Excessive alcohol consumption is a significant cause of hepatitis and is the most common cause of cirrhosis. Alcoholic hepatitis is within the spectrum of alcoholic liver disease. This ranges in order of severity and reversibility from alcoholic steatosis (least severe, most reversible), alcoholic hepatitis, cirrhosis, and liver cancer (most severe, least reversible). Hepatitis usually develops over years-long exposure to alcohol, occurring in 10 to 20% of alcoholics. The most important risk factors for the development of alcoholic hepatitis are quantity and duration of alcohol intake. Long-term alcohol intake in excess of 80 grams of alcohol a day in men and 40 grams a day in women is associated with development of alcoholic hepatitis (1 beer or 4 ounces of wine is equivalent to 12g of alcohol). Alcoholic hepatitis can vary from asymptomatic hepatomegaly (enlarged liver) to symptoms of acute or chronic hepatitis to liver failure.

ii.) Toxic and drug-induced hepatitis
Many chemical agents, including medications, industrial toxins, and herbal and dietary supplements, can cause hepatitis. The spectrum of drug-induced liver injury varies from acute hepatitis to chronic hepatitis to acute liver failure. Toxins and medications can cause liver injury through a variety of mechanisms, including direct cell damage, disruption of cell metabolism, and causing structural changes. Some drugs such as paracetamol exhibit predictable dose-dependent liver damage while others such as isoniazid cause idiosyncratic and unpredictable reactions that vary among individuals. There are wide variations in the mechanisms of liver injury and latency period from exposure to development of clinical illness. Many types of drugs can cause liver injury, including the analgesic paracetamol; antibiotics such as isoniazid, nitrofurantoin, amoxicillin-clavulanate, erythromycin, and trimethoprim-sulfamethoxazole; anticonvulsants such as valproate and phenytoin; cholesterol-lowering statins; steroids such as oral contraceptives and anabolic steroids; and highly active anti-retroviral therapy used in the treatment of HIV/AIDS. Of these, amoxicillin-clavulanate is the most common cause of drug-induced liver injury, and paracetamol toxicity the most common cause of acute liver failure in the United States and Europe. Herbal remedies and dietary supplements are another important cause of hepatitis; these are the most common causes of drug-induced hepatitis in Korea. The United-States-based Drug Induced Liver Injury Network linked more than 16% of cases of hepatotoxicity to herbal and dietary supplements. In the United States, herbal and dietary supplements – unlike pharmaceutical drugs – are unregulated by the Food and Drug Administration. However, the National Institutes of
Health maintains the LiverTox database for consumers to track all known prescription and non-prescription compounds associated with liver injury.

Exposure to other hepatotoxins can occur accidentally or intentionally through ingestion, inhalation, and skin absorption. The industrial toxin carbon tetrachloride and the wild mushroom Amanita phalloides are other known hepatotoxins.

### iii. Non-alcoholic fatty liver disease

Non-alcoholic hepatitis is within the spectrum of non-alcoholic liver disease (NALD), which ranges in severity and reversibility from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH) to cirrhosis to liver cancer, similar to the spectrum of alcoholic liver disease.

Non-alcoholic liver disease occurs in people with little or no history of alcohol use, and is instead strongly associated with metabolic syndrome, obesity, insulin resistance and diabetes, and hypertriglyceridemia. Over time, non-alcoholic fatty liver disease can progress to non-alcoholic steatohepatitis, which additionally involves liver cell death, liver inflammation and possible fibrosis. Factors accelerating progression from NAFLD to NASH are obesity, older age, non-African American ethnicity, female gender, diabetes mellitus, hypertension, higher ALT or AST level, higher AST/ALT ratio, low platelet count, and an ultrasound steatosis score.

In the early stages (as with NAFLD and early NASH), most patients are asymptomatic or have mild right upper quadrant pain, and diagnosis is suspected on the basis of abnormal liver function tests. As the disease progresses, symptoms typical of chronic hepatitis may develop. While imaging can show fatty liver, only liver biopsy can demonstrate inflammation and fibrosis characteristic of NASH. 9 to 25% of patients with NASH develop cirrhosis. NASH is recognized as the third most common cause of liver disease in the United States.

### Autoimmune

Autoimmune hepatitis is a chronic disease caused by an abnormal immune response against liver cells. The disease is thought to have a genetic predisposition as it is associated with certain human leukocyte antigens involved in the immune response. As in other autoimmune diseases, circulating auto-antibodies may be present and are helpful in diagnosis. Auto-antibodies found in patients with autoimmune hepatitis include the sensitive but less specific anti-nuclear antibody (ANA), smooth muscle antibody (SMA), and atypical perinuclear antineutrophil cytoplasmic antibody (p-ANCA). Other autoantibodies that are less common but more specific to autoimmune hepatitis are the antibodies against liver kidney microsome 1 (LKM1) and soluble liver antigen (SLA). Autoimmune hepatitis can also be triggered by drugs (such as nitrofurantoin, hydralazine, and methyldopa), after liver transplant, or by viruses (such as hepatitis A, Epstein-Barr virus, or measles).

Autoimmune hepatitis can present anywhere within the spectrum from asymptomatic to acute or chronic hepatitis to fulminant liver failure. Patients are asymptomatic 25–34% of the time, and the diagnosis is suspected on the basis of abnormal liver function tests. Up to 40% of cases present with signs and symptoms of acute hepatitis. As with other autoimmune diseases, autoimmune hepatitis usually affects young women (though it can affect patients of either sex of any age), and patients can exhibit classic signs and symptoms of autoimmunity such as fatigue, anemia, anorexia, amenorrhea, acne, arthritis, pleurisy, thyroiditis, ulcerative colitis, nephritis, and maculopapular rash. Autoimmune hepatitis increases the risk for cirrhosis, and the risk for liver cancer is increased by about 1% for each year of the disease.

Many people with autoimmune hepatitis have other autoimmune diseases. Autoimmune hepatitis is distinct from the other autoimmune diseases of the liver: primary biliary cirrhosis and primary
sclerosing cholangitis. However, all of these diseases can lead to scarring, fibrosis, and cirrhosis of the liver.

Genetic
Genetic causes of hepatitis include alpha-1-antitrypsin deficiency, hemochromatosis, and Wilson's disease. In alpha-1-antitrypsin deficiency, a co-dominant mutation in the gene for alpha-1-antitrypsin results in the abnormal accumulation of the protein within liver cells, leading to liver disease. Hemochromatosis and Wilson's disease are both autosomal recessive diseases involving abnormal storage of minerals. In hemochromatosis, excess amounts of iron accumulate in multiple body sites, including the liver, which can lead to cirrhosis. In Wilson's disease, excess amounts of copper accumulate in the liver and brain, causing cirrhosis and dementia. When the liver is involved, alpha-1-antitrypsin deficiency and Wilson's disease tend to present as hepatitis in the neonatal period or in childhood. Hemochromatosis typically presents in adulthood, with the onset of clinical disease usually after age 50.

Ischemic hepatitis
Ischemic hepatitis (also known as shock liver) results from reduced blood flow to the liver as in shock, heart failure, or vascular insufficiency. The condition is most often associated with heart failure but can also be caused by shock or sepsis. Blood testing of a person with ischemic hepatitis will show very high levels of transaminase enzymes (AST and ALT). The condition usually resolves if the underlying cause is treated successfully. Ischemic hepatitis rarely causes permanent liver damage.

Other
Hepatitis can also occur in neonates and is attributable to a variety of causes, some of which are not typically seen in adults. Congenital or perinatal infection with the hepatitis viruses, toxoplasma, rubella, cytomegalovirus, and syphilis can cause neonatal hepatitis. Structural abnormalities such as biliary atresia and choledochal cysts can lead to cholestatic liver injury leading to neonatal hepatitis. Metabolic diseases such as glycogen storage disorders and lysosomal storage disorders are also implicated. Neonatal hepatitis can be idiopathic, and in such cases, biopsy often shows large multinucleated cells in the liver tissue. This disease is termed giant cell hepatitis and may be associated with viral infection, autoimmune disorders, and drug toxicity.

MECHANISM

- Viral hepatitis
- Steatohepatitis

The specific mechanism varies and depends on the underlying cause of the hepatitis. Generally, there is an initial insult that causes liver injury and activation of an inflammatory response, which can become chronic, leading to progressive fibrosis and cirrhosis.

Viral hepatitis
The pathway by which hepatic viruses cause viral hepatitis is best understood in the case of hepatitis B and C. The viruses do not directly cause apoptosis (cell death). Rather, infection of liver cells activates the innate and adaptive arms of the immune system leading to an inflammatory response which causes cellular damage and death.
Depending on the strength of the immune response, the types of immune cells involved and the ability of the virus to evade the body's defense, infection can either lead to clearance (acute disease) or persistence (chronic disease) of the virus. The chronic presence of the virus within liver cells results in multiple waves of inflammation, injury and wound healing that overtime lead to scarring or fibrosis and culminate in hepatocellular carcinoma. Individuals with an impaired immune response are at greater risk of developing chronic infection. Natural killer cells are the primary drivers of the initial innate response and create a cytokine environment that results in the recruitment of CD4 T-helper and CD8 cytotoxic T-cells. Type I interferons are the cytokines that drive the antiviral response. In chronic Hepatitis B and C, natural killer cell function is impaired.

### Steatohepatitis

Steatohepatitis is seen in both alcoholic and non-alcoholic liver disease and is the culmination of a cascade of events that began with injury. In the case of non-alcoholic steatohepatitis, this cascade is initiated by changes in metabolism associated with obesity, insulin resistance, and lipid dysregulation. In alcoholic hepatitis, chronic excess alcohol use is the culprit. Though the inciting event may differ, the progression of events is similar and begins with accumulation of free fatty acids (FFA) and their breakdown products in the liver cells in a process called steatosis. This initially reversible process overwhelms the hepatocyte's ability to maintain lipid homeostasis leading to a toxic effect as fat molecules accumulate and are broken down in the setting of an oxidative stress response. Overtime, this abnormal lipid deposition triggers the immune system via toll-like receptor 4 (TLR4) resulting in the production of inflammatory cytokines such as TNF that cause liver cell injury and death. These events mark the transition to steatohepatitis and in the setting of chronic injury, fibrosis eventually develops setting up events that lead to cirrhosis and hepatocellular carcinoma. Microscopically, changes that can be seen include steatosis with large and swollen hepatocytes (ballooning), evidence of cellular injury and cell death (apoptosis, necrosis), evidence of inflammation in particular in zone 3 of the liver, variable degrees of fibrosis and Mallory bodies.
### DIAGNOSIS

- Viral hepatitis
- Alcoholic versus non-alcoholic

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<th>Predominantly elevated aminotransferase</th>
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<td>ALT</td>
<td>Chronic hepatitis B, C, and D</td>
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<td>Nonalcoholic liver disease</td>
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<td><em>Ischemic hepatitis</em> (severe elevation up to thousands)</td>
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<td>Cirrhosis</td>
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Diagnosis of hepatitis is made on the basis of some or all of the following: a patient's signs and symptoms, medical history including sexual and substance use history, blood tests, imaging, and liver biopsy. In general, for viral hepatitis and other acute causes of hepatitis, the patient's blood tests and clinical picture are sufficient for diagnosis. For other causes of hepatitis, especially chronic causes, blood tests may not be useful. In this case, liver biopsy is the gold standard for establishing the diagnosis as histopathologic analysis is able to reveal the precise extent and pattern of inflammation and fibrosis. However, liver biopsy is typically not the initial diagnostic test because it is invasive and is associated with a small but significant risk of bleeding that is increased in patients with liver injury and cirrhosis.

Blood testing includes liver enzymes, serology (i.e. for autoantibodies), nucleic acid testing (i.e. for hepatitis virus DNA/RNA), blood chemistry, and complete blood count. Characteristic patterns of liver enzyme abnormalities can point to certain causes or stages of hepatitis. Generally, AST and ALT are elevated in most cases of hepatitis regardless of whether the patient shows any symptoms. However, the degree of elevation (i.e. levels in the hundreds vs. in the thousands), the predominance for AST vs. ALT elevation, and the ratio between AST and ALT are informative of the diagnosis.

Ultrasound, CT, and MRI can all identify steatosis (fatty changes) of the liver tissue and nodularity of the liver surface suggestive of cirrhosis. CT and especially MRI are able to provide a higher level of detail, allowing visualization and characterize such structures as vessels and tumors within the liver. Unlike steatosis and cirrhosis, no imaging test is able to detect liver inflammation (i.e. hepatitis) or fibrosis. Liver biopsy is the only definitive diagnostic test that is able to assess inflammation and fibrosis of the liver.
Viral hepatitis
Viral hepatitis is primarily diagnosed through blood tests for levels of viral antigens (such as the hepatitis B surface or core antigen), anti-viral antibodies (such as the anti-hepatitis B surface antibody or anti-hepatitis A antibody), or viral DNA/RNA. In early infection (i.e. within 1 week), IgM antibodies are found in the blood. In late infection and after recovery, IgG antibodies are present and remain in the body for up to years. Therefore, when a patient is positive for IgG antibody but negative for IgM antibody, he is considered immune from the virus via either prior infection and recovery or prior vaccination.

In the case of hepatitis B, blood tests exist for multiple virus antigens (which are different components of the virion particle) and antibodies. The combination of antigen and antibody positivity can provide information about the stage of infection (acute or chronic), the degree of viral replication, and the infectivity of the virus.

Alcoholic versus non-alcoholic
The most apparent distinguishing factor between alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) is a history of alcohol use or abuse. Thus, in patients who have no or negligible alcohol use, the diagnosis is unlikely to be alcoholic hepatitis. However, in those who use alcohol, the diagnosis may just as likely be alcoholic or nonalcoholic hepatitis especially if there is concurrent obesity, diabetes, and metabolic syndrome. In this case, alcoholic and nonalcoholic hepatitis can be distinguished by the pattern of liver enzyme abnormalities; specifically, in alcoholic steatohepatitis AST>ALT with ratio of AST:ALT>2:1 while in nonalcoholic steatohepatitis ALT>AST with ratio of ALT:AST>1.5:1.

Of note, liver biopsy shows identical findings in patients with ASH and NASH, specifically, the presence of polymorphonuclear infiltration, hepatocyte necrosis and apoptosis in the form of ballooning degeneration, Mallory bodies, and fibrosis around veins and sinuses.

SCREENING

Viral hepatitis
The purpose of screening for viral hepatitis is to identify people infected with the disease as early as possible. This allows for early treatment, which can prevent disease progression, and decreases transmission to others.

i.) Hepatitis A
Hepatitis A causes an acute illness that does not progress to chronic liver disease. Therefore, the role of screening is to assess immune status in people who are at high risk of contracting the virus, as well as in people with known liver disease for whom hepatitis A infection could lead to liver failure. People in these groups who are not already immune can receive the hepatitis A vaccine.

Those at high risk and in need of screening include:
- People with poor sanitary habits such as not washing hands after using the restroom or changing diapers
- People who do not have access to clean water
- People in close contact (either living with or having sexual contact) with someone who has hepatitis A
- Illicit drug users
ii.) **Hepatitis B**

The CDC, WHO, USPSTF, and ACOG recommend routine hepatitis B screening for certain high-risk populations. Specifically, these populations include people who are:

- Born in countries where the prevalence of hepatitis B is high (defined as ≥2% of the population), whether or not they have been vaccinated
- Born in the United States whose parents are from countries where the prevalence of hepatitis B is very high (defined as ≥8% of the population), and who were not vaccinated
- HIV positive
- Intravenous drug users
- Men who have sex with men
- In close contact with (i.e. live or have sex with) people known to have hepatitis B
- Pregnant
- Beginning immunosuppressive or cytotoxic therapy
- Found to have elevated liver enzymes without a known cause
- Blood, organ, or tissue donors
- Incarcerated
- On hemodialysis

Screening consists of a blood test that detects hepatitis B surface antigen (HBsAg). If HBsAg is present, a second test – usually done on the same blood sample – that detects the antibody for the hepatitis B core antigen (anti-HBcAg) can differentiate between acute and chronic infection. People who are high-risk whose blood tests negative for HBsAg can receive the hepatitis B vaccine to prevent future infection.

iii.) **Hepatitis C**

The CDC, WHO, USPSTF, AASLD, and ACOG recommend screening people at high risk for hepatitis C infection. These populations include people who are:

- Intravenous drug users (past or current)
- Intranasal illicit drug users
- HIV-positive
- Men who have sex with men
- Incarcerated, or who have been in the past
- On long-term hemodialysis, or who have been in the past
- Recipients of tattoos in an "unregulated setting"
- Recipients of blood products or organs
- Born to HCV-positive mothers
- Pregnant, and engaging in high-risk behaviors
- Workers in a healthcare setting who have had a needlestick injury
- Blood or organ donors.
- Sex workers
Screening consists of a blood test that detects anti-hepatitis C virus antibody. If anti-hepatitis C virus antibody is present, a confirmatory test to detect HCV RNA indicates chronic disease.

PREVENTION

- Vaccines
- Behavioral changes
- Successes

Vaccines

i.) Hepatitis A
The CDC recommends the hepatitis A vaccine for all children beginning at age one, as well as for those who have not been previously immunized and are at high risk for contracting the disease.
For children 12 months of age or older, the vaccination is given as a shot into the muscle in two doses 6–18 months apart and should be started before the age 24 months. The dosing is slightly different for adults depending on the type of the vaccine. If the vaccine is for hepatitis A only, two doses are given 6–18 months apart depending on the manufacturer. If the vaccine is combined hepatitis A and hepatitis B, up to 4 doses may be required.

ii.) Hepatitis B
The CDC recommends the routine vaccination of all children under the age of 19 with the hepatitis B vaccine. They also recommend it for those who desire it or are at high risk.
Routine vaccination for hepatitis B starts with the first dose administered as a shot into the muscle before the newborn is discharged from the hospital. An additional two doses should be administered before the child is 18 months.
For babies born to a mother with hepatitis B surface antigen positivity, the first dose is unique – in addition to the vaccine, the hepatitis immune globulin should also be administered, both within 12 hours of birth. These newborns should also be regularly tested for infection for at least the first year of life.
There is also a combination formulation that includes both hepatitis A and B vaccines.

iii.) Other
There are currently no vaccines available for hepatitis C or E.

Behavioral changes

i.) Hepatitis A
Because hepatitis A is transmitted primarily through the oral-fecal route, the mainstay of prevention aside from vaccination is good hygiene, access to clean water and proper handling of sewage.

ii.) Hepatitis B and C
As hepatitis B and C are transmitted through blood and multiple bodily fluids, prevention is aimed at screening blood prior to transfusion, abstaining from the use of injection drugs, safe needle and sharps practices in healthcare settings, and safe sex practices.
iii.) Hepatitis D
The hepatitis D virus requires that a person first be infected with hepatitis B virus, so prevention efforts should focus on limiting the spread of hepatitis B. In people who have chronic hepatitis B infection and are at risk for superinfection with the hepatitis D virus, the preventive strategies are the same as for hepatitis B.

iv.) Hepatitis E
Hepatitis E is spread primarily through the oral-fecal route but may also be spread by blood and from mother to fetus. The mainstay of hepatitis E prevention is similar to that for hepatitis A (namely, good hygiene and clean water practices).

v.) Alcoholic hepatitis
As excessive alcohol consumption can lead to hepatitis and cirrhosis, the following are maximal recommendations for alcohol consumption:

- Women – ≤ 3 drinks on any given day and ≤ 7 drinks per week
- Men – ≤ 4 drinks on any given day and ≤ 14 drinks per week

TREATMENT
Treatment of hepatitis varies based on the form (acute versus chronic), severity of disease, and cause.

■ Hepatitis A
Hepatitis A generally does not progress to a chronic state and rarely requires hospitalization. Treatment is supportive and includes such measures as providing intravenous (IV) hydration and maintaining adequate nutrition.
Rarely, people with the hepatitis A virus can rapidly develop liver failure, termed fulminant hepatic failure, especially the elderly and those who had a pre-existing liver disease, especially hepatitis C. Mortality risk factors include greater age and chronic hepatitis C. In these cases, more aggressive supportive therapy and liver transplant may be necessary.

■ Hepatitis B

i.) Acute
In healthy patients, 95–99% recover with no long-lasting effects, and antiviral treatment is not warranted. Age and comorbid conditions can result in a more prolonged and severe illness. Certain patients warrant hospitalization, especially those who present with clinical signs of ascites, peripheral edema, and hepatic encephalopathy, and laboratory signs of hypoglycemia, prolonged prothrombin time, low serum albumin, and very high serum bilirubin.
In these rare, more severe acute cases, patients have been successfully treated with antiviral therapy similar to that used in cases of chronic hepatitis B, with nucleoside analogues such as entecavir or tenofovir. As there is a dearth of clinical trial data and the drugs used to treat are prone to developing resistance, experts recommend reserving treatment for severe acute cases, not mild to moderate.

ii.) Chronic
Chronic hepatitis B management aims to control viral replication, which is correlated with progression of disease. There have been 7 drug treatments approved to date in the United States:
Injectable interferon alpha was the first therapy approved for chronic hepatitis B. It has several side effects, most of which are reversible with removal of therapy, but it has been supplanted by newer treatments for this indication. These include long-acting interferon bound to polyethylene glycol (pegylated interferon) and the oral nucleoside analogues.

Pegylated interferon (PEG IFN) is dosed just once a week as a subcutaneous injection and is both more convenient and effective than standard interferon. Although it does not develop resistance as do many of the oral antivirals, it is poorly tolerated and requires close monitoring. However, its treatment duration is 48 weeks as opposed to the oral antivirals, which require indefinite treatment for most patients (minimum 1 year). PEG IFN is not effective in patients with high levels of viral activity and cannot be used in immunosuppressed patients or those with cirrhosis.

Lamivudine was the first approved oral nucleoside analogue. While effective and potent, lamivudine has been replaced by newer, more potent treatments in the Western world and is no longer recommended as first-line treatment. However, it is still used in areas where newer agents either have not been approved or are too costly. Generally, the course of treatment is a minimum of one year with a minimum of six additional months of "consolidation therapy." Based on viral response, longer therapy may be required, and certain patients require indefinite long-term therapy. Due to a less robust response in Asian patients, consolidation therapy is recommended to be extended to at least a year. All patients should be monitored for viral reactivation, which, if identified, requires restarting treatment. Lamivudine is generally safe and well-tolerated. Many patients develop resistance, which is correlated with longer treatment duration. If this occurs, an additional antiviral is added. Lamivudine as a single treatment is contraindicated in patients coinfected with HIV, as resistance develops rapidly, but it can be used as part of a multidrug regimen.

Adefovir dipivoxil, a nucleotide analogue, has been used to supplement lamivudine in patients who develop resistance, but is no longer recommended as first-line therapy.

Entecavir is safe, well tolerated, less prone to developing resistance, and the most potent of the existing hepatitis B antivirals; it is thus a first-line treatment choice. It is not recommended for lamivudine-resistant patients or as monotherapy in patients who are HIV positive.

Telbivudine is effective but not recommended as first-line treatment; as compared to entecavir, it is both less potent and more resistance prone.

Tenofovir is a nucleotide analogue and an antiretroviral drug that is also used to treat HIV infection. It is preferred to adefovir both in lamivudine-resistant patients and as initial treatment since it is both more potent and less likely to develop resistance.

First-line treatments currently used include PEG IFN, entecavir, and tenofovir, subject to patient and physician preference. Treatment initiation is guided by recommendations issued by The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) and is based on detectable viral levels, HBeAg positive or negative status, ALT levels, and in certain cases, family history of HCC and liver biopsy. In patients with compensated cirrhosis, treatment is recommended regardless of HBeAg status or ALT level, but recommendations differ regarding HBV DNA levels; AASLD recommends treating at DNA levels detectable above 2x10^5 IU/mL; EASL and WHO recommend treating when HBV DNA levels are detectable at any level. In patients with decompensated cirrhosis, treatment and evaluation for liver transplantation are recommended in all cases if HBV DNA is...
detectable. Currently, multidrug treatment is not recommended in treatment of chronic HBV as it is no more effective in the long term than individual treatment with entecavir or tenofovir.

■ **Hepatitis C**
In contrast to hepatitis A and B, progression to chronic hepatitis C is much more common. The ultimate goal of hepatitis C treatment is prevention of hepatocellular carcinoma (HCC). The best way to reduce the long-term risk of HCC is to achieve sustained virological response (SVR). SVR is defined as an undetectable viral load at 12 weeks after treatment completion and indicates a cure. Currently available treatments include indirect and direct acting antiviral drugs. The indirect acting antivirals include pegylated interferon (PEG IFN) and ribavirin (RBV), which in combination have historically been the basis of therapy for HCV. Duration of and response to these treatments varies based on genotype. These agents are poorly tolerated but are still used in some resource-poor areas. In high-resource countries, they have been supplanted by direct acting antiviral agents, which first appeared in 2011; these agents target proteins responsible for viral replication and include the following three classes:

- NS3/4A protease inhibitors, including telaprevir, boceprevir, simeprevir, and others
- NS5A inhibitors, including ledipasvir, daclatasvir, and others
- NS5B polymerase inhibitors, including sofosbuvir, dasabuvir, and others

These drugs are used in various combinations, sometimes combined with ribavirin, based on the patient's genotype (delineated as genotypes 1-6). Genotype 1 (GT1), which is the most prevalent genotype around the world, can now be cured with a direct acting antiviral regimen. First-line therapy for GT1 is a combination of sofosbuvir and ledipasvir (SOF/LDV) for 12 weeks for most patients, including those with advanced fibrosis or cirrhosis. Certain patients with early disease need only 8 weeks of treatment while those with advanced fibrosis or cirrhosis who have not responded to prior treatment require 24 weeks.

■ **Hepatitis D**
Hepatitis D is difficult to treat, and effective treatments are lacking. Interferon alpha has proven effective at inhibiting viral activity but only on a temporary basis.^[99]

■ **Hepatitis E**
Similar to hepatitis A, treatment of hepatitis E is supportive and includes rest and ensuring adequate nutrition and hydration. Hospitalization may be required for particularly severe cases or for pregnant women.

■ **Alcoholic hepatitis**
First-line treatment of alcoholic hepatitis is treatment of alcoholism. For those who abstain completely from alcohol, reversal of liver disease and a longer life are possible; patients at every disease stage have been shown to benefit by prevention of additional liver injury. In addition to referral to psychotherapy and other treatment programs, treatment should include nutritional and psychosocial evaluation and treatment. Patients should also be treated appropriately for related signs and symptoms, such as ascites, hepatic encephalopathy, and infection. Severe alcoholic hepatitis has a poor prognosis and is notoriously difficult to treat. Without any treatment, 20-50% of patients may die within a month, but evidence shows treatment may extend life beyond one month (i.e., reduce short-term mortality). Available treatment options include pentoxifylline (PTX), which is a nonspecific TNF inhibitor, corticosteroids, such as prednisone or prednisolone (CS), corticosteroids with N-acetylcysteine (CS with NAC), and corticosteroids with pentoxifylline (CS with PTX). Data suggest that CS alone or CS with NAC are most
effective at reducing short-term mortality. Unfortunately, corticosteroids are contraindicated in some patients, such as those who have active gastrointestinal bleeding, infection, kidney failure, or pancreatitis. In these cases PTX may be considered on a case by case basis in lieu of CS; some evidence shows PTX is better than no treatment at all and may be comparable to CS while other data show no evidence of benefit over placebo. Unfortunately, there are currently no drug treatments that decrease these patients’ risk of dying in the longer term, at 3–12 months and beyond.

Weak evidence suggests milk thistle extracts may improve survival in alcoholic liver disease and improve certain liver tests (serum bilirubin and GGT) without causing side effects, but a firm recommendation cannot be made for or against milk thistle without further study.
1. ALCOHOLIC LIVER DISEASE

Alcoholic liver disease is a term that encompasses the liver manifestations of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis. It is the major cause of liver disease in Western countries. Although steatosis (fatty liver) will develop in any individual who consumes a large quantity of alcoholic beverages over a long period of time, this process is transient and reversible. Of all chronic heavy drinkers, only 15–20% develop hepatitis or cirrhosis, which can occur concomitantly or in succession. The mechanism behind this is not completely understood. 80% of alcohol passes through the liver to be detoxified. Chronic consumption of alcohol results in the secretion of pro-inflammatory cytokines (TNF-alpha, Interleukin 6 [IL6] and Interleukin 8 [IL8]), oxidative stress, lipid peroxidation, and acetaldehyde toxicity. These factors cause inflammation, apoptosis and eventually fibrosis of liver cells. Why this occurs in only a few individuals is still unclear. Additionally, the liver has tremendous capacity to regenerate and even when 75% of hepatocytes are dead, it continues to function as normal.

RISK FACTORS

The risk factors presently known are:

- **Quantity of alcohol taken**: Consumption of 60–80g per day (14g is considered one standard drink in the USA, i.e., 1.5 fl oz hard liquor, 5 fl oz wine, 12 fl oz beer; drinking a six-pack of beer daily would be in the middle of the range) for 20 years or more in men, or 20g/day for women significantly increases the risk of hepatitis and fibrosis by 7% to 47%.
- **Pattern of drinking**: Drinking outside of meal times increases up to 3 times the risk of alcoholic liver disease.
- **Sex**: Women are twice as susceptible to alcohol-related liver disease, and may develop alcoholic liver disease with shorter durations and doses of chronic consumption. The lesser amount of alcohol dehydrogenase secreted in the gut, higher proportion of body fat in women, and changes in fat absorption due to the menstrual cycle may explain this phenomenon.
- **Hepatitis C infection**: A concomitant hepatitis C infection significantly accelerates the process of liver injury.
- **Genetic factors**: Genetic factors predispose both to alcoholism and to alcoholic liver disease. Both monozygotic twins are more likely to be alcoholics and to develop liver cirrhosis than both dizygotic twins. Polymorphisms in the enzymes involved in the metabolism of alcohol, such as ADH, ALDH, CYP4502E1, mitochondrial dysfunction, and cytokine polymorphism may partly explain this genetic component. However, no specific polymorphisms have currently been firmly linked to alcoholic liver disease.
- **Iron overload (Hemochromatosis)**
- **Diet**: Malnutrition, particularly vitamin A and E deficiencies, can worsen alcohol-induced liver damage by preventing regeneration of hepatocytes. This is particularly a concern as alcoholics are usually malnourished because of a poor diet, anorexia, and encephalopathy.
**Fatty change**

Fatty change, or steatosis is the accumulation of fatty acids in liver cells. These can be seen as fatty globules under the microscope. Alcoholism causes development of large fatty globules (macrovesicular steatosis) throughout the liver and can begin to occur after a few days of heavy drinking.\(^5\) Alcohol is metabolized by alcohol dehydrogenase (ADH) into acetaldehyde, then further metabolized by aldehyde dehydrogenase (ALDH) into acetic acid, which is finally oxidized into carbon dioxide (CO\(_2\)) and water (H\(_2\)O). This process generates NADH, and increases the NADH/NAD\(^+\) ratio. A higher NADH concentration induces fatty acid synthesis while a decreased NAD level results in decreased fatty acid oxidation. Subsequently, the higher levels of fatty acids signal the liver cells to compound it to glycerol to form triglycerides. These triglycerides accumulate, resulting in fatty liver.

**Alcoholic hepatitis**

Alcoholic hepatitis is characterized by the inflammation of hepatocytes. Between 10% and 35% of heavy drinkers develop alcoholic hepatitis (NIAAA, 1993). While development of hepatitis is not directly related to the dose of alcohol, some people seem more prone to this reaction than...
others. This is called alcoholic steato necrosis and the inflammation appears to predispose to liver fibrosis. Inflammatory cytokines (TNF-alpha, IL6 and IL8) are thought to be essential in the initiation and perpetuation of liver injury by inducing apoptosis and necrosis. One possible mechanism for the increased activity of TNF-α is the increased intestinal permeability due to liver disease. This facilitates the absorption of the gut-produced endotoxin into the portal circulation. The Kupffer cells of the liver then phagocytose endotoxin, stimulating the release of TNF-α. TNF-α then triggers apoptotic pathways through the activation of caspases, resulting in cell death.

■ Cirrhosis
Cirrhosis is a late stage of serious liver disease marked by inflammation (swelling), fibrosis (cellular hardening) and damaged membranes preventing detoxification of chemicals in the body, ending in scarring and necrosis (cell death). Between 10% to 20% of heavy drinkers will develop cirrhosis of the liver. Acetaldehyde may be responsible for alcohol-induced fibrosis by stimulating collagen deposition by hepatic stellate cells. The production of oxidants derived from NADPH oxi- dase and/or cytochrome P-450 2E1 and the formation of acetaldehyde-protein adducts damage the cell membrane. Symptoms include jaundice (yellowing), liver enlargement, and pain and tenderness from the structural changes in damaged liver architecture. Without total abstinence from alcohol use, cirrhosis will eventually lead to liver failure. Late complications of cirrhosis or liver failure include portal hypertension (high blood pressure in the portal vein due to the increased flow resistance through the damaged liver), coagulation disorders (due to impaired production of coagulation factors), ascites (heavy abdominal swelling due to buildup of fluids in the tissues) and other complications, including hepatic encephalopathy and the hepatorenal syndrome. Cirrhosis can also result from other causes than alcohol abuse, such as viral hepatitis and heavy exposure to toxins other than alcohol. The late stages of cirrhosis may look similar medically, regardless of cause. This phenomenon is termed the "final common pathway" for the disease. Fatty change and alcoholic hepatitis with abstinence can be reversible. The later stages of fibrosis and cirrhosis tend to be irreversible, but can usually be contained with abstinence for long periods of time.

DIAGNOSIS
In the early stages, patients with ALD exhibits subtle and often no abnormal physical findings. It is usually not until development of advanced liver disease that stigmata of chronic liver disease become apparent. Early ALD is usually discovered during routine health examinations when liver enzyme levels are found to be elevated. These usually reflect alcoholic hepatic steatosis. Microvesicular and macrovesicular steatosis with inflammation are seen in liver biopsy specimens. These histologic features of ALD are indistinguishable from those of nonalcoholic fatty liver disease. Steatosis usually resolves after discontinuation of alcohol use. Continuation of alcohol use will result in a higher risk of progression of liver disease and cirrhosis. In patients with acute alcoholic hepatitis, clinical manifestations include fever, jaundice, hepatomegaly, and possible hepatic decompensation with hepatic encephalopathy, variceal bleeding, and ascites accumulation. Tender hepatomegaly may be present, but abdominal pain is unusual. Occasionally, the patient may be asymptomatic.

■ Laboratory findings
In people with alcoholic hepatitis, the serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio is greater than 2:1. AST and ALT levels are almost always less than 500. The elevated AST to ALT ratio is due to deficiency of pyridoxal-6-phosphate, which is
required in the ALT enzyme synthetic pathway. Furthermore, alcohol metabolite-induced injury of hepatic mitochondria results in AST isoenzyme release. Other laboratory findings include red blood cell macrocytosis (mean corpuscular volume > 100) and elevations of serum \( \gamma \)-glutamyl transferase, alkaline phosphatase, and bilirubin levels. Folate level is reduced in alcoholic patients due to decreased intestinal absorption, increased bone marrow requirement for folate in the presence of alcohol, and increased urinary loss. The magnitude of leukocytosis reflects severity of liver injury. Histologic features include Mallory bodies, giant mitochondria, hepatocyte necrosis, and neutrophil infiltration at the perivenular area. Mallory bodies, which are also present in other liver diseases, are condensations of cytokeratin components in the hepatocyte cytoplasm and do not contribute to liver injury. Up to 70% of patients with moderate to severe alcoholic hepatitis already have cirrhosis identifiable on biopsy examination at the time of diagnosis.

**TREATMENT**

Not drinking further alcohol is the most important part of treatment. People with chronic HCV infection should abstain from any alcohol intake, due to the risk for rapid acceleration of liver disease.

■ **Medications**

Corticosteroids are sometimes used; however, this is recommended only when severe liver inflammation is present. Sylimarin has been investigated as a possible treatment, with ambiguous results. One review claimed benefit for S-adenosyl methionine in disease models. The effects of anti-tumor necrosis factor medications such as infliximab and etanercept are unclear and possibly harmful. Evidence is unclear for pentoxifylline. Propylthiouracil may result in harm. Evidence does not support supplemental nutrition in liver disease.

■ **Transplantation**

Although in rare cases liver cirrhosis is reversible, the disease process remains mostly irreversible. Liver transplantation remains the only definitive therapy.
Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body. The disease may also affect other parts of the body. This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart. Fever and low energy may also be present. Often, symptoms come on gradually over weeks to months.

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage. The diagnosis is made mostly on the basis of a person's signs and symptoms. X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, fibromyalgia among others.

The goals of treatment are to reduce pain, decrease inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. Disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine and methotrexate, may be used to try to slow the progression of disease. Biological DMARDs may be used when disease does not respond to other treatments. However, they may have a greater rate of adverse effects. Surgery to repair, replace,
or fuse joints may help in certain situations. Most alternative medicine treatments are not supported by evidence.

**SIGNS AND SYMPTOMS**

RA primarily affects joints, but it also affects other organs in more than 15–25% of cases. Associated problems include cardiovascular disease, osteoporosis, interstitial lung disease, infection, cancer, feeling tired, depression, mental difficulties, and trouble working.

### Joints

Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender and warm, and stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are the small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.

RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking or following prolonged inactivity. Increased stiffness early in the morning is often a prominent feature of the disease and typically lasts for more than an hour. Gentle movements may relieve symptoms in early stages of the disease. These signs help distinguish rheumatoid from non-inflammatory problems of the joints, such as osteoarthritis. In arthritis of non-inflammatory causes, signs of inflammation and early morning stiffness are less prominent. The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic. The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical.

As the pathology progresses the inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in osteoarthritis, include ulnar deviation, boutonniere deformity (also "buttonhole deformity", flexion of proximal interphalangeal joint and extension of distal interphalangeal joint of the hand), swan neck deformity (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal joint) and "Z-thumb." "Z-thumb" or "Z-deformity" consists of hyperextension of the interphalangeal joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives a "Z" appearance to the thumb. The hammer toe deformity may be seen. In the worst case, joints are known as arthritis mutilans due to the mutilating nature of the deformities.

### Skin

The rheumatoid nodule, which is sometimes in the skin, is the most common non-joint feature and occurs in 30% of people who have RA. It is a type of inflammatory reaction known to pathologists as a "necrotizing granuloma". The initial pathologic process in nodule formation is unknown but may be essentially the same as the synovitis, since similar structural features occur in both. The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space. Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the subintimal zone in synovitis. The typical rheumatoid nodule may be a few millimetres to a few centimetres in diameter and is usually
found over bony prominences, such as the elbow, the heel, the knuckles, or other areas that sustain repeated mechanical stress. Nodules are associated with a positive RF (rheumatoid factor) titer, ACPA, and severe erosive arthritis. Rarely, these can occur in internal organs or at diverse sites on the body.

Several forms of vasculitis occur in RA, but are mostly seen with long-standing and untreated disease. The most common presentation is due to involvement of small- and medium-sized vessels. Rheumatoid vasculitis can thus commonly present with skin ulceration and vasculitic nerve infarction known as mononeuritis multiplex.

Other, rather rare, skin associated symptoms include pyoderma gangrenosum, Sweet's syndrome, drug reactions, erythema nodosum, lobe panniculitis, atrophy of finger skin, palmar erythema, and skin fragility (often worsened by corticosteroid use).

Diffuse alopecia areata (Diffuse AA) occurs more commonly in people with rheumatoid arthritis. RA is also seen more often in those with relatives who have AA.

■ Lungs

Lung fibrosis is a recognized complication of rheumatoid arthritis. It is also a rare but well-recognized consequence of therapy (for example with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust. Exudative pleural effusions are also associated with RA.

■ Heart and blood vessels

People with RA are more prone to atherosclerosis, and risk of myocardial infarction (heart attack) and stroke is markedly increased. Other possible complications that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis. Many people with RA do not experience the same chest pain that others feel when they have angina or myocardial infarction. To reduce cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA (which may be involved in causing the cardiovascular risk), and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure. Doctors who treat people with RA should be sensitive to cardiovascular risk when prescribing anti-inflammatory medications, and may want to consider prescribing routine use of low doses of aspirin if the gastrointestinal effects are tolerable.

■ Blood

Anemia is by far the most common abnormality of the blood cells which can be caused by a variety of mechanisms. The chronic inflammation caused by RA leads to raised hepcidin levels, leading to anemia of chronic disease where iron is poorly absorbed and also sequestered into macrophages. The red cells are of normal size and color (normocytic and normochromic). A low white blood cell count usually only occurs in people with Felty's syndrome with an enlarged liver and spleen. The mechanism of neutropenia is complex. An increased platelet count occurs when inflammation is uncontrolled.

■ Other

   i.) Kidneys

Renal amyloidosis can occur as a consequence of untreated chronic inflammation. Treatment with penicillamine and gold salts are recognized causes of membranous nephropathy.
ii.) Eyes
The eye can be directly affected in the form of episcleritis or scleritis, which when severe can very rarely progress to perforating scleromalacia. Rather more common is the indirect effect of keratoconjunctivitis sicca, which is a dryness of eyes and mouth caused by lymphocyte infiltration of lacrimal and salivary glands. When severe, dryness of the cornea can lead to keratitis and loss of vision as well as being painful. Preventive treatment of severe dryness with measures such as nasolacrimal duct blockage is important.

iii.) Liver
Liver problems in people with rheumatoid arthritis may be due to the underlying disease process or as a result of the medications used to treat the disease. A coexisting autoimmune liver disease, such as primary biliary cirrhosis or autoimmune hepatitis may also cause problems.

■ Neurological
Peripheral neuropathy and mononeuritis multiplex may occur. The most common problem is carpal tunnel syndrome caused by compression of the median nerve by swelling around the wrist. Rheumatoid disease of the spine can lead to myelopathy. Atlanto-axial subluxation can occur, owing to erosion of the odontoid process and/or transverse ligaments in the cervical spine's connection to the skull. Such an erosion (>3mm) can give rise to vertebrae slipping over one another and compressing the spinal cord. Clumsiness is initially experienced, but without due care, this can progress to quadriplegia or even death.

■ Constitutional symptoms
Constitutional symptoms including fatigue, low grade fever, malaise, morning stiffness, loss of appetite and loss of weight are common systemic manifestations seen in people with active RA.

■ Bones
Local osteoporosis occurs in RA around inflamed joints. It is postulated to be partially caused by inflammatory cytokines. More general osteoporosis is probably contributed to by immobility, systemic cytokine effects, local cytokine release in bone marrow and corticosteroid therapy.

■ Cancer
The incidence of lymphoma is increased, although it is uncommon and associated with the chronic inflammation, not the treatment of RA. The risk of non-melanoma skin cancer is increased in people with RA compared to the general population, an association possibly due to the use of immunosuppression agents for treating RA.

■ Teeth
Periodontitis and tooth loss are common in people with rheumatoid arthritis.

RISK FACTORS
RA is a systemic (whole body) autoimmune disease. Some genetic and environmental factors affect the risk for RA.

■ Genetic
A family history of RA increases the risk around three to five times; as of 2016 it was estimated that genetics may account for between 40 and 65% of cases of seropositive RA, but only around
20% for seronegative RA. RA is strongly associated with genes of the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DR4 is the major genetic factor implicated – the relative importance varies across ethnic groups. Genome-wide association studies examining single-nucleotide polymorphisms have found around one hundred genes associated with RA risk, with most of them involving the HLA system (particularly HLA-DRB1) which controls recognition of self versus nonself molecules; other mutations affecting co-stimulatory immune pathways, for example CD28 and CD40, cytokine signaling, lymphocyte receptor activation threshold (e.g., PTPN22), and innate immune activation appear to have less influence than HLA mutations.

■ Environmental

There are established epigenetic and environmental risk factors for RA. Smoking is an established risk factor for RA in Caucasian populations, increasing the risk three times compared to non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive. Modest alcohol consumption may be protective. Silica exposure has been linked to RA.

■ Negative findings

No infectious agent has been consistently linked with RA and there is no evidence of disease clustering to indicate its infectious cause, but periodontal disease has been consistently associated with RA.

The many negative findings suggest that either the trigger varies, or that it might, in fact, be a chance event inherent with the immune response.

PATHOPHYSIOLOGY

RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in joints and other organs where it manifests. The initial site of disease is the synovial membrane, where swelling and congestion lead to infiltration by immune cells. Three phases of progression of RA are an initiation phase (due to non-specific inflammation), an amplification phase (due to T cell activation), and chronic inflammatory phase, with tissue injury resulting from the cytokines, IL-1, TNF-alpha and IL-6.

■ Non-specific inflammation

Factors allowing an abnormal immune response, once initiated, become permanent and chronic. These factors are genetic disorders which change regulation of the adaptive immune response. Genetic factors interact with environmental risk factors for RA, with cigarette smoking as the most clearly defined risk factor.

Other environmental and hormonal factors may explain higher risks for women, including onset after childbirth and hormonal medications. A possibility for increased susceptibility is that negative feedback mechanisms – which normally maintain tolerance – are overtaken by positive feedback mechanisms for certain antigens, such as IgG Fc bound by rheumatoid factor and citrullinated fibrinogen bound by antibodies to citrullinated peptides (ACP A - Anti–citrullinated protein antibody). A debate on the relative roles of B-cell produced immune complexes and T cell products in inflammation in RA has continued for 30 years, but neither cell is necessary at the site of inflammation, only autoantibodies to IgGFc, known as rheumatoid factors and ACPA, with ACPA having an 80% specificity for diagnosing RA. As with other autoimmune diseases,
people with RA have abnormally glycosylated antibodies, which are believed to promote joint inflammation.

**Amplification in the synovium**

Once the generalized abnormal immune response has become established – which may take several years before any symptoms occur – plasma cells derived from B lymphocytes produce rheumatoid factors and ACPA of the IgG and IgM classes in large quantities. These activate macrophages through Fc receptor and complement binding, which is part of the intense inflammation in RA. Binding of an autoreactive antibody to the Fc receptors is mediated through the antibody's N-glycans, which are altered to promote inflammation in people with RA. This contributes to local inflammation in a joint, specifically the synovium with edema, vasodilation and entry of activated T-cells, mainly CD4 in microscopically nodular aggregates and CD8 in microscopically diffuse infiltrates. Synovial macrophages and dendritic cells function as antigen-presenting cells by expressing MHC class II molecules, which establishes the immune reaction in the tissue.

**Chronic inflammation**

The disease progresses by forming granulation tissue at the edges of the synovial lining, pannus with extensive angiogenesis and enzymes causing tissue damage. The synovium thickens, cartilage and underlying bone disintegrate, and the joint deteriorates, with raised calprotectin levels serving as a biomarker of these events. Cytokines and chemokines attract and accumulate immune cells, i.e. activated T- and B cells, monocytes and macrophages from activated fibroblasts, in the joint space. By signalling through RANKL and RANK, they eventually trigger osteoclast production, which degrades bone tissue. Tumor necrosis factor alpha (TNF-α) plays a major role and several theories exist on how TNF release happens in RA. TNF-α is a proinflammatory cytokine that plays a pivotal role in regulating the inflammatory response in rheumatoid arthritis (RA). If TNF release is stimulated by B cell products in the form of RF or ACPA-containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity. As of 1999, if TNF release is stimulated by T cell products such as interleukin-17 it might be closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful. Although TNF appears to be the dominant chemical mediator other cytokines are involved in inflammation in RA, because blocking TNF does not benefit all persons and all tissues, particularly lung disease and nodules may get worse. Blocking IL-1, IL-15 and IL-6 have beneficial effects and IL-17 may be important.

**DIAGNOSIS**

**Imaging**

X-rays of the hands and feet are generally performed when many joints affected. In RA, there may be no changes in the early stages of the disease or the x-ray may show osteopenia near the joint, soft tissue swelling, and a smaller than normal joint space. As the disease advances, there may be bony erosions and subluxation. Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA.
This is important, since in the early stages of RA, the synovium is primarily affected, and synovitis seems to be the best predictive marker of future joint damage.

**Blood tests**
When RA is clinically suspected, a physician may test for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs measured as anti-CCP antibodies). It is positive in 75-85%, but a negative RF or CCP antibody does not rule out RA, rather, the arthritis is called *seronegative*, which is in about 15-25% of people with RA. During the first year of illness, rheumatoid factor is more likely to be negative with some individuals becoming seropositive over time. RF is a non-specific antibody and seen in about 10% of healthy people, in many other chronic infections like hepatitis C, and chronic autoimmune diseases such as Sjögren's syndrome and systemic lupus erythematosus. Therefore, the test is not specific for RA.

Other blood tests are usually done to differentiate from other causes of arthritis, like the erythrocyte sedimentation rate (ESR), C-reactive protein, full blood count, kidney function, liver enzymes and other immunological tests (e.g., antinuclear antibody/ANA) are all performed at this stage. Elevated ferritin levels can reveal hemochromatosis, a mimic of RA, or be a sign of Still's disease, a seronegative, usually juvenile, variant of rheumatoid arthritis.

**CLASSIFICATION CRITERIA**

- **joint involvement**, designating the metacarpophalangeal joints, proximal interphalangeal joints, the interphalangeal joint of the thumb, second through fifth metatarsophalangeal joint and wrist as *small joints*, and shoulders, elbows, hip joints, knees, and ankles as *large joints*:
  - Involvement of 1 large joint gives 0 points
  - Involvement of 2–10 large joints gives 1 point
  - Involvement of 1–3 small joints (with or without involvement of large joints) gives 2 points
  - Involvement of 4–10 small joints (with or without involvement of large joints) gives 3 points
  - Involvement of more than 10 joints (with involvement of at least 1 small joint) gives 5 points
- **serological parameters** – including the rheumatoid factor as well as ACPA – "ACPA" stands for "anti-citrullinated protein antibody":
  - Negative RF and negative ACPA gives 0 points
  - Low-positive RF or low-positive ACPA gives 2 points
  - High-positive RF or high-positive ACPA gives 3 points
- **acute phase reactants**: 1 point for elevated erythrocyte sedimentation rate, ESR, or elevated CRP value (c-reactive protein)
- **duration of arthritis**: 1 point for symptoms lasting six weeks or longer

**DIFFERENTIAL DIAGNOSES**

*Synovial fluid examination*
Several other medical conditions can resemble RA, and need to be distinguished from it at the time of diagnosis:

- **Crystal induced arthritis (gout, and pseudogout)** – usually involves particular joints (knee, MTP1, heels) and can be distinguished with an aspiration of joint fluid if in doubt. Redness, asymmetric distribution of affected joints, pain occurs at night and the starting pain is less than an hour with gout.

- **Osteoarthritis** – distinguished with X-rays of the affected joints and blood tests, older age, starting pain less than an hour, asymmetric distribution of affected joints and pain worsens when using joint for longer periods.

- **Systemic lupus erythematosus (SLE)** – distinguished by specific clinical symptoms and blood tests (antibodies against double-stranded DNA)

- One of the several types of **psoriatic arthritis resembles RA** – nail changes and skin symptoms distinguish between them

- **Lyme disease causes erosive arthritis** and may closely resemble RA – it may be distinguished by blood test in endemic areas

- **Reactive arthritis** – asymmetrically involves heel, sacroiliac joints and large joints of the leg. It is usually associated with urethritis, conjunctivitis, iritis, painless buccal ulcers, and keratoderma blennorrhagica.

- **Axial spondyloarthritis (including ankylosing spondylitis)** – this involves the spine, although an RA-like symmetrical small-joint polyarthritis may occur in the context of this condition.

- **Hepatitis C** – RA-like symmetrical small-joint polyarthritis may occur in the context of this condition. Hepatitis C may also induce rheumatoid factor auto-antibodies.

Rarer causes which usually behave differently but may cause joint pains:

- Sarcoidosis, amyloidosis, and Whipple's disease can also resemble RA.
- Hemochromatosis may cause hand joint arthritis.
- Acute rheumatic fever can be differentiated by a migratory pattern of joint involvement and evidence of antecedent streptococcal infection.
• Bacterial arthritis (such as by Streptococcus) is usually asymmetric, while RA usually involves both sides of the body symmetrically.
• Gonococcal arthritis (a bacterial arthritis) is also initially migratory and can involve tendons around the wrists and ankles.

PREVENTION
There is no known prevention for the condition other than the reduction of risk factors.

MANAGEMENT
There is no cure for RA, but treatments can improve symptoms and slow the progress of the disease. Disease-modifying treatment has the best results when it is started early and aggressively.

The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity (for example, bone erosions visible in X-rays), and to maintain day-to-day functioning. This is primarily addressed with disease-modifying antirheumatic drugs (DMARDs); dosed physical activity; analgesics and physical therapy may be used to help manage pain. RA should generally be treated with at least one specific anti-rheumatic medication. The use of benzodiazepines (such as diazepam) to treat the pain is not recommended as it does not appear to help and is associated with risks.

■ Lifestyle
Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function.
Occupational therapy has a positive role to play in improving functional ability in people with rheumatoid arthritis. Weak evidence supports the use of wax baths (thermotherapy) to treat arthritis in the hands.

■ Disease modifying agents
Disease-modifying antirheumatic drugs (DMARDs) are the primary treatment for RA. They have been found to improve symptoms, decrease joint damage, and improve overall functional abilities.
The following drugs are considered as DMARDs: methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, TNF-alpha inhibitors (certolizumab, infliximab and etanercept), abatacept, and anakinra. Rituximab and tocilizumab are monoclonal antibodies and are also DMARDs. Use of tocilizumab is associated with a risk of increased cholesterol levels. Hydroxychloroquine, apart from its low toxicity profile, is considered effective in the moderate RA treatment. The most commonly used agent is methotrexate with other frequently used agents including sulfasalazine and leflunomide.

■ Anti-inflammatory and analgesic agents
Glucocorticoids can be used in the short term. Non-NSAID drugs to relieve pain, like paracetamol may be used to help relieve the pain symptoms; they do not change the underlying disease.
NSAIDs reduce both pain and stiffness in those with RA but do not affect the underlying disease and appear to have no effect on people's long term disease course and thus are no longer first line agents. Use of methotrexate together with NSAIDs is safe, if adequate monitoring is done. COX-2 inhibitors, such as celecoxib, and NSAIDs are equally effective.

- **Surgery**
  Especially for affected fingers, hands, and wrists, synovectomy may be needed to prevent pain or tendon rupture when drug treatment has failed. Severely affected joints may require joint replacement surgery, such as knee replacement.

- **Physiotherapy**
  For people with RA, physiotherapy may be used together with medical management. This may include cold and heat application, electronic stimulation, and hydrotherapy.

- **Alternative medicine**
  Some mind and body practices and dietary supplements may help people with symptoms and therefore may be beneficial additions to conventional treatments

- **Dietary supplements**
  i) **Fatty acids**
  Gamma-linolenic acid, an omega-6 fatty acid, may reduce pain, tender joint count and stiffness, and is generally safe.
1. OSTEOPOROSIS

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INTRODUCTION

Osteoporosis is a disease where increased bone weakness increases the risk of a broken bone. It is the most common reason for a broken bone among the elderly. Bones that commonly break include the vertebrae in the spine, the bones of the forearm, and the hip. Until a broken bone occurs there are typically no symptoms. Bones may weaken to such a degree that a break may occur with minor stress or spontaneously. Chronic pain and a decreased ability to carry out normal activities may occur following a broken bone.

Osteoporosis may be due to lower than normal bone mass and greater than normal bone loss. Bone loss increases after menopause due to lower levels of estrogen. Osteoporosis may also occur due to a number of diseases or treatments including alcoholism, anorexia, hyperthyroidism, kidney disease, and surgical removal of the ovaries. Certain medications increase the rate of bone loss including some antiseizure medications, chemotherapy, proton pump inhibitors, selective serotonin reuptake inhibitors, and glucocorticosteroids. Not enough exercise and smoking are also risk factors. Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult. This is typically measured by dual-energy X-ray absorptiometry at the hip.

Prevention of osteoporosis includes a proper diet during childhood and efforts to avoid medications that cause the condition. Efforts to prevent broken bones in those with osteoporosis include a good diet, exercise, and fall prevention. Lifestyle changes such as stopping smoking and not drinking alcohol may help. Bisphosphonate medications are useful in those with previous broken bones due to osteoporosis. In those with osteoporosis but no previous broken bones they are less effective. A number of other medications may also be useful.

SIGNS AND SYMPTOMS

Osteoporosis itself has no symptoms; its main consequence is the increased risk of bone fractures. Osteoporotic fractures occur in situations where healthy people would not normally break a bone; they are therefore regarded as fragility fractures. Typical fragility fractures occur in the vertebral column, rib, hip and wrist.
Osteoporosis is an age-related disorder that causes the gradual loss of bone density and strength. When the thoracic vertebrae are affected, there can be a gradual collapse of the vertebrae. This results in kyphosis, an excessive curvature of the thoracic region.

**Figure:** Illustration depicting normal standing posture and osteoporosis
■ Fractures
Fractures are the most dangerous aspect of osteoporosis. Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis and can lead to further disability and early mortality.16e These fractures may also be asymptomatic. The most common osteoporotic fractures are of the wrist, spine, shoulder and hip. The symptoms of a vertebral collapse ("compression fracture") are sudden back pain, often with radicular pain (shooting pain due to nerve root compression) and rarely with spinal cord compression or cauda equina syndrome. Multiple vertebral fractures lead to a stooped posture, loss of height, and chronic pain with resultant reduction in mobility.
Fractures of the long bones acutely impair mobility and may require surgery. Hip fracture, in particular, usually requires prompt surgery, as serious risks are associated with it, such as deep vein thrombosis and pulmonary embolism, and increased mortality. Osteoporosis is a part of frailty syndrome.

■ Falls risk
The increased risk of falling associated with aging leads to fractures of the wrist, spine, and hip. The risk of falling, in turn, is increased by impaired eyesight due to any cause (e.g. glaucoma, macular degeneration), balance disorder, movement disorders (e.g. Parkinson's disease), dementia, and sarcopenia (age-related loss of skeletal muscle). Collapse (transient loss of postural tone with or without loss of consciousness) leads to a significant risk of falls; causes of syncope are manifold, but may include cardiac arrhythmias (irregular heart beat), vasovagal syncope, orthostatic hypotension (abnormal drop in blood pressure on standing up), and seizures.

■ Risk factors
Risk factors for osteoporotic fracture can be split between nonmodifiable and (potentially) modifiable. In addition, osteoporosis is a recognized complication of specific diseases and disorders. Medication use is theoretically modifiable, although in many cases, the use of medication that increases osteoporosis risk may be unavoidable. Caffeine is not a risk factor for osteoporosis.

■ Nonmodifiable
- The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; estrogen deficiency following menopause or surgical removal of the ovaries is correlated with a rapid reduction in bone mineral density, while in men, a decrease in testosterone levels has a comparable (but less pronounced) effect.
- Race: While osteoporosis occurs in people from all ethnic groups, European or Asian ancestry predisposes for osteoporosis.
- Heredity: Those with a family history of fracture or osteoporosis are at an increased risk; the heritability of the fracture, as well as low bone mineral density, is relatively high, ranging from 25 to 80%. At least 30 genes are associated with the development of osteoporosis.
- Those who have already had a fracture are at least twice as likely to have another fracture compared to someone of the same age and sex. Early menopause/hysterectomy is another predisposing factor.
Build: A small stature is also a nonmodifiable risk factor associated with the development of osteoporosis.

Potential modifiable

- **Excess consumption of alcohol:** Although small amounts of alcohol are probably beneficial (bone density increases with increasing alcohol intake), chronic heavy drinking (alcohol intake greater than three units/day) probably increases fracture risk despite any beneficial effects on bone density.

- **Vitamin D deficiency:** Low circulating Vitamin D is common among the elderly worldwide. Mild vitamin D insufficiency is associated with increased parathyroid hormone (PTH) production. PTH increases bone resorption, leading to bone loss. A positive association exists between serum 1,25-dihydroxycholecalciferol levels and bone mineral density, while PTH is negatively associated with bone mineral density.

- **Tobacco smoking:** Many studies have associated smoking with decreased bone health, but the mechanisms are unclear. Tobacco smoking has been proposed to inhibit the activity of osteoblasts, and is an independent risk factor for osteoporosis. Smoking also results in increased breakdown of exogenous estrogen, lower body weight and earlier menopause, all of which contribute to lower bone mineral density.

- **Malnutrition:** Nutrition has an important and complex role in maintenance of good bone. Identified risk factors include low dietary calcium and/or phosphorus, magnesium, zinc, boron, iron, fluoride, copper, vitamins A, K, E and C (and D where skin exposure to sunlight provides an inadequate supply). Excess sodium is a risk factor. High blood acidity may be diet-related, and is a known antagonist of bone. Some have identified low protein intake as associated with lower peak bone mass during adolescence and lower bone mineral density in elderly populations. Conversely, some have identified low protein intake as a positive factor, protein is among the causes of dietary acidity. Imbalance of omega-6 to omega-3 polyunsaturated fats is yet another identified risk factor.

- **High dietary protein from animal sources:** Research has found an association between diets high in animal protein and increased urinary calcium, and have been linked to an increase in fractures. However, the relevance of this observation to bone density is unclear, since higher protein diets tend to increase absorption of calcium from the diet and are associated with higher bone density. Indeed, it has recently been argued that low protein diets cause poor bone health. No interventional trials have been performed on dietary protein in the prevention and treatment of osteoporosis.

- **Underweight/inactive:** Bone remodeling occurs in response to physical stress, so physical inactivity can lead to significant bone loss. Weight bearing exercise can increase peak bone mass achieved in adolescence, and a highly significant correlation between bone strength and muscle strength has been determined. The incidence of osteoporosis is lower in overweight people.

- **Endurance training:** In female endurance athletes, large volumes of training can lead to decreased bone density and an increased risk of osteoporosis. This effect might be caused by intense training suppressing menstruation, producing amenorrhea, and it is part of the female athlete triad. However, for male athletes, the situation is less clear, and although some studies have reported low bone density in elite male endurance athletes, others have instead seen increased leg bone density.
Heavy metals: A strong association between cadmium and lead with bone disease has been established. Low-level exposure to cadmium is associated with an increased loss of bone mineral density readily in both genders, leading to pain and increased risk of fractures, especially in the elderly and in females. Higher cadmium exposure results in osteomalacia (softening of the bone).

Soft drinks: Some studies indicate soft drinks (many of which contain phosphoric acid) may increase risk of osteoporosis, at least in women. Others suggest soft drinks may displace calcium-containing drinks from the diet rather than directly causing osteoporosis.

Proton pump inhibitors (such as lansoprazole, esomeprazole, or omeprazole) that decrease stomach acid, are a risk for bone fractures if taken for two or more years, due to decreased absorption of calcium in the stomach.

Medical disorders

Many diseases and disorders have been associated with osteoporosis. For some, the underlying mechanism influencing the bone metabolism is straightforward, whereas for others the causes are multiple or unknown.

Figure: The body regulates calcium homeostasis with two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated.
In general, immobilization causes bone loss (following the 'use it or lose it' rule). For example, localized osteoporosis can occur after prolonged immobilization of a fractured limb in a cast. This is also more common in active people with a high bone turn-over (for example, athletes). Other examples include bone loss during space flight or in people who are bedridden or use wheelchairs for various reasons.

Hypogonadal states can cause secondary osteoporosis. These include Turner syndrome, Klinefelter syndrome, Kallmann syndrome, anorexia nervosa, andropause,[55] hypothalamic amenorrhea or hyperprolactinemia. In females, the effect of hypogonadism is mediated by estrogen deficiency. It can appear as early menopause (<45 years) or from prolonged premenopausal amenorrhea (>1 year). Bilateral oophorectomy (surgical removal of the ovaries) and premature ovarian failure cause deficient estrogen production. In males, testosterone deficiency is the cause (for example, andropause or after surgical removal of the testes).

Endocrine disorders that can induce bone loss include Cushing's syndrome, hyperparathyroidism, hyperthyroidism, hypothyroidism, diabetes mellitus type 1 and 2, acromegaly, and adrenal insufficiency.

Malnutrition, parenteral nutrition and malabsorption can lead to osteoporosis. Nutritional and gastrointestinal disorders that can predispose to osteoporosis include undiagnosed and untreated coeliac disease (both symptomatic and asymptomatic people), Crohn's disease, ulcerative colitis, cystic fibrosis, surgery (after gastrectomy, intestinal bypass surgery or bowel resection) and severe liver disease (especially primary biliary cirrhosis). People with lactose intolerance or milk allergy may develop osteoporosis due to restrictions of calcium-containing foods. Individuals with bulimia can also develop osteoporosis. Those with an otherwise adequate calcium intake can develop osteoporosis due to the inability to absorb calcium and/or vitamin D. Other micronutrients such as vitamin K or vitamin B₁₂ deficiency may also contribute.

People with rheumatologic disorders such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus and polyarticular juvenile idiopathic arthritis are at increased risk of osteoporosis, either as part of their disease or because of other risk factors (notably corticosteroid therapy). Systemic diseases such as amyloidosis and sarcoidosis can also lead to osteoporosis.

Renal insufficiency can lead to renal osteodystrophy.

Hematologic disorders linked to osteoporosis are multiple myeloma and other monoclonal gammopathies, lymphoma, leukemia, mastocytosis, hemophilia, sickle-cell disease and thalassemia.

Several inherited disorders have been linked to osteoporosis. These include osteogenesis imperfecta, Marfan syndrome, hemochromatosis, hypophosphatasia (for which it is often misdiagnosed), glycogen storage diseases, homocystinuria, Ehlers–Danlos syndrome, porphyria, Menkes' syndrome, epidermolysis bullosa and Gaucher's disease.

People with scoliosis of unknown cause also have a higher risk of osteoporosis. Bone loss can be a feature of complex regional pain syndrome. It is also more frequent in people with Parkinson's disease and chronic obstructive pulmonary disease.

People with Parkinson's disease have a higher risk of broken bones. This is related to poor balance and poor bone density. In Parkinson’s disease there may be a link between the loss of dopaminergic neurons and altered calcium metabolism (and iron metabolism) causing a stiffening of the skeleton and kyphosis.
Medication

Certain medications have been associated with an increase in osteoporosis risk; only glucocorticosteroids and anticonvulsants are classically associated, but evidence is emerging with regard to other drugs.

- Steroid-induced osteoporosis (SIOP) arises due to use of glucocorticoids – analogous to Cushing’s syndrome and involving mainly the axial skeleton. The synthetic glucocorticoid prescription drug prednisone is a main candidate after prolonged intake. Some professional guidelines recommend prophylaxis in patients who take the equivalent of more than 30 mg hydrocortisone (7.5 mg of prednisolone), especially when this is in excess of three months. Alternate day use may not prevent this complication.
- Barbiturates, phenytoin and some other enzyme-inducing antiepileptics – these probably accelerate the metabolism of vitamin D.
- L-Thyroxine over-replacement may contribute to osteoporosis, in a similar fashion as thyrotoxicosis does. This can be relevant in subclinical hypothyroidism.
- Several drugs induce hypogonadism, for example aromatase inhibitors used in breast cancer, methotrexate and other antimitabolite drugs, depot progesterone and gonadotropin-releasing hormone agonists.
- Anticoagulants – long-term use of heparin is associated with a decrease in bone density,[67] and warfarin (and related coumarins) have been linked with an increased risk in osteoporotic fracture in long-term use.
- Proton pump inhibitors – these drugs inhibit the production of stomach acid; this is thought to interfere with calcium absorption. Chronic phosphate binding may also occur with aluminium-containing antacids.
- Thiazolidinediones (used for diabetes) – rosiglitazone and possibly pioglitazone, inhibitors of PPARγ, have been linked with an increased risk of osteoporosis and fracture.

Chronic lithium therapy has been associated with osteoporosis.

Evolutionary

Age-related bone loss is common among humans due to exhibiting less dense bones than other primate species.[71] Because of the more porous bones of humans, frequency of severe osteoporosis and osteoporosis related fractures is higher.

PATHOGENESIS

The underlying mechanism in all cases of osteoporosis is an imbalance between bone resorption and bone formation. In normal bone, matrix remodeling of bone is constant; up to 10% of all bone mass may be undergoing remodeling at any point in time. The process takes place in bone multicellular units (BMUs). Osteoclasts are assisted by transcription factor PU.1 to degrade the bone matrix, while osteoblasts rebuild the bone matrix. Low bone mass density can then occur when osteoclasts are degrading the bone matrix faster than the osteoblasts are rebuilding the bone.
The three main mechanisms by which osteoporosis develops are an inadequate peak bone mass (the skeleton develops insufficient mass and strength during growth), excessive bone resorption, and inadequate formation of new bone during remodeling, likely due to MSC biasing away from the osteoblast and toward the marrow adipocyte lineage. An interplay of these three mechanisms underlies the development of fragile bone tissue. Hormonal factors strongly determine the rate of bone resorption; lack of estrogen (e.g., as a result of menopause) increases bone resorption, as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. The amount of estrogen needed to suppress this process is lower than that normally needed to stimulate the uterus and breast gland. The $\alpha$-form of the estrogen receptor appears to be the most important in regulating bone turnover. In addition to estrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (parathormone, PTH), which increases bone resorption to ensure sufficient calcium in the blood. The role of calcitonin, a hormone generated by the thyroid that increases bone deposition, is less clear and probably not as significant as that of PTH. The activation of osteoclasts is regulated by various molecular signals, of which RANKL (receptor activator of nuclear factor kappa-B ligand) is one of the best studied. This molecule is produced by osteoblasts and other cells (e.g., lymphocytes), and stimulates RANK (receptor activator of nuclear factor $\kappa$B). Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption. RANKL, RANK and OPG are closely related to tumor necrosis factor and its receptors. The role of the Wnt signaling pathway is recognized, but less well understood. Local production of eicosanoids and interleukins is thought to participate in the regulation of bone turnover, and excess or reduced production of these mediators may underlie the development of osteoporosis. Trabecular bone (or cancellous bone) is the sponge-like bone in the ends of long bones and vertebrae. Cortical bone is the hard outer shell of bones and the middle of long bones. Because osteoblasts and osteoclasts inhabit the surface of bones, trabecular bone is more active and is
more subject to bone turnover and remodeling. Not only is bone density decreased, but the microarchitecture of bone is also disrupted. The weaker spicules of trabecular bone break ("microcracks"), and are replaced by weaker bone. Common osteoporotic fracture sites, the wrist, the hip and the spine, have a relatively high trabecular bone to cortical bone ratio. These areas rely on the trabecular bone for strength, so the intense remodeling causes these areas to degenerate most when the remodeling is imbalanced. Around the ages of 30–35, cancellous or trabecular bone loss begins. Women may lose as much as 50%, while men lose about 30%.

**DIAGNOSIS**

The diagnosis of osteoporosis can be made using conventional radiography and by measuring the bone mineral density (BMD). The most popular method of measuring BMD is dual-energy X-ray absorptiometry.

In addition to the detection of abnormal BMD, the diagnosis of osteoporosis requires investigations into potentially modifiable underlying causes; this may be done with blood tests. Depending on the likelihood of an underlying problem, investigations for cancer with metastasis to the bone, multiple myeloma, Cushing's disease and other above-mentioned causes may be performed.

- **Conventional radiography**
  Conventional radiography is useful, both by itself and in conjunction with CT or MRI, for detecting complications of osteopenia.

- **Dual-energy X-ray**
  Dual-energy X-ray absorptiometry (DEXA scan) is considered the gold standard for the diagnosis of osteoporosis.

- **Biomarkers**
  Chemical biomarkers are a useful tool in detecting bone degradation. The enzyme cathepsin K breaks down type-I collagen protein, an important constituent in bones. Prepared antibodies can recognize the resulting fragment, called a neoepitope, as a way to diagnose osteoporosis.

**PREVENTION**

Lifestyle prevention of osteoporosis is in many aspects the inverse of the potentially modifiable risk factors. As tobacco smoking and high alcohol intake have been linked with osteoporosis, smoking cessation and moderation of alcohol intake are commonly recommended as ways to help prevent it.

In people with coeliac disease adherence to a gluten-free diet decreases the risk of developing osteoporosis and increases bone density. The diet must ensure optimal calcium intake (of at least one gram daily) and measuring vitamin D levels is recommended, and to take specific supplements if necessary.

- **Nutrition**
  supplementation with calcium and vitamin D are conflicting, possibly because most studies did not have people with low dietary intakes.

- **Physical exercise**
  small benefit of physical exercise on bone density of postmenopausal women. The chances of having a fracture were also slightly reduced.
MANAGEMENT

■ **Lifestyle**
Weight-bearing endurance exercise and/or exercises to strengthen muscles improve bone strength in those with osteoporosis. Aerobics, weight bearing, and resistance exercises all maintain or increase BMD in postmenopausal women. Fall prevention can help prevent osteoporosis complications. There is some evidence for hip protectors specifically among those who are in care homes.

■ **Medications**
Bisphosphonates are useful in decreasing the risk of future fractures in those who have already sustained a fracture due to osteoporosis.
INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. These contrast with benign tumors, which do not spread. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements. While these symptoms may indicate cancer, they can also have other causes. Over 100 types of cancers affect humans. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity or excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation and environmental pollutants. In the developing world, 15% of cancers are due to infections such as Helicobacter pylori, hepatitis B, hepatitis C, human papillomavirus infection, Epstein–Barr virus and human immunodeficiency virus (HIV). These factors act, at least partly, by changing the genes of a cell. Typically, many genetic changes are required before cancer develops. Approximately 5–10% of cancers are due to inherited genetic defects from a person's parents. Cancer can be detected by certain signs and symptoms or screening tests. It is then typically further investigated by medical imaging and confirmed by biopsy.

Many cancers can be prevented by not smoking, maintaining a healthy weight, not drinking too much alcohol, eating plenty of vegetables, fruits and whole grains, vaccination against certain infectious diseases, not eating too much processed and red meat and avoiding too much sunlight exposure. Early detection through screening is useful for cervical and colorectal cancer. The benefits of screening in breast cancer are controversial. Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy and targeted therapy. Pain and symptom management are an important part of care. Palliative care is particularly important in people with advanced disease. The chance of survival depends on the type of cancer and extent of disease at the start of treatment.

DEFINITIONS

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasms. A neoplasm or
A tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely. All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor. They include:

- Cell growth and division absent the proper signals
- Continuous growth and division even given contrary signals
- Avoidance of programmed cell death
- Limitless number of cell divisions
- Promoting blood vessel construction
- Invasion of tissue and formation of metastases

The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.

**SIGNS AND SYMPTOMS**

When cancer begins, it produces no symptoms. Signs and symptoms appear as the mass grows or ulcerates. The findings that result depend on the cancer's type and location. Few symptoms are specific. Many frequently occur in individuals who have other conditions. Cancer can be difficult to diagnose and can be considered a "great imitator."

- **Local symptoms**
  Local symptoms may occur due to the mass of the tumor or its ulceration. For example, mass effects from lung cancer can block the bronchus resulting in cough or pneumonia; esophageal cancer can cause narrowing of the esophagus, making it difficult or painful to swallow; and colorectal cancer may lead to narrowing or blockages in the bowel, affecting bowel habits. Masses in breasts or testicles may produce observable lumps. Ulceration can cause bleeding that can lead to symptoms such as coughing up blood (lung cancer), anemia or rectal bleeding (colon cancer), blood in the urine (bladder cancer), or abnormal vaginal bleeding (endometrial or cervical cancer). Although localized pain may occur in advanced cancer, the initial tumor is usually painless. Some cancers can cause a buildup of fluid within the chest or abdomen.

- **Systemic symptoms**
  Systemic symptoms may occur due to the body's response to the cancer. This may include fatigue, unintentional weight loss, or skin changes. Some cancers can cause a systemic inflammatory state that leads to ongoing muscle loss and weakness, known as cachexia. Some types of cancer such as Hodgkin disease, leukemias and cancers of the liver or kidney can cause a persistent fever. Some systemic symptoms of cancer are caused by hormones or other molecules produced by the tumor, known as paraneoplastic syndromes. Common paraneoplastic syndromes include hypercalcemia which can cause altered mental state, constipation and dehydration, or hyponatremia that can also cause altered mental status, vomiting, headache or seizures.

- **Metastasis**
  Cancer can spread from its original site by local spread, lymphatic spread to regional lymph nodes or by hematogenous spread via the blood to distant sites, known as metastasis. When cancer spreads through the blood, it may spread through the body but is more likely to travel to certain areas depending on the cancer type. The symptoms of metastatic cancers depend on the
tumor location and can include enlarged lymph nodes (which can be felt or sometimes seen under the skin and are typically hard), enlarged liver or enlarged spleen, which can be felt in the abdomen, pain or fracture of affected bones and neurological symptoms.

**CAUSES**

The majority of cancers, some 90–95% of cases, are due to genetic mutations from environmental and lifestyle factors. The remaining 5–10% are due to inherited genetics. *Environmental* refers to any cause that is not inherited genetically, such as lifestyle, economic, and behavioral factors and not merely pollution. Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), lack of physical activity, and pollution. Psychological stress does not appear to be a risk factor for the onset of cancer, though it may worsen outcomes in those who already have cancer.

It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints. For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease.

- **Chemicals**

  Exposure to particular substances have been linked to specific types of cancer. These substances are called *carcinogens*.

  Tobacco smoke, for example, causes 90% of lung cancer. It also causes cancer in the larynx, head, neck, stomach, bladder, kidney, esophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons.

  Tobacco is responsible for about one in five cancer deaths worldwide and about one in three in the developed world. Lung cancer death rates in the United States have mirrored smoking patterns, with increases in smoking followed by dramatic increases in lung cancer death rates.

- **Diet and exercise**

  Diet, physical inactivity and obesity are related to up to 30–35% of cancer deaths. In the United States, excess body weight is associated with the development of many types of cancer and is a factor in 14–20% of cancer deaths. A UK study including data on over 5 million people showed higher body mass index to be related to at least 10 types of cancer and responsible for around 12,000 cases each year in that country. Physical inactivity is believed to contribute to cancer risk, not only through its effect on body weight but also through negative effects on the immune system and endocrine system. More than half of the effect from diet is due to overnutrition (eating too much), rather than from eating too few vegetables or other healthful foods.

  Some specific foods are linked to specific cancers. A high-salt diet is linked to gastric cancer. Aflatoxin B1, a frequent food contaminant, causes liver cancer. Betel nut chewing can cause oral cancer. National differences in dietary practices may partly explain differences in cancer incidence. For example, gastric cancer is more common in Japan due to its high-salt diet while colon cancer is more common in the United States. Immigrant cancer profiles mirror those of their new country, often within one generation.
Infection

Viruses are the usual infectious agents that cause cancer but cancer bacteria and parasites may also play a role. Oncoviruses (viruses that can cause cancer) include human papillomavirus (cervical cancer), Epstein–Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma), Kaposi’s sarcoma herpesvirus (Kaposi’s sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma) and human T-cell leukemia virus-1 (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma. Parasitic infections associated with cancer include Schistosoma haematobium (squamous cell carcinoma of the bladder) and the liver flukes, Opisthorchis viverrini and Clonorchis sinensis (cholangiocarcinoma).

Radiation

Radiation exposure such as ultraviolet radiation and radioactive material is a risk factor for cancer. Many non-melanoma skin cancers are due to ultraviolet radiation, mostly from sunlight. Sources of ionizing radiation include medical imaging and radon gas.

Ionizing radiation is not a particularly strong mutagen. Residential exposure to radon gas, for example, has similar cancer risks as passive smoking. Radiation is a more potent source of cancer when combined with other cancer-causing agents, such as radon plus tobacco smoke.\(^{59}\) Radiation can cause cancer in most parts of the body, in all animals and at any age. Children are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect.

Medical use of ionizing radiation is a small but growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of medical imaging.

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the non-ionizing medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.

Non-ionizing radio frequency radiation from mobile phones, electric power transmission and other similar sources has been described as a possible carcinogen by the World Health Organization's International Agency for Research on Cancer. Evidence, however, has not supported a concern. This includes that studies have not found a consistent link between mobile phone radiation and cancer risk.

Heredity

The vast majority of cancers are non-hereditary (sporadic). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation that has a large effect on cancer risk and these cause less than 3–10% of cancer. Some of these syndromes include: certain inherited mutations in the genes BRCA1 and BRCA2 with a more than 75% risk of breast cancer and ovarian cancer, and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which is present in about 3% of people with colorectal cancer, among others.
Taller people have an increased risk of cancer because they have more cells than shorter people. Since height is genetically determined to a large extent, taller people have a heritable increase of cancer risk.

- **Physical agents**
  Some substances cause cancer primarily through their physical, rather than chemical, effects. A prominent example of this is prolonged exposure to asbestos, naturally occurring mineral fibers that are a major cause of mesothelioma (cancer of the serous membrane) usually the serous membrane surrounding the lungs. Other substances in this category, including both naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool and rock wool, are believed to have similar effects. Non-fibrous particulate materials that cause cancer include powdered metallic cobalt and nickel and crystalline silica (quartz, cristobalite and tridymite). Usually, physical carcinogens must get inside the body (such as through inhalation) and require years of exposure to produce cancer.

  Chronic inflammation has been hypothesized to directly cause mutation. Inflammation can contribute to proliferation, survival, angiogenesis and migration of cancer cells by influencing the tumor microenvironment. Oncogenes build up an inflammatory pro-tumorigenic microenvironment.

- **Hormones**
  Some hormones play a role in the development of cancer by promoting cell proliferation. Insulin-like growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis.

  Hormones are important agents in sex-related cancers, such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain their higher risk of breast cancer, even in the absence of a breast-cancer gene. Similarly, men of African ancestry have significantly higher levels of testosterone than men of European ancestry and have a correspondingly higher level of prostate cancer. Men of Asian ancestry, with the lowest levels of testosterone-activating androstanediol glucuronide, have the lowest levels of prostate cancer.

  Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer. Osteosarcoma may be promoted by growth hormones. Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.

- **Autoimmune diseases**
  There is an association between celiac disease and an increased risk of all cancers. People with untreated celiac disease have a higher risk, but this risk decreases with time after diagnosis and strict treatment, probably due to the adoption of a gluten-free diet. Rates of gastrointestinal cancers are increased in people with Crohn's disease and ulcerative colitis, due to chronic inflammation. Also, immunomodulators and biologic agents used to treat these diseases may promote developing extra-intestinal malignancies.
Cancer is fundamentally a disease of tissue growth regulation. In order for a normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered.

The affected genes are divided into two broad categories. Oncogenes are genes that promote cell growth and reproduction. Tumor suppressor genes are genes that inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in multiple genes are required to transform a normal cell into a cancer cell.

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA. Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, leading to the expression of viral oncogenes in the affected cell and its descendants.

Replication of the data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If a significant error occurs, the damaged cell can self-destruct through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation or hypoxia.

The errors that cause cancer are self-amplifying and compounding, for example:

- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.

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- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly.
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
- A further mutation may cause loss of a tumor suppressor gene, disrupting the apoptosis signaling pathway and immortalizing the cell.
- A further mutation in the signaling machinery of the cell might send error-causing signals to nearby cells.
- The transformation of a normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape more controls that limit normal tissue growth. This rebellion-like scenario is an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ongoing process, termed clonal evolution, drives progression towards more invasive stages. Clonal evolution leads to intra-tumour heterogeneity (cancer cells with heterogeneous mutations) that complicates designing effective treatment strategies.
- Characteristic abilities developed by cancers are divided into categories, specifically evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential, metastasis, reprogramming of energy metabolism and evasion of immune destruction.

### Epigenetics

The classical view of cancer is a set of diseases that are driven by progressive genetic abnormalities that include mutations in tumor-suppressor genes and oncogenes and chromosomal abnormalities. Later epigenetic alterations' role was identified. Epigenetic alterations are functionally relevant modifications to the genome that do not change the nucleotide sequence. Examples of such modifications are changes in DNA methylation (hypermethylation and hypomethylation), histone modification and changes in chromosomal architecture (caused by inappropriate expression of proteins such as HMG A2 or HMG A1). Each of these alterations regulates gene expression without altering the underlying DNA sequence. These changes may remain through cell divisions, last for multiple generations and can be considered to be epimutations (equivalent to mutations). Reduced expression of DNA repair genes disrupts DNA repair. This is shown in the figure at the 4th level from the top. (In the figure, red wording indicates the central role of DNA damage and defects in DNA repair in progression to cancer.) When DNA repair is deficient DNA damage remains in cells at a higher than usual level (5th level) and cause increased frequencies of mutation and/or epimutation (6th level). Mutation rates increase substantially in cells defective in DNA mismatch repair or in homologous recombinational repair (HRR). Chromosomal rearrangements and aneuploidy also increase in HRR defective cells. Higher levels of DNA damage cause increased mutation (right side of figure) and increased epimutation. During repair of DNA double strand breaks, or repair of other DNA damage, incompletely cleared repair sites can cause epigenetic gene silencing.

### Metastasis

Metastasis is the spread of cancer to other locations in the body. The dispersed tumors are called metastatic tumors, while the original is called the primary tumor. Almost all cancers can metastasize. Most cancer deaths are due to cancer that has metastasized.
Metastasis is common in the late stages of cancer and it can occur via the blood or the lymphatic system or both. The typical steps in metastasis are local invasion, intravasation into the blood or lymph, circulation through the body, extravasation into the new tissue, proliferation and angiogenesis. Different types of cancers tend to metastasize to particular organs, but overall the most common places for metastases to occur are the lungs, liver, brain and the bones.

**DIAGNOSIS**

Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these leads to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, (contrast) CT scans and endoscopy. The tissue diagnosis from the biopsy indicates the type of cell that is proliferating, its histological grade, genetic abnormalities and other features. Together, this information is useful to evaluate the prognosis and to choose the best treatment. Cytogenetics and immunohistochemistry are other types of tissue tests. These tests provide information about molecular changes (such as mutations, fusion genes and numerical chromosome changes) and may thus also indicate the prognosis and best treatment.

**CLASSIFICATION**

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

- **Carcinoma**: Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.

- **Sarcoma**: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow.

- **Lymphoma and leukemia**: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.¹⁰⁴

- **Germ cell tumor**: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

- **Blastoma**: Cancers derived from immature “precursor” cells or embryonic tissue.

Cancers are usually named using -carcinoma, -sarcoma or -blastoma as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root. For example, cancers of the liver parenchyma arising from malignant epithelial cells is called hepatocarcinoma, while a malignancy arising from primitive liver precursor cells is called a hepatoblastoma and a cancer arising from fat cells is called a liposarcoma. For some common cancers, the English organ name is used. For example, the most common type of breast cancer is called ductal carcinoma of the breast. Here, the adjective ductal refers to the appearance of cancer under the microscope, which suggests that it has originated in the milk ducts.

Benign tumors (which are not cancers) are named using -oma as a suffix with the organ name as the root. For example, a benign tumor of smooth muscle cells is called a leiomyoma (the common name of this frequently occurring benign tumor in the uterus is fibroid). Confusingly, some types of cancer use the -noma suffix, examples including melanoma and seminoma.
Some types of cancer are named for the size and shape of the cells under a microscope, such as giant cell carcinoma, spindle cell carcinoma and small-cell carcinoma.

**PREVENTION**

Cancer prevention is defined as active measures to decrease cancer risk. The vast majority of cancer cases are due to environmental risk factors. Many of these environmental factors are controllable lifestyle choices. Thus, cancer is generally preventable. Between 70% and 90% of common cancers are due to environmental factors and therefore potentially preventable.

Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, excess weight/obesity, poor diet, physical inactivity, alcohol, sexually transmitted infections and air pollution. Not all environmental causes are controllable, such as naturally occurring background radiation and cancers caused through hereditary genetic disorders and thus are not preventable via personal behavior.

■ **Dietary**

While many dietary recommendations have been proposed to reduce cancer risks, the evidence to support them is not definitive. The primary dietary factors that increase risk are obesity and alcohol consumption. Diets low in fruits and vegetables and high in red meat have been implicated but reviews and meta-analyses do not come to a consistent conclusion. A 2014 meta-analysis found no relationship between fruits and vegetables and cancer. Coffee is associated with a reduced risk of liver cancer.

- Dietary recommendations for cancer prevention typically include an emphasis on vegetables, fruit, whole grains and fish and an avoidance of processed and red meat (beef, pork, lamb), animal fats, pickled foods and refined carbohydrates.

■ **Medication**

Medications can be used to prevent cancer in a few circumstances. In the general population, NSAIDs reduce the risk of colorectal cancer; however, due to cardiovascular and gastrointestinal side effects, they cause overall harm when used for prevention. Aspirin has been found to reduce the risk of death from cancer by about 7%. COX-2 inhibitors may decrease the rate of polyp formation in people with familial adenomatous polyposis; however, it is associated with the same adverse effects as NSAIDs.

- Daily use of tamoxifen or raloxifene reduce the risk of breast cancer in high-risk women. The benefit versus harm for 5-alpha-reductase inhibitor such as finasteride is not clear.

- Vitamin D supplementation does not appear to be effective at preventing cancer. While low blood levels of vitamin D are correlated with increased cancer risk, whether this relationship is causal and vitamin D supplementation is protective is not determined. One 2014 review found that supplements had no significant effect on cancer risk. Another 2014 review concluded that vitamin D3 may decrease the risk of death from cancer (one fewer death in 150 people treated over 5 years), but concerns with the quality of the data were noted.

- Beta-carotene supplementation increases lung cancer rates in those who are high risk. Folic acid supplementation is not effective in preventing colon cancer and may increase colon polyps. Selenium supplementation has not been shown to reduce the risk of cancer.
Vaccination

Vaccines have been developed that prevent infection by some carcinogenic viruses. Human papillomavirus vaccine (Gardasil and Cervarix) decrease the risk of developing cervical cancer. The hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer. The administration of human papillomavirus and hepatitis B vaccinations is recommended where resources allow.

SCREENING

Unlike diagnostic efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear. This may involve physical examination, blood or urine tests or medical imaging. Cancer screening is not available for many types of cancers. Even when tests are available, they may not be recommended for everyone. Universal screening or mass screening involves screening everyone. Selective screening identifies people who are at higher risk, such as people with a family history. Several factors are considered to determine whether the benefits of screening outweigh the risks and the costs of screening. These factors include:

- Possible harms from the screening test: for example, X-ray images involve exposure to potentially harmful ionizing radiation
- The likelihood of the test correctly identifying cancer
- The likelihood that cancer is present: Screening is not normally useful for rare cancers.
- Possible harms from follow-up procedures
- Whether suitable treatment is available
- Whether early detection improves treatment outcomes
- Whether the cancer will ever need treatment
- Whether the test is acceptable to the people: If a screening test is too burdensome (for example, extremely painful), then people will refuse to participate.
- Cost

MANAGEMENT

Many treatment options for cancer exist. The primary ones include surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care. Which treatments are used depends on the type, location and grade of the cancer as well as the patient's health and preferences. The treatment intent may or may not be curative.

Chemotherapy

Chemotherapy is the treatment of cancer with one or more cytotoxic anti-neoplastic drugs (chemotherapeutic agents) as part of a standardized regimen. The term encompasses a variety of drugs, which are divided into broad categories such as alkylating agents and antimetabolites. Traditional chemotherapeutic agents act by killing cells that divide rapidly, a critical property of most cancer cells.

It was found that providing combined cytotoxic drugs is better than a single drug; a process called the combination therapy; which has an advantage in the statistics of survival and response to the tumor and in the progress of the disease. A Cochrane review concluded that combined therapy was more effective to treat metastasized breast cancer. However, generally it is not certain whether combination chemotherapy leads to better health outcomes, when both survival and toxicity are considered.
Targeted therapy is a form of chemotherapy that targets specific molecular differences between cancer and normal cells. The first targeted therapies blocked the estrogen receptor molecule, inhibiting the growth of breast cancer. Another common example is the class of Bcr-Abl inhibitors, which are used to treat chronic myelogenous leukemia (CML). Currently, targeted therapies exist for many of the most common cancer types, including bladder cancer, breast cancer, colorectal cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, pancreatic cancer, prostate cancer, skin cancer, and thyroid cancer as well as other cancer types.

The efficacy of chemotherapy depends on the type of cancer and the stage. In combination with surgery, chemotherapy has proven useful in cancer types including breast cancer, colorectal cancer, pancreatic cancer, osteogenic sarcoma, testicular cancer, ovarian cancer and certain lung cancers. Chemotherapy is curative for some cancers, such as some leukemias, ineffective in some brain tumors, and needless in others, such as most non-melanoma skin cancers. The effectiveness of chemotherapy is often limited by its toxicity to other tissues in the body. Even when chemotherapy does not provide a permanent cure, it may be useful to reduce symptoms such as pain or to reduce the size of an inoperable tumor in the hope that surgery will become possible in the future.

### Radiation

Radiation therapy involves the use of ionizing radiation in an attempt to either cure or improve symptoms. It works by damaging the DNA of cancerous tissue, killing it. To spare normal tissues (such as skin or organs, which radiation must pass through to treat the tumor), shaped radiation beams are aimed from multiple exposure angles to intersect at the tumor, providing a much larger dose there than in the surrounding, healthy tissue. As with chemotherapy, cancers vary in their response to radiation therapy.

Radiation therapy is used in about half of cases. The radiation can be either from internal sources (brachytherapy) or external sources. The radiation is most commonly low energy X-rays for treating skin cancers, while higher energy X-rays are used for cancers within the body. Radiation is typically used in addition to surgery or chemotherapy. For certain types of cancer, such as early head and neck cancer, it may be used alone. For painful bone metastasis, it has been found to be effective in about 70% of patients.

### Surgery

Surgery is the primary method of treatment for most isolated, solid cancers and may play a role in palliation and prolongation of survival. It is typically an important part of definitive diagnosis and staging of tumors, as biopsies are usually required. In localized cancer, surgery typically attempts to remove the entire mass along with, in certain cases, the lymph nodes in the area. For some types of cancer this is sufficient to eliminate the cancer.

### Palliative care

Palliative care is treatment that attempts to help the patient feel better and may be combined with an attempt to treat the cancer. Palliative care includes action to reduce physical, emotional, spiritual and psycho-social distress. Unlike treatment that is aimed at directly killing cancer cells, the primary goal of palliative care is to improve quality of life.

People at all stages of cancer treatment typically receive some kind of palliative care. In some cases, medical specialty professional organizations recommend that patients and physicians respond to cancer only with palliative care. This applies to patients who:

1. display low performance status, implying limited ability to care for themselves
2. received no benefit from prior evidence-based treatments
3. are not eligible to participate in any appropriate clinical trial
4. no strong evidence implies that treatment would be effective

Palliative care may be confused with hospice and therefore only indicated when people approach end of life. Like hospice care, palliative care attempts to help the patient cope with their immediate needs and to increase comfort. Unlike hospice care, palliative care does not require people to stop treatment aimed at the cancer. Multiple national medical guidelines recommend early palliative care for patients whose cancer has produced distressing symptoms or who need help coping with their illness. In patients first diagnosed with metastatic disease, palliative care may be immediately indicated. Palliative care is indicated for patients with a prognosis of less than 12 months of life even given aggressive treatment.

■ Immunotherapy

A variety of therapies using immunotherapy, stimulating or helping the immune system to fight cancer, have come into use since 1997. Approaches include antibodies, checkpoint therapy, and adoptive cell transfer.

■ Laser therapy

Laser therapy uses high-intensity light to treat cancer by shrinking or destroying tumors or precancerous growths. Lasers are most commonly used to treat superficial cancers that are on the surface of the body or the lining of internal organs. It is used to treat basal cell skin cancer and the very early stages of others like cervical, penile, vaginal, vulvar, and non-small cell lung cancer. It is often combined with other treatments, such as surgery, chemotherapy, or radiation therapy. Laser-induced interstitial thermotherapy (LITT), or interstitial laser photocoagulation, uses lasers to treat some cancers using hyperthermia, which uses heat to shrink tumors by damaging or killing cancer cells. Laser are more precise than surgery and cause less damage, pain, bleeding, swelling, and scarring. A disadvantage is surgeons must have specialized training. It may be more expensive than other treatments.

■ Alternative medicine

Complementary and alternative cancer treatments are a diverse group of therapies, practices and products that are not part of conventional medicine. "Complementary medicine" refers to methods and substances used along with conventional medicine, while "alternative medicine" refers to compounds used instead of conventional medicine. Most complementary and alternative medicines for cancer have not been studied or tested using conventional techniques such as clinical trials. Some alternative treatments have been investigated and shown to be ineffective but still continue to be marketed and promoted. Cancer researcher Andrew J. Vickers stated, 'The label 'unproven' is inappropriate for such therapies; it is time to assert that many alternative cancer therapies have been 'disproven'."