

Jaundice

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Jaundice (also known as **icterus**;^[1] attributive adjective: **icteric**) is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by hyperbilirubinemia (increased levels of bilirubin in the blood). This hyperbilirubinemia subsequently causes increased levels of bilirubin in the extracellular fluid. Concentration of bilirubin in blood plasma does not normally exceed 1 mg/dL (>17μmol/L). A concentration higher than 1.8 mg/dL (>30μmol/L) leads to jaundice.^[2] The term jaundice comes from the French word *jaune*, meaning yellow.

Jaundice is often seen in liver disease such as hepatitis or liver cancer. It may also indicate obstruction of the biliary tract, for example by gallstones or pancreatic cancer, or less commonly be congenital in origin.

Yellow discoloration of the skin, especially on the palms and the soles, but not of the sclera and mucous membranes (i.e. oral cavity) is due to carotenemia - a harmless condition^[3] important to differentiate from jaundice.

Signs and symptoms

A 4-year-old boy with icteric (jaundiced) sclera which later proved to be a manifestation of hemolytic anemia due to G6PD deficiency following fava bean consumption.

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*. However, the sclera themselves are not "icteric" (stained with bile pigment) but rather the conjunctival membranes that overlie them. The yellowing of the "white of the eye" is thus more properly termed *conjunctival icterus*.^[4] The term "icterus" itself is sometimes incorrectly used to refer to jaundice that is noted in the sclera of the eyes, however its more common and more correct meaning is entirely synonymous with jaundice.^{[1][5]}

Differential diagnosis

When a pathological process interferes with the normal functioning of the metabolism and excretion of bilirubin just described, jaundice may be the result. Jaundice is classified into three categories, depending on which part of the physiological mechanism the pathology affects. The three categories are:

| Category | Definition |
|--------------|---|
| Pre-hepatic | The pathology is occurring prior to the <u>liver</u> . |
| Hepatic | The pathology is located within the liver. |
| Post-Hepatic | The pathology is located after the conjugation of bilirubin in the liver. |

Pre-hepatic

Pre-hepatic jaundice is caused by anything which causes an increased rate of hemolysis (breakdown of red blood cells). In tropical countries, malaria can cause jaundice in this manner. Certain genetic diseases, such as sickle cell anemia, spherocytosis, thalassemia 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. Defects in bilirubin metabolism also present as jaundice, as in Gilbert's syndrome (a genetic disorder of bilirubin metabolism which can result in mild jaundice, which is found in about 5% of the population) and Crigler-Najjar syndrome.

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.

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 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^[6] 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.

Laboratory findings depend on the cause of jaundice.

- Urine: Conjugated bilirubin present, urobilinogen > 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. However, excretion is the rate-limiting step, and usually impaired to the greatest extent. As a result, conjugated hyperbilirubinaemia predominates.^[7]

Post-hepatic

Post-hepatic jaundice, also called obstructive jaundice, is caused by an interruption to the drainage of bile 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 and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome.

In complete obstruction of the bile duct, no urobilinogen is found in the urine, since bilirubin has no access to the intestine and it is in the intestine that bilirubin gets converted to urobilinogen to be later released into the general circulation. In this case,

presence of bilirubin (conjugated) in the urine without urine-urobilinogen 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. However, although pale stools and dark urine are a feature of biliary obstruction, they can occur in many intra-hepatic illnesses and are therefore not a reliable clinical feature to distinguish obstruction from hepatic causes of jaundice.^[8]

Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus" because of the deposition of 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.

Pathophysiology

In order to understand how jaundice results, the pathological processes that cause jaundice to take their effect must be understood. 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.

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 tetrapyrrole 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.^[11] The majority of this bilirubin comes from the breakdown of heme from expired red blood cells in the process just described. However approximately 20 percent comes from other heme sources, including ineffective erythropoiesis, and the breakdown of other heme-containing proteins, such as muscle myoglobin and cytochromes.^[11]

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 the 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.