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The Thistle QA CEU No is: **MT00025**.

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## CHEMISTRY LEGEND

**MARCH 2009**

### JAUNDICE

Jaundice, also known as icterus (attributive adjective: icteric), is a yellowish discoloration 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 fluids. Typically, the concentration of Bilirubin in the plasma must exceed 1.5 mg/dL, three times the usual value of approximately 0.5mg/dL for the coloration to be easily visible. Jaundice comes from the French word jaune, meaning yellow. One of the first tissues to change colour as Bilirubin levels rise in jaundice is the conjunctiva of the eye, a condition 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 conjunctival icterus.



Jaundice in a man with hepatic failure



Yellowing of the skin and Conjunctiva overlying the Sclera caused by Hepatitis A

#### Normal Physiology

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.

## Pre-hepatic events

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 haemoglobin, are subsequently released into the blood. The haemoglobin 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 colour pigment), iron and carbon monoxide. The next step is the reduction of biliverdin to a yellow colour tetrapyrrol pigment called by cytosolic enzyme biliverdin reductase. This Bilirubin is "unconjugated," "free" or "indirect" Bilirubin. Approximately 4 mg per kg of Bilirubin 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. 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.

## 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-glucuronide 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 faeces, 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 faeces and urine, respectively.

## Causes

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:

Pre-hepatic: The pathology is occurring prior the liver.

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 anaemia, spherocytosis and glucose 6-phosphate dehydrogenase deficiency can lead to increased red cell lysis and therefore haemolytic jaundice. Commonly, diseases of the kidney, such as haemolytic uremic syndrome, can also lead to coloration. Defects in Bilirubin metabolism also present as jaundice.

Laboratory findings include:

- 🚰 Urine - no bilirubin present, urobilinogen > 2 units (except in infants where gut flora has not developed) and
- 🚰 Serum - increased unconjugated Bilirubin.

## Hepatic

Hepatic jaundice causes include acute hepatitis, hepatotoxicity and alcoholic liver disease, whereby cell necrosis reduces the liver's ability to metabolise and excrete Bilirubin leading to a buildup in the blood. Less common causes include primary biliary cirrhosis, Gilbert's syndrome (a genetic disorder of Bilirubin metabolism which can result in mild jaundice, which is found in about 5% of the population), Crigler-Najjar syndrome, metastatic carcinoma and Niemann-Pick disease, type C. Jaundice seen in the newborn, known as neonatal jaundice, is common, occurring in almost every newborn as hepatic machinery for the conjugation and excretion of Bilirubin does not fully mature until approximately two weeks of age.

Laboratory findings include:

- 🚰 Urine - Conjugated Bilirubin present, urobilinogen > 2 units but variable (except in children).

## 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" live in the common bile duct, causing obstructive jaundice. Other causes include strictures of the common bile duct, biliary atresia, ductal carcinoma, pancreatitis and pancreatic pseudocysts. A rare cause of obstructive jaundice is Mirizzi's syndrome. The presence of pale stools and dark urine suggests an obstructive or post-hepatic cause as normal faeces get their colour from bile pigments. Patients also can present with elevated serum cholesterol, and often complain of severe itching or "pruritus".

No one test can differentiate between various classifications of jaundice. A combinations of liver function tests is essential to

arrive at a diagnosis

	Pre-hepatic Jaundice	Hepatic Jaundice	Post-hepatic Jaundice
Total Bilirubin	Normal / Increased	Increased	Increased
Conjugated Bilirubin	Increased	Normal	Increased
Unconjugated Bilirubin	Increased	Normal / Increased	Normal
Urobilinogen	Increased	Normal / Increased	Decreased / Negative
Urine Colour	Dark	Light	Dark
Stool Colour	Dark	Normal	Pale
Alkaline phosphatase levels	Normal	Increased	Increased
Alanine transferase and Aspartate transferase levels	Normal	Increased	Increased
Conjugated Bilirubin in Urine	Not Present	Present	Present

## Diagnostic tree for the patient with abnormal liver panel

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 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 lab 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 AST and ALT rise in a separate pattern.

If the ALP and GGT levels rise proportionately about as high as the AST and ALT 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 a 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.

Lab results for liver panels are frequently compared by the magnitude of their differences, not the pure number, as well as by their ratios. The AST:ALT ratio can be a good indicator of whether the disorder is alcoholic liver damage (10), some other form of liver damage (above 1), or hepatitis (less than 1). Bilirubin levels greater than 10x normal could indicate neoplastic or intrahepatic cholestasis. Levels lower than this tends to indicate hepatocellular causes. AST levels greater than 15x tends to indicate acute hepatocellular damage. Less than this tend to indicate obstructive causes.

ALP levels greater than 5x normal tend to indicate obstruction, while levels greater than 10x normal can indicate drug (toxic) induced cholestatic hepatitis or Cytomegalovirus. Both of these conditions can also have ALT and AST greater than 20x normal. GGT levels greater than 10x normal typically indicate cholestasis. Levels 5x-10x tend to indicate viral hepatitis. Levels less than 5x normal, tend to indicate drug toxicity. Acute hepatitis will typically have ALT and AST levels rising 20-30x normal (above 1000 U/L), and may remain significantly elevated for several weeks. Acetaminophen toxicity can result in ALT and AST levels greater than 50x normal.

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## References

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## Questions

1. Discuss the three pathological processes which cause jaundice.
  2. Discuss the differences in the laboratory findings between the three processes.
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