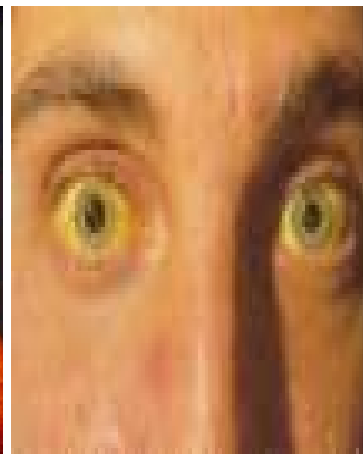


# A Jaundice Presentation By Doc GP



- The symptoms of jaundice as described is caused by the **deposition of bilirubin in the tissues secondary to increased bilirubin levels in the blood.**
- **Jaundice is not a disease in itself, but rather a sign that occurs in many different diseases in which there is an elevated plasma bilirubin.**
- **Jaundice then is usually a symptom of an underlying disorder.**

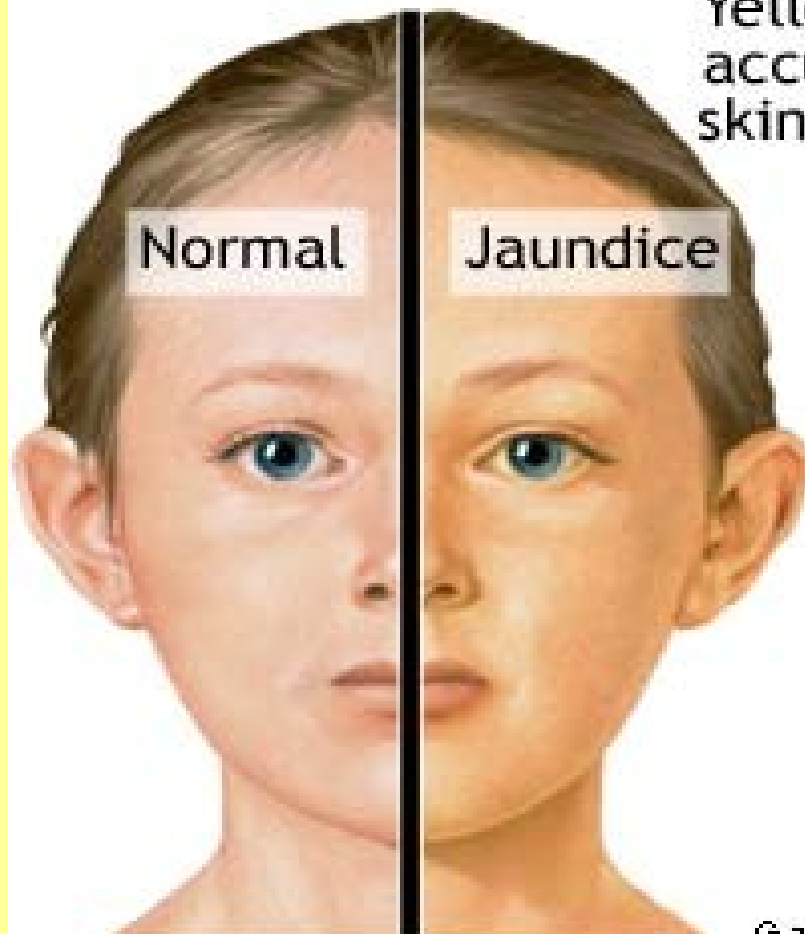
- Usually the concentration of bilirubin in the blood must exceed 2-3mg/dL for the coloration to be easily visible.
- The color of the skin and sclerae vary depending on the level of bilirubin.
- When the bilirubin level is mildly elevated, they are yellowish.
- When the bilirubin level is high, they tend to be brown.
- The classic definition of jaundice is a serum bilirubin level greater than 2.5 to 3 mg per dL (42.8 to 51.3  $\mu\text{mol}$  per L)
- Normal range of serum bilirubin is 5-17 m mol/l
- Jaundice is clinically obvious at 50 m mol/l

- Jaundice occurs when there is
- 1) too much bilirubin being produced for the liver to remove from the blood. (For example, patients with hemolytic anemia have an abnormally rapid rate of destruction of their red blood cells that releases large amounts of bilirubin into the blood),
- 2) a defect in the liver that prevents bilirubin from being removed from the blood, converted to bilirubin/glucuronic acid (conjugated) or secreted in bile, or
- 3) blockage of the bile ducts that decreases the flow of bile and bilirubin from the liver into the intestines. (For example, the bile ducts can be blocked by cancers, gallstones, or inflammation of the bile ducts).
- The decreased conjugation, secretion, or flow of bile that can result in jaundice is referred to as cholestasis: however, cholestasis does not always result in jaundice.

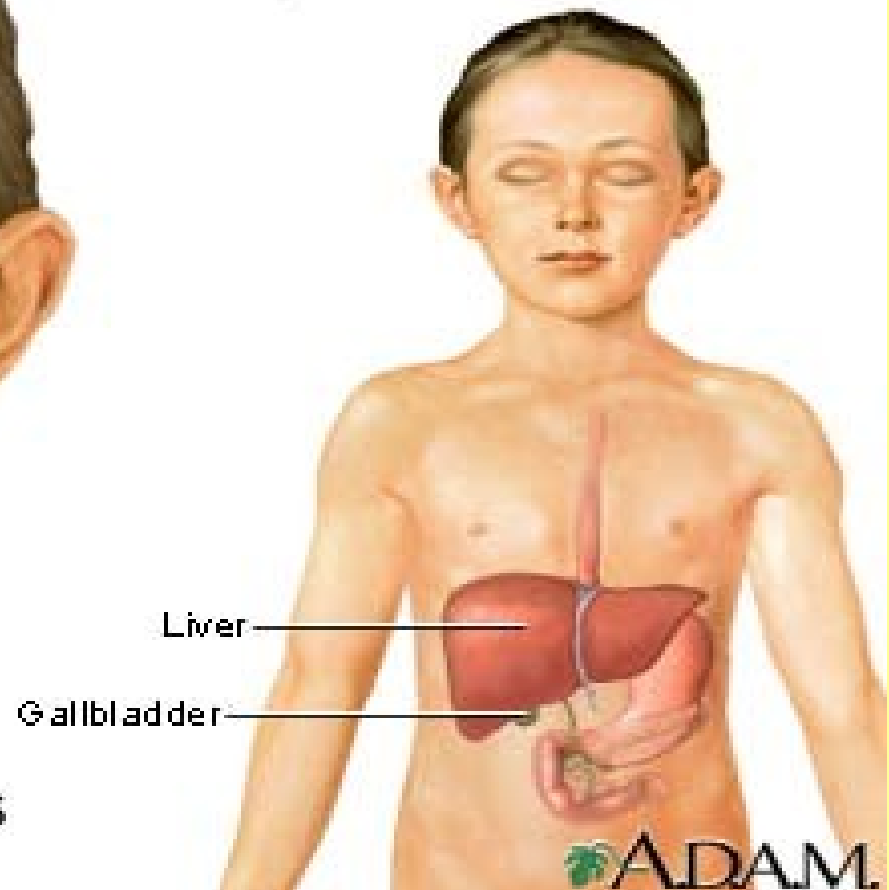
# Jaundice



Yellowing is associated with the accumulation of bilirubin in the skin, most often caused by liver and gallbladder disorders



Jaundice is a symptom where the skin and eyes become yellow









- **Bilirubin and Jaundice**
- Jaundice (yellow color of skin, whites of the eyes) may occur when blood levels of bilirubin exceed normal (icterus).
- Jaundice may be characterized by **an increase in unconjugated (indirect) bilirubin,**
- **conjugated (direct) bilirubin,**
- **or both.**
- Accumulation of bilirubin (usually unconjugated) in the brain (kernicterus) may result in death.
- **When conjugated bilirubin increases, it may be excreted, giving a deep yellow-red color to the urine.**

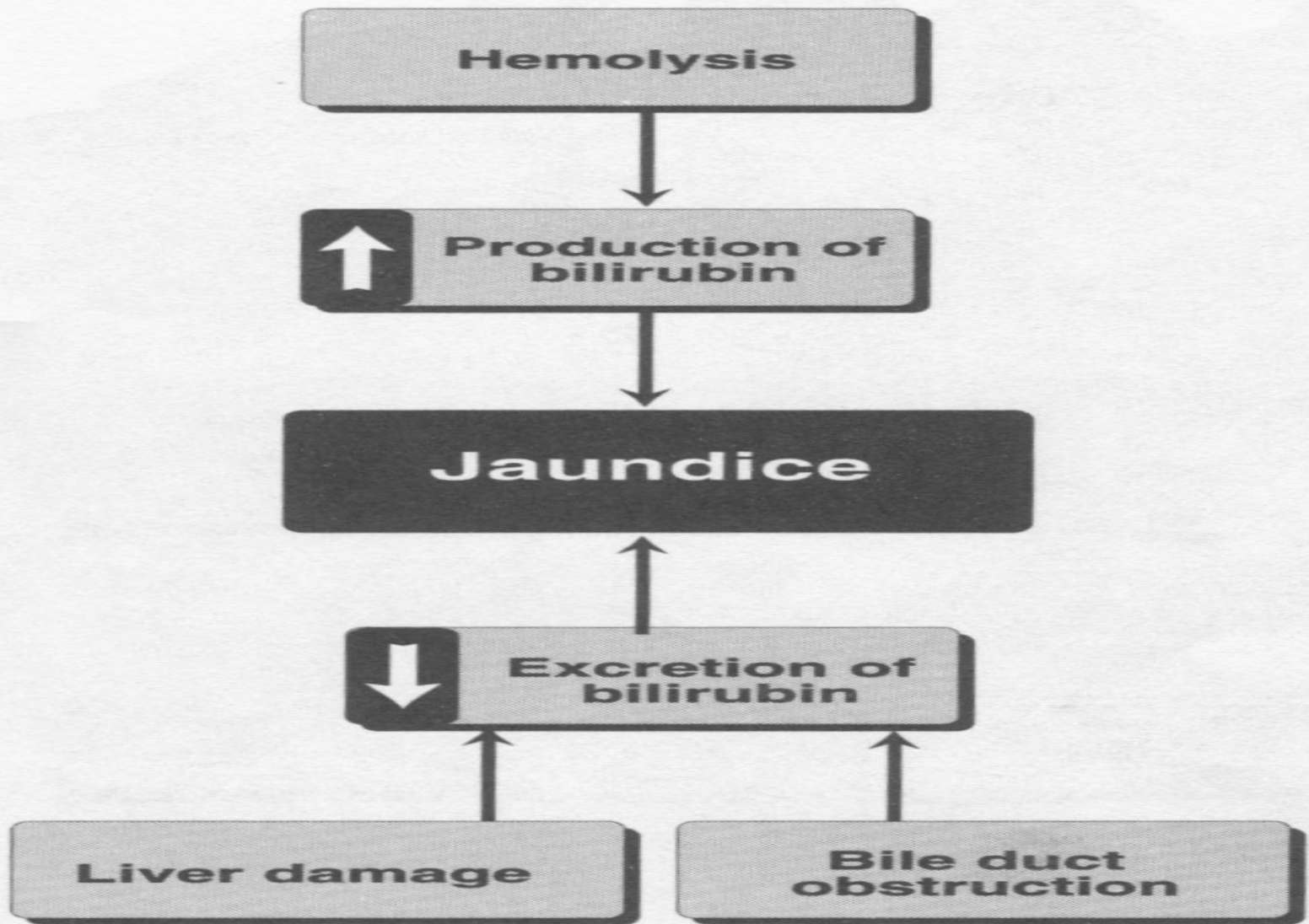
# CLASSIFICATION

- Jaundice is **usually classified into three major forms** as described below.
- However, **in clinical practice jaundice is often more complex than indicated in this simple classification** since **the accumulation of bilirubin may be due to defects at more than one step in the metabolism of bilirubin.**

- **1- PREHEPATIC or HEMOLYTIC JAUNDICE** usually due to excess hemolysis of red blood cells for whatever cause.
- **2- HEPATIC or HEPATOCELLULAR JAUNDICE**
- **3- POST HEPATIC or OBSTRUCTIVE JAUNDICE**

- **Hemolytic jaundice**

- The liver has the capacity to conjugate and excrete over 3000 mg bilirubin per day, whereas the normal production of bilirubin is only 300 mg/day.
- This excess capacity allows the liver to respond to increased heme degradation with a corresponding increase in conjugation and secretion of bilirubin diglucuronide.
- **However, massive lysis of red blood cells (for example, in patients with sickle cell anemia or malaria) may produce bilirubin faster than the liver can conjugate it.**
- **More bilirubin is excreted into the bile, the amount of urobilinogen entering the enterohepatic circulation is increased, and urinary urobilinogen is increased. Unconjugated bilirubin is elevated in blood**



**Figure 23.8**  
Causes of jaundice.

- **Hepatocellular jaundice:**
- **Damage to liver cells (for example, in patients with cirrhosis or hepatitis) causes a decrease in both bilirubin uptake and production of conjugated bilirubin. Unconjugated bilirubin occurs in the blood and increased urobilinogen in the urine. The urine is dark in color and stools are a pale, clay color. Plasma levels of AST (SGOT) and ALT (SOPT) are elevated and the patient experiences nausea and anorexia.**

- **Obstructive jaundice:**
- **In this instance jaundice** is not due to overproduction of bilirubin, but **results from obstruction of the bile duct.** For example, the presence of a hepatic tumor or bile stones may block the bile ducts, preventing passage of bilirubin into the intestine. **Patients with obstructive jaundice** experience GI pain, nausea, and **produce stools that are a pale, clay color. The liver “regurgitates” conjugated bilirubin into the blood, which is excreted in the urine.**
- [ Prolonged obstruction of the bile duct can lead to liver damage and a subsequent rise in unconjugated bilirubin.]

# Table of the causes of jaundice

Jaundice	Cause
<b>Pre-hepatic</b>	<p>Caused by anything which causes an increased rate of hemolysis (breakdown of RBC's).</p> <ul style="list-style-type: none"><li>□ <i>Malaria</i> (in tropical countries)</li><li>□ <i>Genetic diseases</i>, such as glucose 6-phosphate dehydrogenase deficiency.</li><li>□ Defects in <i>bilirubin metabolism</i>.</li></ul>
<b>Hepatic</b>	<ul style="list-style-type: none"><li>□ <i>Acute hepatitis</i></li><li>□ <i>Hepatotoxicity</i></li><li>□ <i>Alcoholic liver disease</i>.</li></ul> <p>Less common causes include:</p> <ul style="list-style-type: none"><li>□ <i>Primary Biliary Cirrhosis</i></li><li>□ <i>Gilbert's syndrome</i></li><li>□ <i>Metastatic carcinoma</i></li><li>□ <i>Neonatal jaundice</i></li></ul>



**Infiltrative diseases of the liver**

Diseases in which the liver is filled with cells or substances that don't belong there. Example:

Most common

- Metastatic cancer to the liver (usually from cancers within the abdomen).

Uncommon

- Iron (hemochromatosis)
- alpha-one antitrypsin (alpha-one antitrypsin deficiency)
- Copper (Wilson's disease).

**Inflammation of the bile ducts**

Diseases causing inflammation of the bile ducts, for example, *primary biliary cirrhosis* or *sclerosing cholangitis* and some drugs, can stop the flow of bile and elimination of bilirubin and lead to jaundice.

**Blockage of the bile ducts**

Most common:

- *gallstones*
- *pancreatic cancer*

Less common:

- *cancers of the liver and bile ducts*

## Post-hepatic

Caused by an interruption to the drainage of bile in the biliary system.

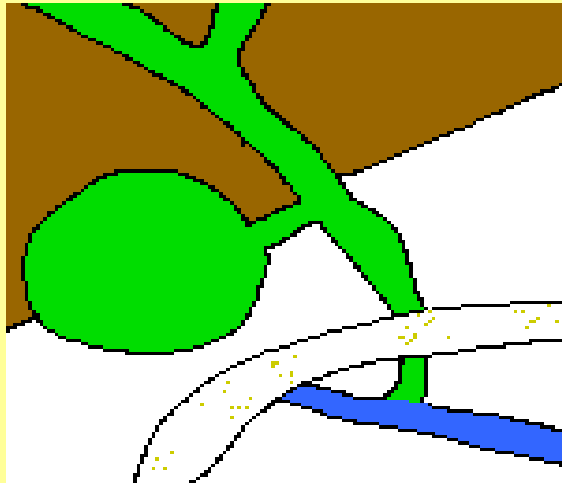
Most common causes:

- *Gallstones in the common bile duct*
- *Pancreatic cancer in the head of the pancreas.*

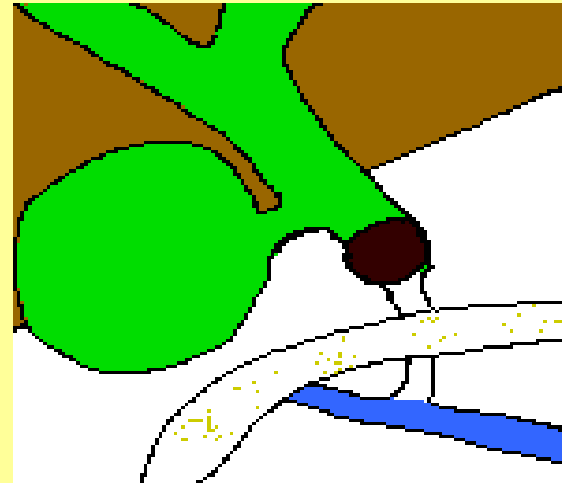
Other causes:

- *Strictures of the common bile duct, ductal carcinoma*
- *Pancreatitis*
- *Pancreatic pseudocysts*
- *Mirizzi's syndrome*

NORMAL



OBSTRUCTIVE



**Developmental abnormalities of bile ducts**

Rare instances in which the bile ducts do not develop normally and the flow of bile is interrupted. These diseases usually are present from birth though some of them may first be recognized in childhood or even adulthood.

Examples are:

- *Cysts of the bile duct* (choledochal cysts)
- *Caroli's disease*

<b>Pregnancy</b>	
<b>Intrahepatic cholestasis of pregnancy</b>	<ul style="list-style-type: none"><li>□ Bile pools in the gallbladder because of the pressure in the abdomen with pregnancy.</li></ul>
<b>Cholestasis of pregnancy</b>	<ul style="list-style-type: none"><li>□ Occur during the third trimester</li><li>□ Is often accompanied by itching, the itching can be severe, but there is treatment (ursodeoxycholic acid or ursodiol).</li><li>□ Pregnant women with cholestasis usually do well although they may be at greater risk for developing gallstones.</li><li>□ There appears to be an increased risk to the fetus for developmental abnormalities.</li><li>□ It has been hypothesized that it is the increased estrogens during pregnancy that are responsible for the cholestasis of pregnancy.</li></ul>

## **Pre-eclampsia**

- Previously called *toxemia of pregnancy*
  - Occurs during the second half of pregnancy
- It may result in
- *high blood pressure*
  - *fluid retention*
  - *damage to the kidneys*
  - *anemia ,reduced numbers of platelets* due to destruction of red blood cells and platelets.
  - It often causes *problems for the fetus*.
  - Although the bilirubin level in the blood is elevated in pre-eclampsia, it usually is mildly elevated, and jaundice is uncommon. Treatment of pre-eclampsia usually involves delivery of the fetus as soon as possible if the fetus is mature.

## **Acute fatty liver of pregnancy**

- Unclear cause
- Often is associated with pre-eclampsia
- Occurs late in pregnancy and results in failure of the liver.
- There is an increased risk of infant death. Jaundice is common, but not always present in AFLP.
- Treatment usually involves delivery of the fetus as soon as possible.

# Causes of Jaundice

## PRE-HEPATIC

- Physiologic Jaundice/Neonatal Jaundice
- Hemolytic Anemia
- Hemolysis caused by genetic diseases, such as glucose 6-phosphate dehydrogenase deficiency
- Hereditary RBC Disorders ex. Sickle cell anemia, spherocytosis
- Hemolysis in Malaria
- Splenomegaly
- Ineffective erythropoiesis
- Side effects of drugs
- Defects in bilirubin metabolism
- Kidney failure
- Erythroblastosis fetalis
- Transfusions
- Diseases of small blood vessels ex. microangiopathic hemolysis
- Poisons ex. Snake venom
- Artificial heart valves

# Causes of Jaundice

## **INTRA-HEPATIC**

- Hepatitis
- Hepatotoxicity
- Hypoxic
- Autoimmune
- Alcoholic liver disease ex. cirrhosis
- Primary biliary cirrhosis
- Failure of conjugation eg. Crigler-Najjar
- Gilbert's Syndrome
- Metastatic Carcinoma.
- Neonatal Jaundice
- Starvation
- Side effects of drugs
- Circulating infections

# Causes of Jaundice

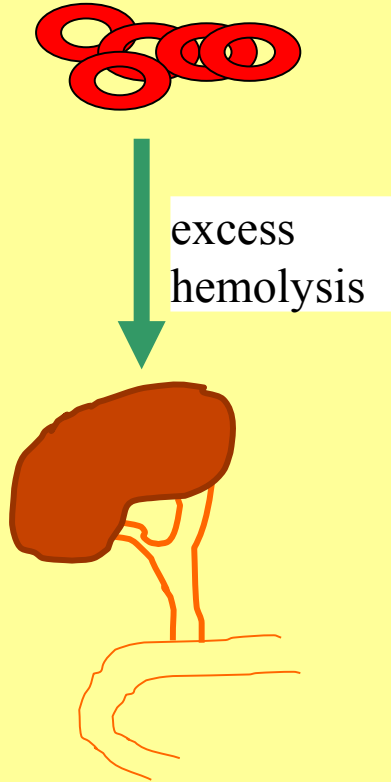
## POST-HEPATIC (obstructive)

- Gallstones
- Pancreatic cancer in the head of the pancreas.
- Strictures of the common bile duct
- Ductal Carcinoma
- Pancreatitis
- Pancreatic pseudocysts
- Mirizzi's Syndrome
- Birth defects
- infections that damage the bile ducts
- Side effects of drugs
- Physical injury.
- Pregnancy



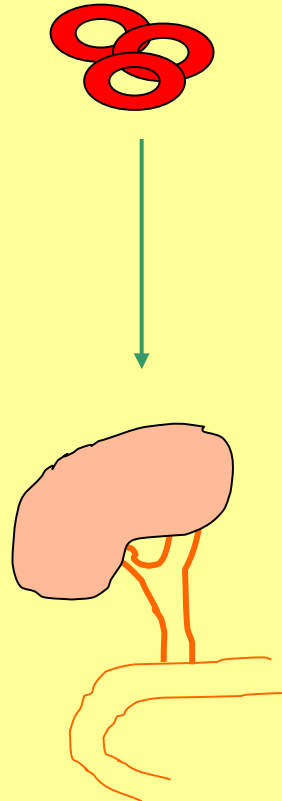
# Examples of hyperbilirubinemia

## A. Hemolytic anemia



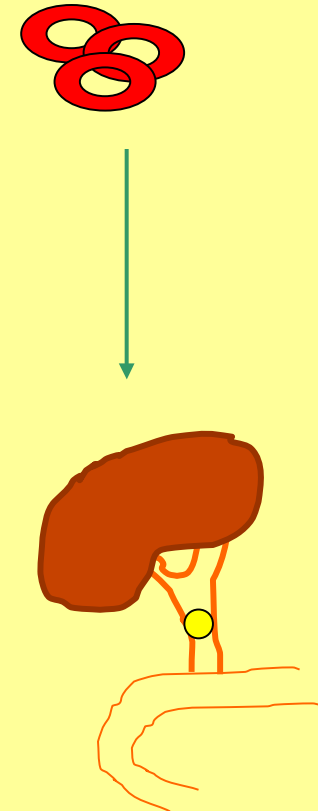
- ↑ unconjugated bilirubin (in blood)
- ↑ conjugated bilirubin (released to bile duct)

## B. Hepatitis



- ↑ unconjugated bilirubin (in blood)
- ↑ conjugated bilirubin (in blood)

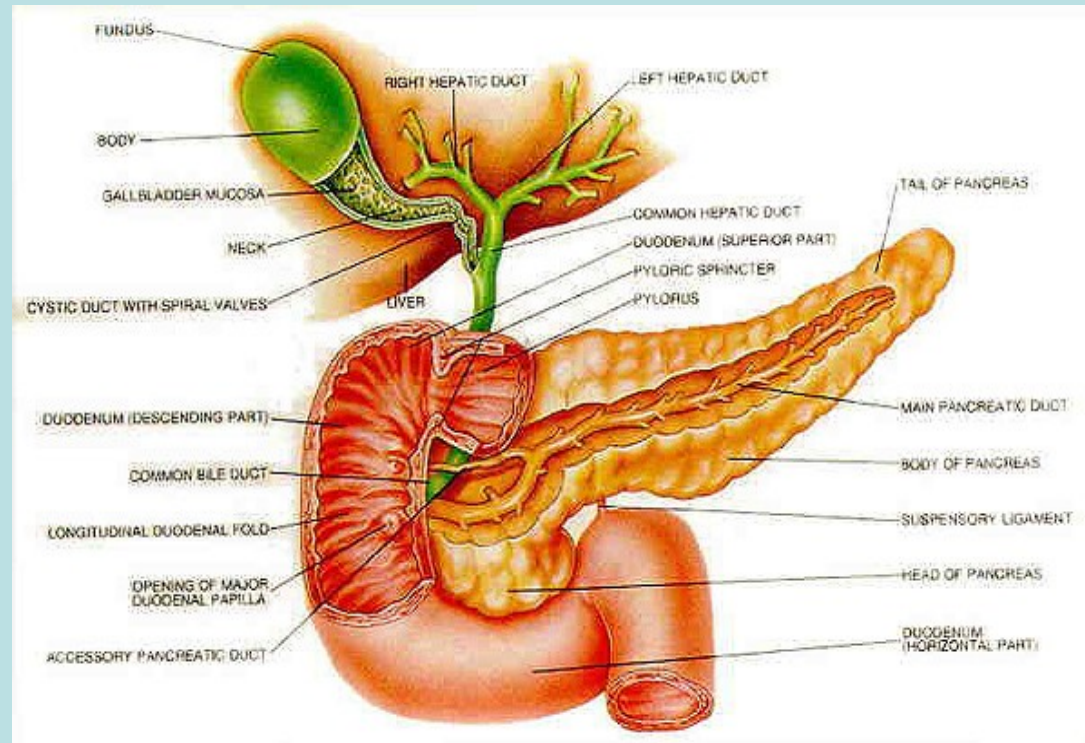
## C. Biliary duct stone



- ↑ unconjugated bilirubin (in blood)
- ↑ conjugated bilirubin (in blood)

# Hepatobiliary System & Jaundice

1. Overload bilirubin that the liver can't remove
2. Defect in the liver that prevents removal bilirubin from blood, subsequent conjugation or secretion into bile.
3. Bile duct obstruction
4. The decreased conjugation, secretion, or flow of bile that can result in jaundice is referred to as cholestasis: however, cholestasis does not always result in jaundice.

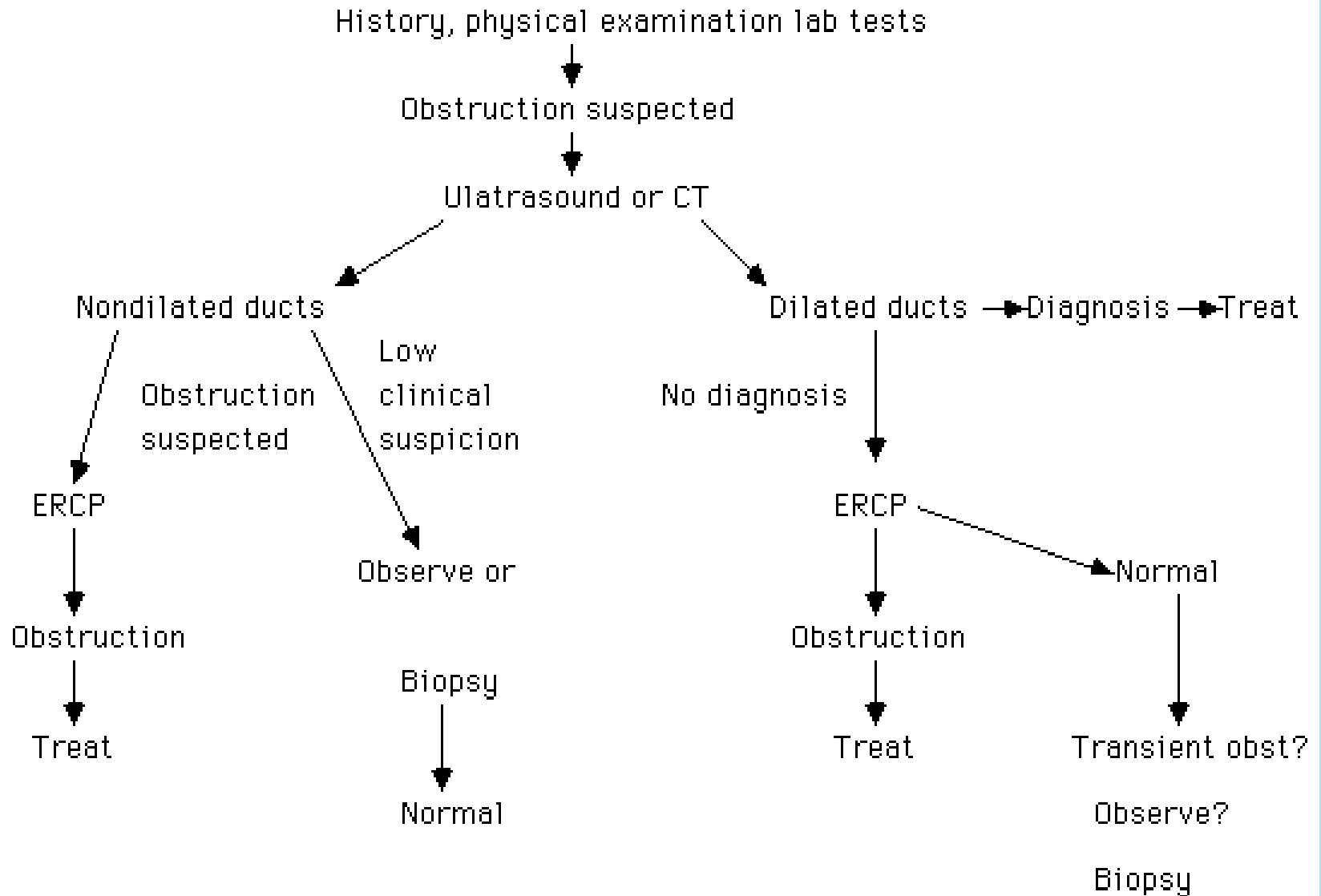


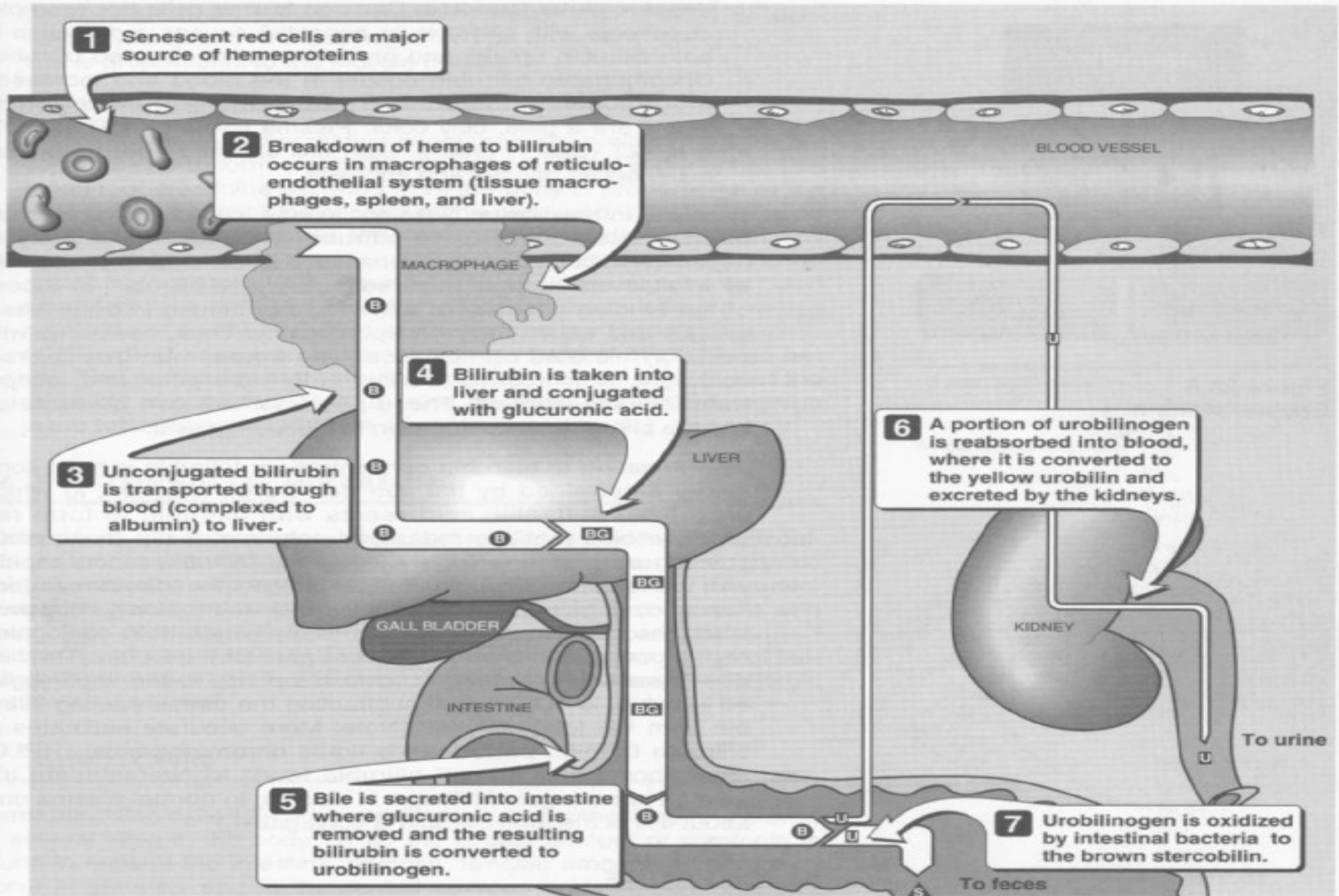
- Not all causes of jaundice are the direct result of liver disease (e.g. extravascular hemolysis and extrahepatic bile duct obstruction).
- Most diseases resulting in jaundice are acquired with viral hepatitis representing the most common cause in adults and physiologic jaundice of the newborn, the most common cause in children.
- A few genetic diseases also directly involve the liver (e.g. Gilbert syndrome, Wilson's disease).

# Causes of Jaundice

- Jaundice occurs when there is
- **1) Too much bilirubin being produced for the liver to remove from the blood.** (For example, patients with hemolytic anemia have an abnormally rapid rate of destruction of their red blood cells that releases large amounts of bilirubin into the blood).
- **2) A defect in the liver that prevents bilirubin from being removed from the blood, converted to bilirubin/glucuronic acid (conjugated) or secreted in bile.**
- **3) Blockage of the bile ducts that decreases the flow of bile and bilirubin from the liver into the intestines.** (For example, the bile ducts can be blocked by cancers, gallstones, or inflammation of the bile ducts).
- The decreased conjugation, secretion, or flow of bile that can result in jaundice are collectively referred to as cholestasis: \*remember that cholestasis does not always result in jaundice.

## Algorithm for Workup of Jaundice





**Figure 23.7**

Catabolism of heme ● = bilirubin; BG = bilirubin diglucuronide; U = urobilinogen; A = stercobilin.

Check urinalysis; measure serum total and direct bilirubin levels.

All tests normal

Look for "pseudojaundice."

High vegetable intake

Urine positive for bilirubin; increased total bilirubin level and increased direct bilirubin level

Conjugated hyperbilirubinemia

Liver function tests (AST, ALT, AP, GGT, and CBC)

No diagnosis apparent?

Screen for hepatitis A, B, and C.

No diagnosis apparent?

Screen for autoimmune disorders (ANA, anti-LKM, anti-smooth muscle)

If no obvious diagnosis, abdominal US or CT

Intrahepatic disease (see Table 1)

Extrahepatic disease (see Table 2)

Still no apparent diagnosis?

Consider cholangiography or liver biopsy.

Urine negative for bilirubin; increased total bilirubin level and normal direct bilirubin level

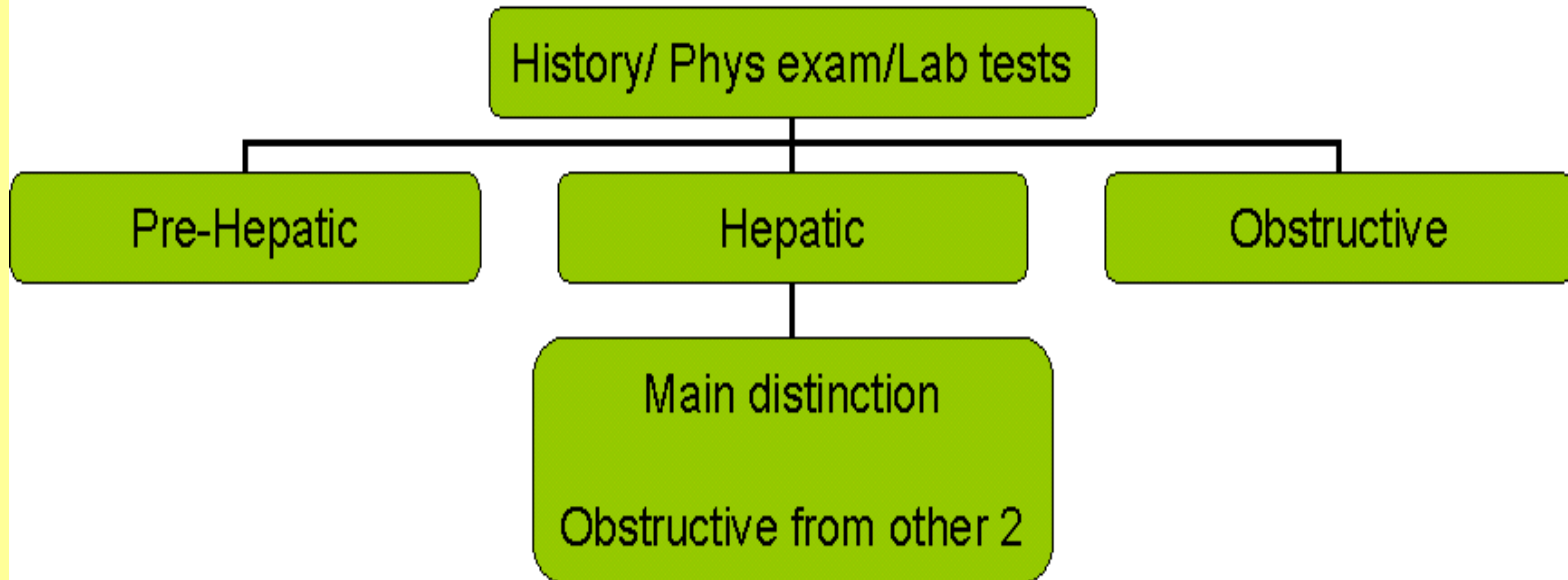
Unconjugated hyperbilirubinemia

Hemolysis, drug toxicity, genetic syndrome (Gilbert syndrome), hematoma

# Clinical diagnosis



# Evaluation of Jaundice

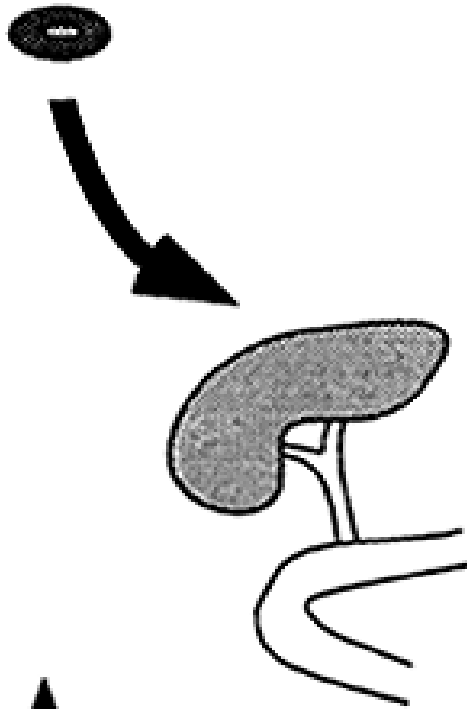


# Jaundice - Laboratory Tests

	<b>Haemolytic Jaundice</b>	<b>Obstructive Jaundice</b>	<b>Hepatocellular Jaundice</b>
<b>Plasma Bilirubin</b>	Increased (unconjugated)	Increased (conjugated)	Increased (biphasic)
<b>Urine Bilirubin</b>	Absent	Increased	Often absent
<b>Urine bilinogen</b>	Increased	Absent	May be increased or decreased
<b>Stercobilin and colour of faeces</b>	Increased, Dark	Decreased, Pale	Decreased or Normal, Pale or Normal
<b>Plasma Alkaline Phosphatase</b>	Normal	Increased	Increased
<b>Plasma Amino-transferases (ALT, AST)</b>	Normal	Increased Slightly	Increased
<b>Prothrombin time</b>	Normal	Prolonged, not corrected by IV vitamin K	Prolonged corrected by IV vitamin K

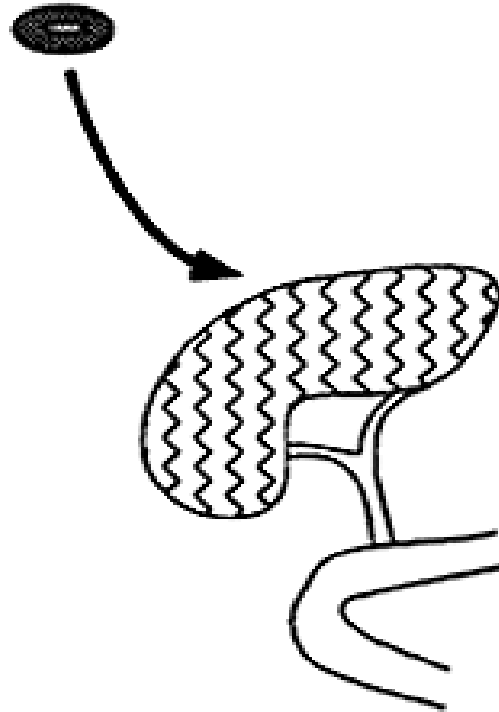
# Hemolytic Anemia ("Indirect"), Hepatitis ("Mixed"), Biliary Duct Stones ("Direct")

**Hemolytic anemia**



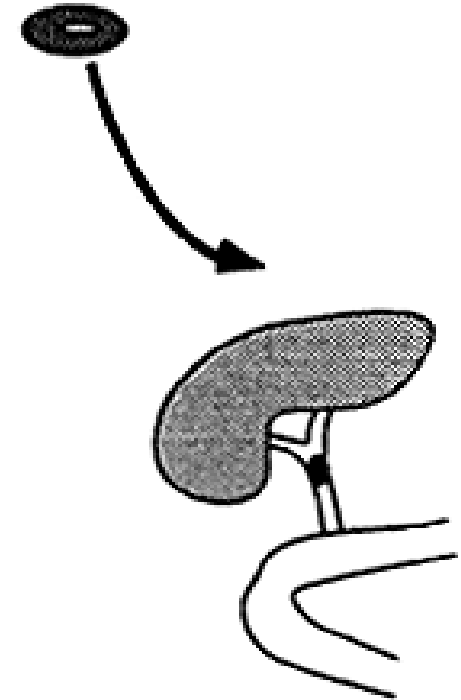
↑ unconjugated bilirubin  
↑ conjugated bilirubin

**Hepatitis**



↑ unconjugated bilirubin  
↑ conjugated bilirubin

**Biliary duct stone**



↑ unconjugated bilirubin  
↑ conjugated bilirubin

**Table 1. Differential Diagnosis of an Unconjugated Hyperbilirubinemia**

Increased production

Decreased Clearance

Physiologic Jaundice

Isoimmunization (ABO, Rh, other)

RBC biochemical defects

RBC structural abnormalities

hemoglobinopathies

Infections

Polycythemia

Sequestered blood

Physiologic Jaundice

Breast milk Jaundice

Deficient conjugation (Crigler-Najjar)

Prematurity

Increased enterohepatic circulation

Infant of a diabetic mother

Hypothyroidism

? deficient hepatic uptake

**Table 2. Differential Diagnosis of a Conjugated Hyperbilirubinemia**

Intrahepatic

Extrahepatic

Idiopathic Neonatal Hepatitis

Inborn errors of metabolism

Other genetic diseases

Congenital infections

Congenital hepatitis

Toxic hepatitis (TPN and certain drugs)

Extrahepatic Biliary Atresia

Bile duct stenosis

Bile duct perforation

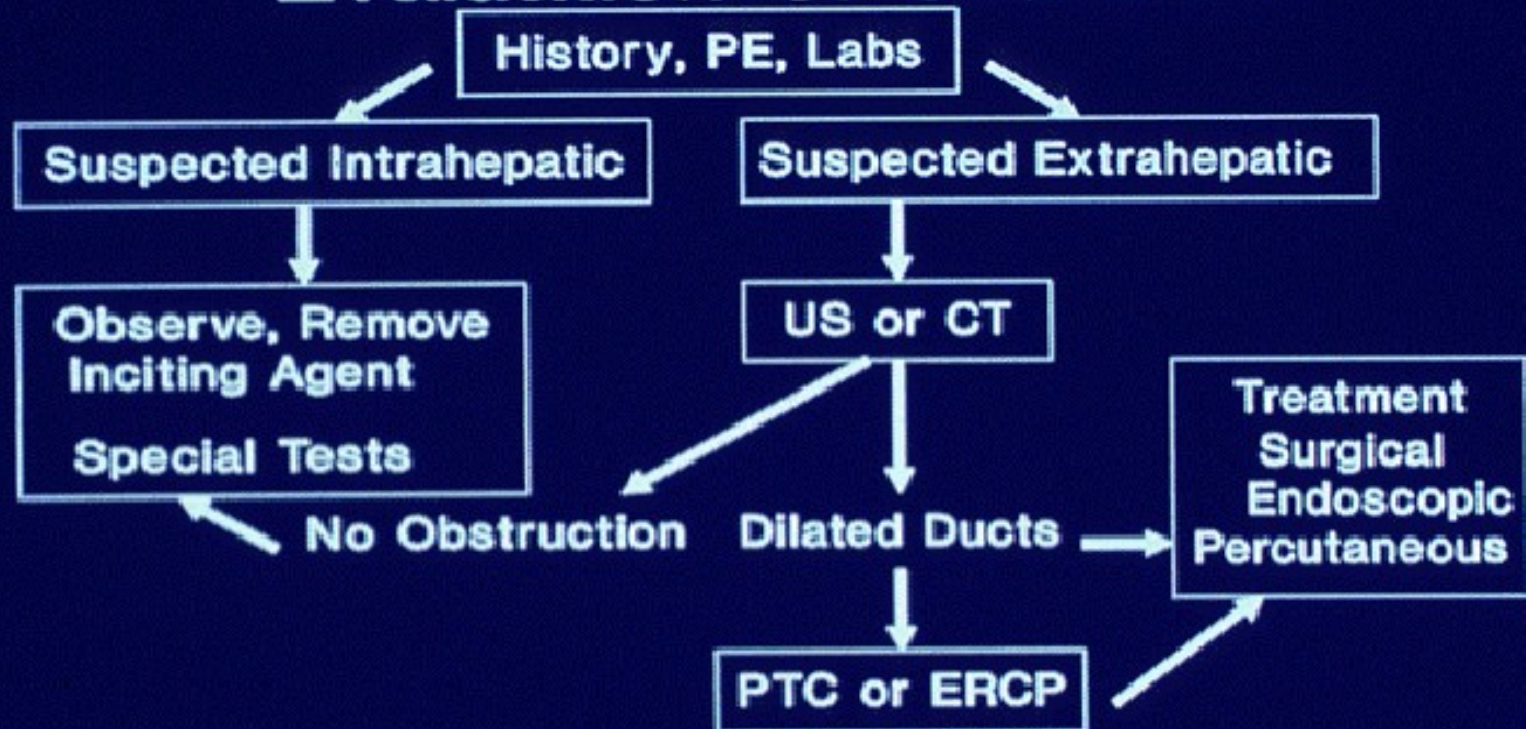
Choledocal cyst

Cholelithiasis

Bile duct plug

# Evaluation Protocol

## Evaluation of Jaundice



- Additional detail for those who want to delve deeper into the issue of Jaundice, follows.

- **Genetic disorders causing jaundice**
- **There are several rare genetic disorders present from birth that give rise to jaundice.**
- **Crigler-Najjar syndrome is caused by a defect in the conjugation of bilirubin in the liver due to a reduction or absence of the enzyme responsible for conjugating the glucuronic acid to bilirubin.**
- **Dubin-Johnson and Rotor's syndromes are caused by abnormal secretion of bilirubin into bile.**
- **The only common genetic disorder that may cause jaundice is Gilbert's syndrome which affects approximately 7% of the population.**



**Jaundice can be caused by a malfunction in  
any of the three phases of bilirubin  
production**

**PREHEPATIC CAUSES**

**INTRAHEPATIC CAUSES**

**POSTHEPATIC CAUSES**

# Pre hepatic Jaundice

**Prehepatic/hemolytic jaundice,**  
where too many red blood cells  
are broken down.

- Normally, the human body produces about 4 mg per kg of bilirubin per day from the metabolism of heme.
- Approximately 80 percent of the heme moiety comes from catabolism of red blood cells, with the remaining 20 percent resulting from ineffective erythropoiesis and breakdown of muscle myoglobin and cytochromes.
- Bilirubin is transported from the plasma to the liver for conjugation and subsequent excretion.

- The liver has the capacity to conjugate and excrete over 3000 mg bilirubin per day, whereas the normal production of bilirubin is only 300 mg/day.
- This excess capacity allows the liver to respond to increased heme degradation with a corresponding **increase in conjugation and secretion of bilirubin diglucoronide.**

- The conditions that lead to pre hepatic jaundice include:
- 1) rapid destruction of red blood cells (referred to as hemolysis),
- 2) a defect in the formation of red blood cells that leads to the over-production of hemoglobin in the bone marrow (called ineffective erythropoiesis), or
- 3) absorption of large amounts of hemoglobin when there has been much bleeding into tissues (e.g., from hematomas, collections of blood in the tissues).
  
- Some of the situations that cause hemolytic crises or and pre hepatic jaundice are listed in the next slide.

- Prehepatic jaundice may result when there is excessive heme degradation as occurs in the hemolytic anemias.....in which there is a reduced abnormal half life of RBC, and haemolysis due to:

### *Intrinsic factors*

#### 1. Membrane disorders

( e.g. Spherocytosis)

#### 2. Enzyme abnormalities

Glucose-6-phosphate dehydrogenase deficiency

#### 3. Autoimmune disorders

Parasite invasion (malaria), bacterial

#### 4. Defect in Hb structure

(e.g. Sickle cell disease, thalasseмииs)

### *Extrinsic factors*

#### 5. Drugs

Chemical haemolysis

- With severe hemolysis, more bilirubin is released into the blood than can be transported to and conjugated in the liver.
- **Unconjugated and total bilirubin increase and may produce jaundice and kernicterus.**

- Prehepatic Jaundice occurs when there is **too much bilirubin being produced for the liver to remove from the blood, as a result of hemolytic crises for what ever cause.**
- Prehepatic jaundice results when there is **bilirubin production beyond the disposal ability of the liver.**
- (For example, patients with hemolytic anemia have an abnormally rapid rate of destruction of their red blood cells that releases large amounts of bilirubin into the blood).

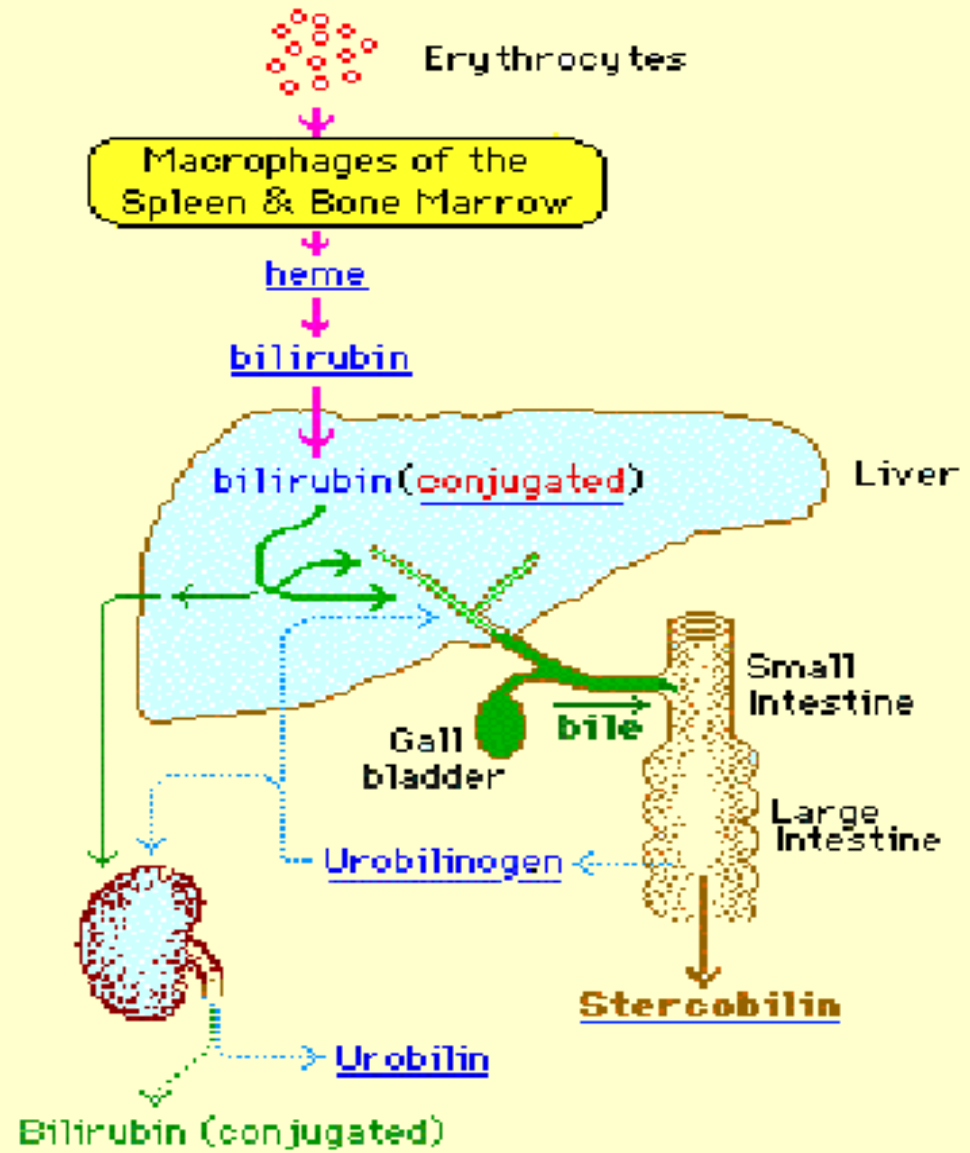


- **Pre-hepatic jaundice results from the inability of the liver to handle an increased bilirubin load, due to the saturation of the enzyme glucuronyl transferase.**
- **When the enzyme glucuronyl transferase becomes saturated conjugation of bilirubin stops resulting in excessive unconjugated bilirubin in the blood resulting in jaundice**
- **As a result of this, the unconjugated bilirubin is elevated in blood.**

- **The yellow discolouration is less marked** than that seen in hepatic and extra-hepatic aetiologies, but it **may be difficult to observe clinically**.
- **Total serum bilirubin is increased and it is predominantly unconjugated.**
- **There is no urinary bilirubin.**
- **Serum aminotransferases, alkaline phosphatase, albumin and globulin are all within the normal range, because there is no damage of liver cells.**
- **Hemolytic crisis may be confirmed by low hemoglobin and elevated reticulocyte counts**

# Pre-Hepatic Jaundice Clinical Features

- Due to excess production of bilirubin by hemolysis or blood disease
- Jaundice not typically severe
- Increase in blood indirect ( bilirubin unconjugated plasma bilirubin
- Normal urobilinogen in urine
- Normal stercobilin with normal stool color
- AP. ALT, AST - normal



# Positive Signs for Pre-Hepatic Jaundice

- Lack of bile in the urine
- Rapid onset of jaundice (acute hemolysis)
- Jaundice with fever
- Jaundice with splenomegaly
- Yellow skin color of a lighter degree than seems indicated for degree of bilirubinemia
- Anemia with microspherocytosis
- Anemia with positive Coombs Test
- Increased urobilinogen in urine or stool especially when urine lacks bile.
- Absence of bradycardia, itching, or hemorrhagic tendency
- Familial history of jaundice - especially if cured by splenectomy
- Cholelithiasis at an early age - or similar history in relatives
- Frank reticulocytosis with jaundice
- Abnormal rouleau formation
- Increase in RBC fragility
- Hyperbilirubinemia of indirect Van den Berg type with negative or low direct type
- Hepatic function tests normal in a jaundiced patient
- Color of stools darker than usual
- Bone marrow showing normoblastic hyperplasia
- History of "abdominal crisis" with jaundice
- Positive blood culture with a hemolytic organism
- Ingestion of chemical with a known hemolytic effective
- Transfusion reaction
- Jaundice in heart failure

- Glucose 6 Phosphate Dehydrogenase is of special interest, and so a few notes are included here.
- Deficiencies of certain enzymes of the pentose phosphate pathway are major causes of hemolysis of red blood cells, resulting in one type of hemolytic anemia.
- **The principal enzyme involved is glucose-6-phosphate dehydrogenase (G6PD).**
- G6PD deficiency is an inherited disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents.

- G6PD deficiency is the most common disease producing enzyme abnormality in humans, affecting more than 200 million individuals worldwide.
- More than 200 million people in the world may have genetically determined low levels of this enzyme.
- A mutation present in some populations causes a deficiency in G6PD, with consequent impairment of the generation of NADPH.
- This X-linked enzyme deficiency is, in fact, a family of deficiencies caused by over 400 different mutations in the gene coding for G6PD.

- The impairment in G6PD deficiency is manifested as red cell hemolysis when the susceptible individual is subjected to oxidants, such as the anti-malarial primaquine, aspirin, or sulfonamides, or when the susceptible individual has eaten fava beans.
- The life span of many individuals with G6PD deficiency is somewhat shortened as a result of complications arising from chronic hemolysis.

# Hepatic Jaundice



- In the hepatocyte, the unconjugated bilirubin is conjugated with a sugar via the enzyme glucuronosyltransferase and is then soluble in the aqueous bile.
- Unconjugated bilirubin is insoluble in water but soluble in fats. Therefore, it can easily cross the blood-brain barrier or enter the placenta.
- Hepatic jaundice results from failure in the function of hepatocytes to take up, metabolize or excrete bilirubin.

# Etiology of intrahepatic hyperbilirubinemia

## Unconjugated Types:

### Gilbert's Syndrome:

- hypofunction liver enzyme: bilirubin-glucuronoside glucuronosyl transferase (5% US population!)

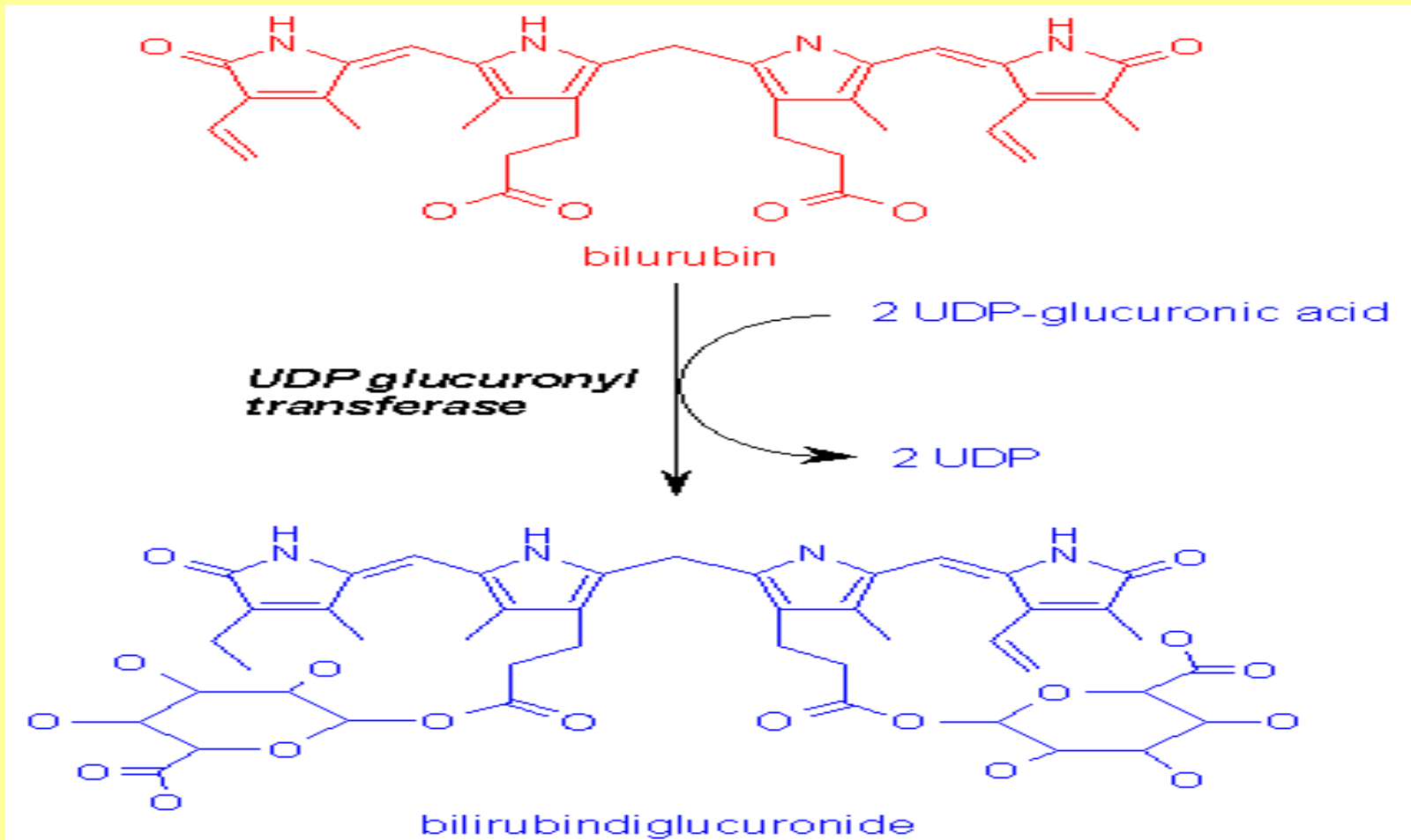
### Crigler-Najjar syndrome:

- complete absence bilirubin-glucuronoside glucuronosyl transferase

### Wilson Disease:

- defect in serum ceruloplasmin leading to abnormal copper metabolism

In Gilbert- & Crigler Najjar - syndrome there is a respiratory hypofunction of bilirubin-glucuronoside glucuronosyl transferase to absence: no complex formation, no excretion of bilirubin into bile duct!



# Gilbert's syndrome

- Gilbert's Syndrome is a common and benign, hereditary disorder that affects approximately 5-7% of the U.S. population.
- This inherited disorder is thought to be due to an inborn error of bilirubin metabolism that causes a mild reduction in the activity of glucuronosyltransferase - the enzyme responsible for conjugating the glucuronic acid to bilirubin.
- The increase in bilirubin in the blood usually is mild and infrequently reaches levels that cause jaundice.
- It manifests itself during periods of stress, fasting or illness with symptoms such as mild jaundice, weakness, fatigue, nausea and abdominal pain.
- There is a slight to moderate increase in the indirect fraction of serum bilirubin but all other liver function values are within normal limits.
- These changes are usually transient in nature and there is no need to pursue treatment or liver biopsy.

# Crigler-Najjar Syndrome

- A rare genetic defect (autosomal recessive) where there is the inability to form bilirubin glucuronide.
- This is due to the absence of the enzyme bilirubin-glucuronoside glucuronosyl transferase leading to jaundice and irreversible brain damage in the severe form.

# Crigler-Najjar Syndrome

## Background

- Crigler-Najjar syndrome (CNS) is a rare disorder of bilirubin metabolism and has 2 distinct forms: type 1 and type 2. Type 1 CNS is associated with neonatal jaundice and neurologic manifestations, whereas type 2 CNS (also called Arias syndrome) manifests as a lower serum bilirubin level. Affected individuals may survive to adulthood without any neurological impairment.

# Pathophysiology

- Effective elimination of bilirubin requires its conversion to polar derivatives. In humans, conjugation of bilirubin with the sugar molecule glucuronic acid accomplishes this conversion in a process called glucuronidation.
- CNS is elicited by a lack or deficiency of the enzyme uridine diphosphate glycosyltransferase (UGT). Type 1 CNS is associated with an almost complete absence of the enzyme, which results in very high levels of unconjugated hyperbilirubinemia (up to 50 mg/dL) at birth. Lower levels of serum bilirubin (up to 20 mg/dL) and markedly depressed activity of hepatic UGT are characteristic of type 2 CNS (Arias syndrome). Importantly, treatment with phenobarbital can induce the expression of UGT in patients with type 2 CNS, with a decrease in the serum bilirubin level of approximately 25%.

# Frequency:

- **Mortality/Morbidity:** If left untreated, type 1 CNS is uniformly lethal secondary to the development of kernicterus by age 2 years. Although much rarer, bilirubin encephalopathy can also occur in type 2 CNS, usually when patients experience a superimposed infection or stress.
- **Race:** CNS is thought to affect all races equally.
- **Sex:** CNS occurs in both sexes equally.
- **Age:** If left untreated, type 1 CNS is uniformly lethal secondary to the development of kernicterus by age 2 years. Although much rarer, bilirubin encephalopathy can also occur in type 2 CNS, usually when patients experience a superimposed infection or stress.



# CLINICAL

- **History:** Because of its autosomal recessive transmission, consanguinity is a risk factor for CNS, especially type 1 CNS.
- **Physical:** Persistent jaundice is present at or soon after birth in type 1 CNS. Jaundice may not manifest until later in infancy or childhood in type 2 CNS. Kernicterus is the most worrisome consequence of hyperbilirubinemia and occurs in virtually all patients with untreated type 1 CNS, especially in the first few days of life. Bilirubin encephalopathy is rare in patients with type 2 CNS, but it can be induced by factors such as infection, anesthesia, or drug use. Clinical manifestations of kernicterus are hypotonia, deafness, oculomotor palsy, lethargy, and, ultimately, death.
- **Causes:** Both type 1 CNS and type 2 are transmitted by autosomal recessive inheritance. Alterations in the coding sequence of the *UGT1* gene result in absent or reduced UGT activity, with marked impairment of bilirubin conjugation. The *UGT1* gene is located on 2q37. Several isoforms of *UGT1* enzyme exist based on the variability in the amino-terminal region of the final protein. These differences are the result of alternative splicing among 10 different types of exon 1 at the 5' end of the *UGT1* gene and constant exons 2-5 at the 3' end. Thus, the different *UGT1* isoforms are distinguished according to the type of exon 1 they contain.

# WORKUP

- **Imaging Studies:**
- Findings on abdominal imaging studies, such as plain x-rays, CT scan, or ultrasound, are normal in CNS.
- **Histologic Findings:** Liver histology findings are normal in CNS.

# TREATMENT

- **Medical Care:** Patients with type 2 CNS may not require any treatment or can be managed with phenobarbital. By contrast, prompt treatment of kernicterus is required in patients with type 1 CNS to avoid the potentially devastating neurological sequelae.
- Emergent management of bilirubin encephalopathy involves plasma exchange transfusion, which acts by removing the bilirubin-saturated albumin and provides free protein, which draws bilirubin from the tissues.
- Plasma exchange should be accompanied by long-term phototherapy, which helps in the conversion of bilirubin to more soluble isoforms that can be excreted in the urine. Oral calcium phosphate may be a useful adjuvant to phototherapy in type 1 CNS.
- Therapies based on gene and cell transfer techniques, although largely experimental at the present time, are likely to play an important role in the management of CNS in the future.
- Inhibitors of heme oxygenase, such as tin protoporphyrin or tin-mesoporphyrin, may be helpful in reducing bilirubin levels emergently, but the effect is short-lived.
- **Surgical Care:** Liver transplantation has been attempted in select patients with type 1 CNS and has achieved good success rates.

# MEDICATION

- The goals of pharmacotherapy are to reduce morbidity and to prevent complications.
- Drug Category: *Barbiturates* -- Used to avoid potentially devastating neurological sequelae in type 1 CNS and for the management of neurological symptoms in type 2 CNS.

# Wilson's Disease

- Is an autosomal recessive disease that is due to abnormal copper metabolism and there is a defect in serum ceruloplasmin.
- Findings: copper deposition in liver, there is most likely to be cirrhosis, there is increased density, degenerative changes in brain, arthritis, and Kayser-Fleischer ring in Descemet's membrane.

# Etiology of intrahepatic hyperbilirubinemia (cont)

## **Conjugated Types**

### **Intrahepatic inflammation:**

- Hepatitis A-C due to viruses, alcohol or autoimmune disorders and also Sarcoidosis

- **Sarcoidosis:** disease of unknown etiology in which there are chronic inflammatory granulomatous lesions in lymph nodes and other organs.

### **Dubin-Johnson Syndrome:**

- Abnormality transport bilirubin from liver leading to intrahepatic Cholestasis

- **Cholestasis:** An arrest of the normal flow of bile. This may occur due to a blockage of the bile ducts resulting in an elevation of bilirubin in the bloodstream (jaundice).

### **Rotor's Syndrome:**

- Defect excretion of unconjugated bilirubin into biliary canaliculi with intrahepatic cholestasis as a result.

- **Acute inflammation of the liver**
- Any condition in which the liver becomes inflamed can reduce the ability of the liver to conjugate (attach glucuronic acid to) and secrete bilirubin.
- Common examples include acute viral hepatitis, alcoholic hepatitis, and Tylenol-induced liver toxicity.

- **Chronic liver diseases**
- Chronic inflammation of the liver can lead to scarring and cirrhosis, and can ultimately result in jaundice.
- Common examples include chronic hepatitis B and C, alcoholic liver disease with cirrhosis, and autoimmune hepatitis.



- **Infiltrative diseases of the liver**

- Infiltrative diseases of the liver refer to diseases in which the liver is filled with cells or substances that don't belong there.
- The most common example would be metastatic cancer to the liver, usually from cancers within the abdomen.
- Uncommon causes include a few diseases in which substances accumulate within the liver cells, for example, iron (hemochromatosis), alpha-one antitrypsin (alpha-one antitrypsin deficiency), and copper (Wilson's disease).

# Dubin-Johnson Syndrome

- Dubin-Johnson Syndrome is an inherited (autosomal recessive) disorder that is characterized by long -standing mild jaundice. This occurs secondary to an abnormality in the transport of bilirubin from the liver to the biliary system which leads to an accumulation of bilirubin in the liver.
- One study confirms that **Dubin-Johnson** syndrome is a cause of neonatal cholestasis.
- Avoidance of alcohol and medications which can affect the liver is important.

# Cholestasis

**Cholestasis = Problems with bile flow.**

- Many drugs have been shown to play a role in the development of cholestatic jaundice.
- Agents classically identified with drug-induced liver disease are **acetaminophen, penicillins, oral contraceptives, chlorpromazine (Thorazine), and estrogenic or anabolic steroids.**
- Cholestasis can develop during the first few months of oral contraceptive use and may result in jaundice.

# Cholestasis

**Alternative Names:** Intrahepatic cholestasis; Extrahepatic cholestasis

**Definition:** Cholestasis is any condition in which bile excretion from the liver is blocked, which can occur either in the liver or in the bile ducts.

**Causes, incidence, and risk factors:**

**Extrahepatic cholestasis** (which occurs outside the liver) can be caused by:

- bile duct tumors
- strictures

- cysts

- diverticula

- stones in the common bile duct

- pancreatitis

- pancreatic tumor or pseudocyst

- primary sclerosing cholangitis

- compression due to a mass or tumor on a nearby organ

- Intrahepatic cholestasis is associated with
- hyper conjugated bilirubinemia
- Increase in both serum indirect and direct bilirubin
- It is caused by liver damage or disease: eg cirrhosis, hepatitis and may also occur in pregnancy:

**Intrahepatic cholestasis** (which occurs inside the liver) can be caused

by: sepsis (generalized infection)

bacterial abscess

*drugs such as: gold salts, nitrofurantoin, anabolic steroids, oral contraceptives, chlorpromazine, prochlorperazine, sulindac, cimetidine, erythromycin, tobutamide, imipramine, ampicillin and other penicillin-based antibiotics.*

lymphoma

tuberculosis

primary biliary cirrhosis

primary sclerosing cholangitis

viral hepatitis (A,B,C, etc.)

alcoholic liver disease

pregnancy

# Jaundice due to DRUGS

- Many drugs can cause jaundice and/or cholestasis.
- Some drugs can cause liver inflammation (hepatitis) similar to viral hepatitis.
- Other drugs can cause inflammation of the bile ducts, resulting in cholestasis and/or jaundice.
- Drugs also may interfere directly with the chemical processes within the cells of the liver and bile ducts that are responsible for the formation and secretion of bile to the intestine. As a result, the constituents of bile, including bilirubin, are retained in the body.
- The best example of a drug that causes this latter type of cholestasis and jaundice is estrogen.
- The primary treatment for jaundice caused by drugs is discontinuation of the drug. Almost always the bilirubin levels will return to normal within a few weeks, though in a few cases it may take several months.

# Drugs

- Drugs that can increase bilirubin measurements:
  - Allopurinol
  - Anabolic steroids
  - Sulfonamides
  - Antimalarials
  - Azathioprine
  - Chlorpropamide
  - Cholinergics
  - Codeine, morphine
  - Diuretics
  - Steroids
  - Nicotinic acid
  - Rifampin
  - Salicylates



- Drugs that can decrease bilirubin measurements include:

- Barbiturates
- Caffeine
- Penicillin
- High-dose salicylates

# List of Drugs causing jaundice-like symptoms

- **Mercury**
- **Certain antibiotics**
- **Erythromycin**
- **Sulfa**
- **Certain antidepressants**
- **Certain cancer drugs**
- **Aldomet**
- **Rifampin**
- **Steroids**
- **Certain anti-diabetic drugs**
- **Chlorpropamide**
- **Tolbutamide**
- **Oral contraceptives**
- **Testosterone**
- **Propylthiouracil**
- **Carbon tetrachloride - a cleaning chemical that causes liver damage if inhaled or swallowed.**
- **Snake venom**

- **Amoxicillin**: Amoxicillin causes a moderate rise in SGOT levels, SGPT levels, or both, but the significance of this finding is unknown.
- Hepatic dysfunction, including jaundice, hepatic cholestasis, and acute cytolytic hepatitis, have been reported.
- Sometimes certain drugs such as **chlorpromazine** (an anti-psychotic drug) may inhibit bilirubin excretion by the liver, causing jaundice

# Acetaminophen (Paracetamol) Poisoning

- **Acetaminophen (Tylenol) Poisoning** Acetaminophen is one of the most common medications found in households. It is used for the treatment of pain and to lower fever.
- **Acetaminophen is the active ingredient in Tylenol.** It is also found in many other over-the-counter medications you can buy at the drug store and in prescription drugs your doctor prescribes: Common names include Actifed, Alka-Seltzer Plus, Benadryl, Butalbital, Co-Gesic, Contac, Darvocet, Excedrin, Fioricet, Lortab, Midrin, Norco, Percocet, Robitussin, Sedapap, Sinutab, Sudafed, TheraFlu, Unisom With Pain, Vick's Nyquil and DayQuil, Vicodin, Wygesic, and Zydone.

- Over many years, it has been used countless times by many people and it has proven to be a safe and effective medication.
- **However, if taken in excess amounts (overdose, whether on purpose or by accident), acetaminophen can cause life-threatening illness.**
- **Acetaminophen in overdose can seriously damage the liver.**
- **Toxic doses (i.e. two to three times the maximum therapeutic dose) cause a serious, potentially fatal hepatotoxicity.**
- **Renal toxicity can also occur.**

- **These toxic effects occur when the liver enzymes catalysing the normal conjugation reactions are saturated, causing the drug to be metabolised by the mixed function oxidases.**
- **The resulting toxic metabolite, N-acetyl-p benzoquinone imine, is inactivated by conjugation with glutathione, but when glutathione is depleted the toxic intermediate accumulates and reacts with nucleophilic constituents in the cell.**
- **This causes necrosis in the liver and also in the kidney tubules.**
- **The initial symptoms of acute paracetamol poisoning are nausea and vomiting, the hepatotoxicity being a delayed manifestation that occurs 24—48 hours later.**

Toxic dose of paracetamol

P450 mixed function oxidases

*N*-Acetyl-*p*-benzoquinone imine (NAPBQI)

Oxidation of SH groups on cellular Ca<sup>2+</sup> ATPases

GSH

NAPBQI-GSH adduct

NAPBQI-protein adducts

Lipid peroxidation

Sustained increase in [Ca<sup>2+</sup>]<sub>i</sub>

GSH depletion

Increased membrane permeability

Oxidative stress

Stimulation of Ca<sup>2+</sup>-activated degradative enzymes

CELL DEATH

**Fig. 52.1** Potential mechanisms of liver cell death resulting from the metabolism of paracetamol to *N*-acetyl-*p*-benzoquinone imine (NAPBQI). (GSH, glutathione.) (Based on data from: Boobis A R et al. 1989, and Nelson S D, Pearson P G 1990 *Annu Rev Pharmacol Toxicol* 30: 169.)

- Hepatotoxicity caused by toxic doses of paracetamol is clinically important as paracetamol was the fourth most common cause of death following self-poisoning in the UK in 1989).
- The body's handling of this drug exemplifies many of the general mechanisms of cell damage
- **With toxic doses of paracetamol, the enzymes catalysing the normal conjugation reactions are saturated and mixed-function oxidases convert the drug to the reactive metabolite N-acetyl-p benzoquinone imine (NAPBQI).**



- **Paracetamol toxicity is increased in patients in whom P450 enzymes have been induced, for instance by chronic excessive consumption of alcohol.**
- NAPBQI initiates several of the covalent and non-covalent interactions described above and illustrated in the Figure 52.1 above.
- **Oxidative stress from GSH depletion is important in leading to cell death, although the precise mechanism is not yet clear.**
- **Synthesis of new GSH depends on the availability of cysteine, the intracellular availability of which can be limiting.**
- **Acetylcysteine or methionine increase GSH availability and reduce mortality in patients with severe paracetamol poisoning.**

- **The antidote to acetaminophen (paracetamol) overdose is N-acetylcysteine (NAC).**
- **It is most effective when given within 8 hours of ingesting acetaminophen.**
- **Indeed, NAC can prevent liver failure if given early enough. For this reason, it is absolutely necessary that acetaminophen poisoning be recognized, diagnosed, and treated as early as possible.**

- **Treatment entails gastric lavage followed by oral activated charcoal.**
- **If the patient is seen sufficiently soon after ingestion, the liver damage can be prevented by giving agents that increase glutathione formation in the liver (acetylcysteine intravenously, or methionine orally).**
- **If more than 12 hours have passed since the ingestion of a large dose, the antidotes, which themselves can cause adverse effects (nausea, allergic reactions), are less likely to be useful.**
- **If the damage is severe, a liver transplant may be necessary in order to save a life.**

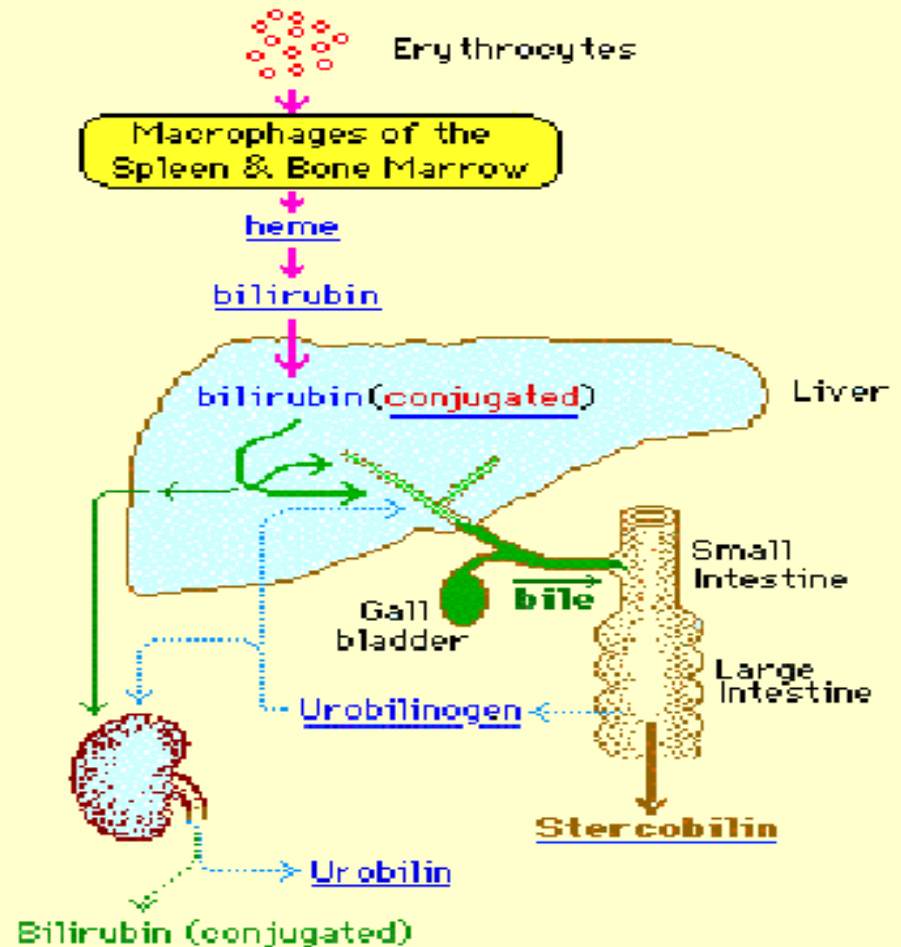
# **Rotor's Syndrome (Synonyms: Manahan and Florentin syndrome)**

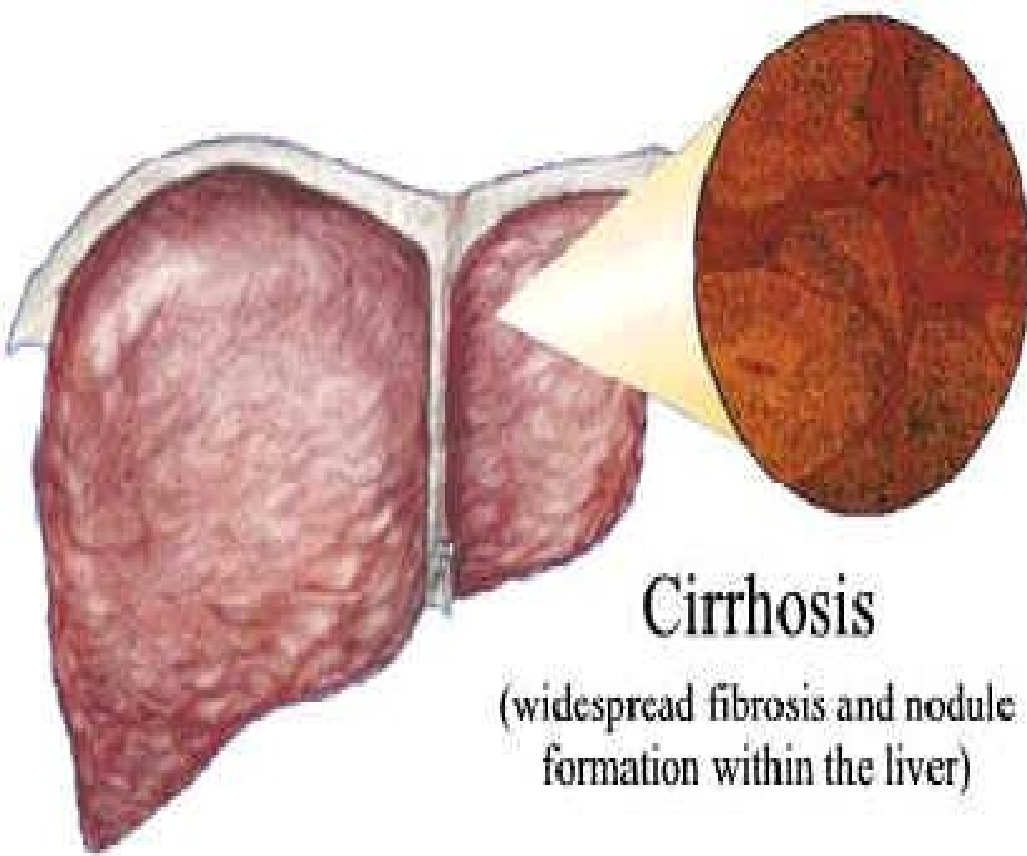
- Rotor's syndrome is a **benign familial chronic idiopathic jaundice** that is associated with **chronic, idiopathic conjugated hyperbilirubinemia**.
- It is most likely inherited as an autosomal recessive disease and is **due to a defect in the excretion of unconjugated bilirubin into the biliary caniculi with the bilirubin being absorbed into the blood and excreted in the urine**. Primarily reported in patients from the Philippines.
- Rotor's syndrome is similar to the Dubin-Johnson syndrome in that both are rare hereditary metabolic defects that disrupt transport.
- It differs from Dubin-Johnson syndrome in that the gall bladder is usually visualized on an oral cholecystogram and there is no secondary appearance of the dye during the performance of bromsulphaphthalien.
- It may be the same condition as hepatic storage disease reported in Japan and France.
- Jaundice appearing in childhood due to impaired biliary excretion; most of the plasma bilirubin is conjugated, liver fraction tests are usually normal, and there is no hepatic pigmentation.

- **In hepatocellular jaundice**, clinically, the jaundice tends to come on rapidly and is of an orange tint.
- Fatigue and malaise are common.
- Signs of hepatocellular failure may be evident.
- Serum transaminases are increased (Plasma levels of AST (SGOT) and ALT (SOPT) are elevated)
- Serum albumin is reduced in chronic disease.
- Prothrombin time is prolonged and does not fall in response to parenteral vitamin K.
- Unconjugated bilirubin occurs in the blood.
- Increased urobilinogen in the urine.
- **The urine is dark in color.**
- **Stools are a pale, clay color**

- Hepatocellular Jaundice
- **Clinical features of liver disease** e.g.
  - nausea and anorexia
  - \*Hepatocyte damage
- Hepatitis
- Cirrhosis
- Jaundice due to excess bilirubin
- Increased mixture unconjugated + conjugated plasma bilirubin due to decreased conjugation
- Increased ALT/AST (6-1000X)

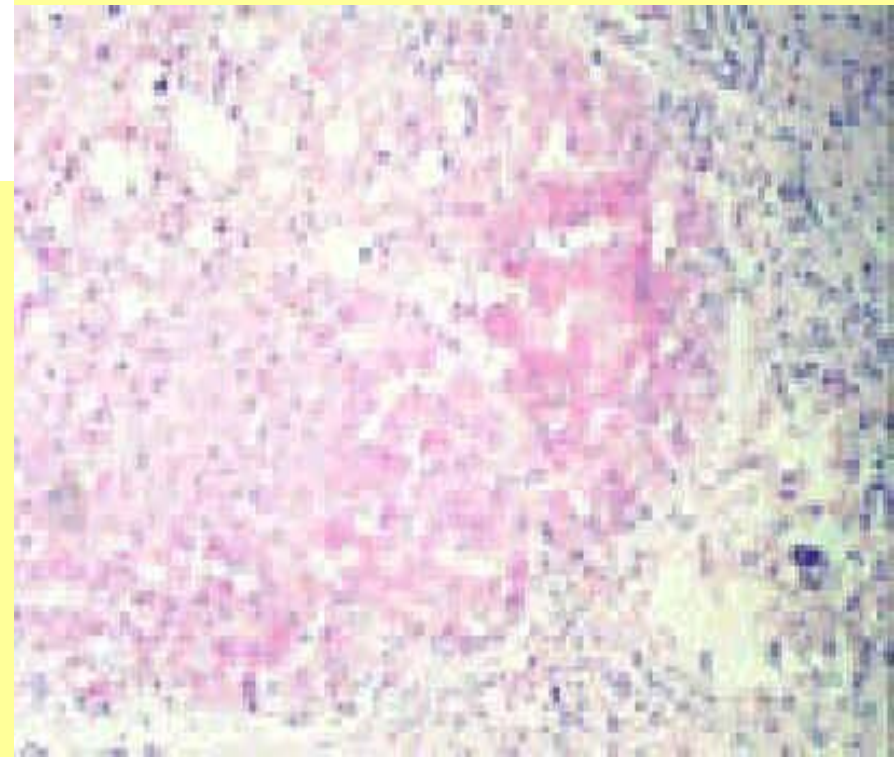
## Hepatocyte damage





## Cirrhosis

(widespread fibrosis and nodule formation within the liver)



- **NOTE that**
- **Viral hepatitis or cirrhosis produces an increase in both direct and indirect bilirubin.**
- **Aminotransferase levels will also be elevated.**
- **Alcoholic liver disease, AST increases more than ALT**
- **Viral hepatitis, ALT increases more than AST**

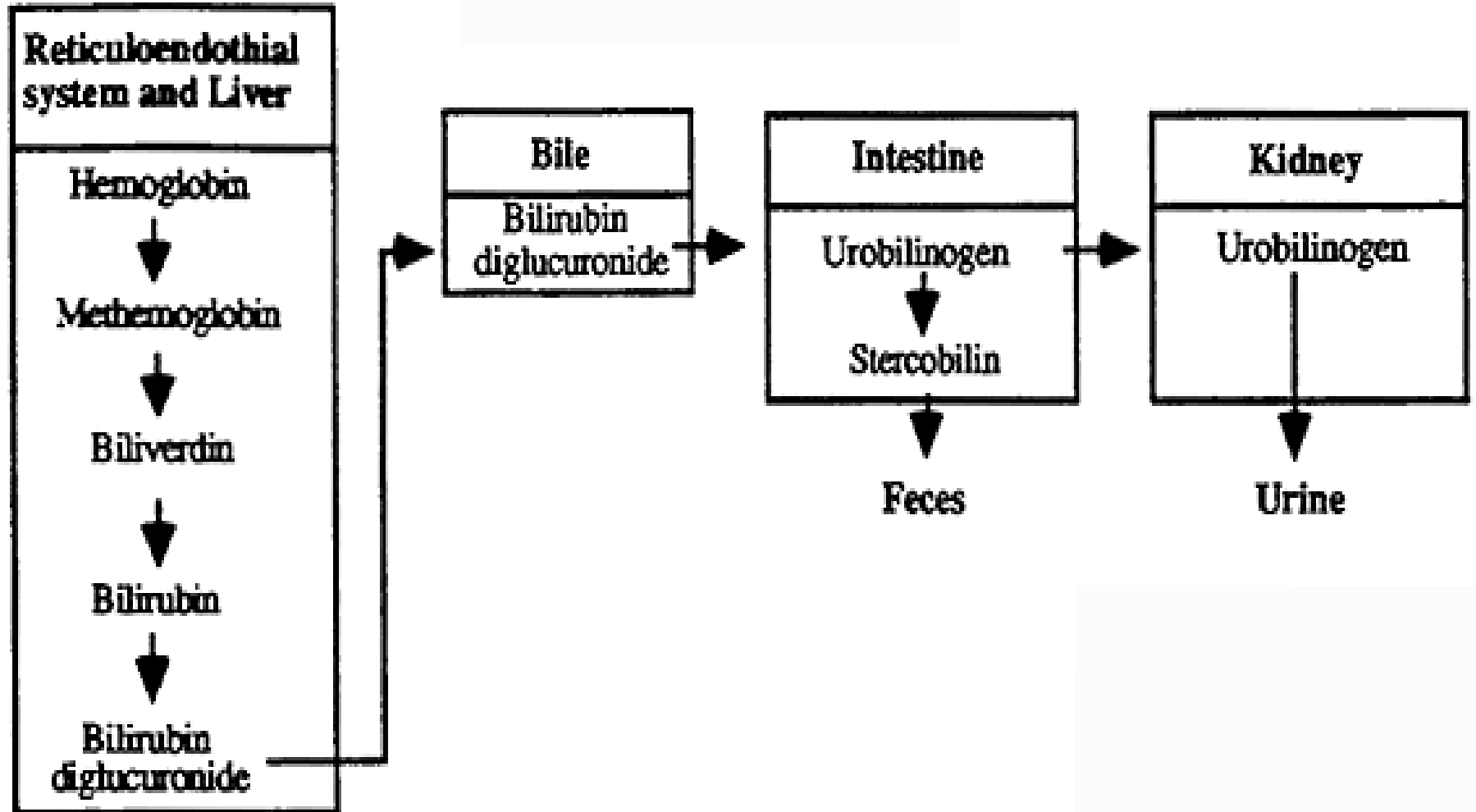


- **Developmental abnormalities of bile ducts**
- There are rare instances in which the bile ducts do not develop normally and the flow of bile is interrupted.
- Jaundice frequently occurs. These diseases usually are present from birth though some of them may first be recognized in childhood or even adulthood.
- Cysts of the bile duct (choledochal cysts) are an example of such a developmental abnormality. Another example is Caroli's disease.

# POST HEPATIC OR OBSTRUCTIVE JAUNDICE

- Once soluble in bile, bilirubin is transported through the biliary and cystic ducts to enter the gallbladder, where it is stored, or it passes through Vater's ampulla to enter the duodenum.
- Inside the intestines, some bilirubin is excreted in the stool, while the rest is metabolized by the gut flora into urobilinogens and then reabsorbed.
- The majority of the urobilinogens are filtered from the blood by the kidney and excreted in the urine.
- A small percentage of the urobilinogens are reabsorbed in the intestines and re-excreted into the bile.

# Post Hepatic Metabolism



# Post-hepatic jaundice

- **Post-hepatic (or obstructive) jaundice** is caused by blockage of the bile ducts that leads to a decreased flow of bile and bilirubin from the liver into the intestines.
- The decreased conjugation, secretion, or flow of bile that can result in jaundice are collectively referred to as cholestasis: \*remember that cholestasis does not always result in jaundice.

- **The most common causes of such an interruption to the drainage of bile in the biliary system are gallstones in the common bile duct and pancreatic cancer in the head of the pancreas.**
- **Other causes include inflammation of the bile ducts, strictures of the common bile duct, cancers of the liver and bile ducts, pancreatitis and pancreatic pseudocysts.**

- **Inflammation of the bile ducts**
- Diseases causing inflammation of the bile ducts, for example, primary biliary cirrhosis or sclerosing cholangitis and some drugs, can also stop the flow of bile and elimination of bilirubin and lead to jaundice.

- A rare cause of obstructive jaundice is Mirizzi's syndrome.
- This is benign obstruction of the hepatic ducts due to spasm and/or fibrous scarring of surrounding connective tissue; often associated with a stone in the cystic duct and chronic cholecystitis.

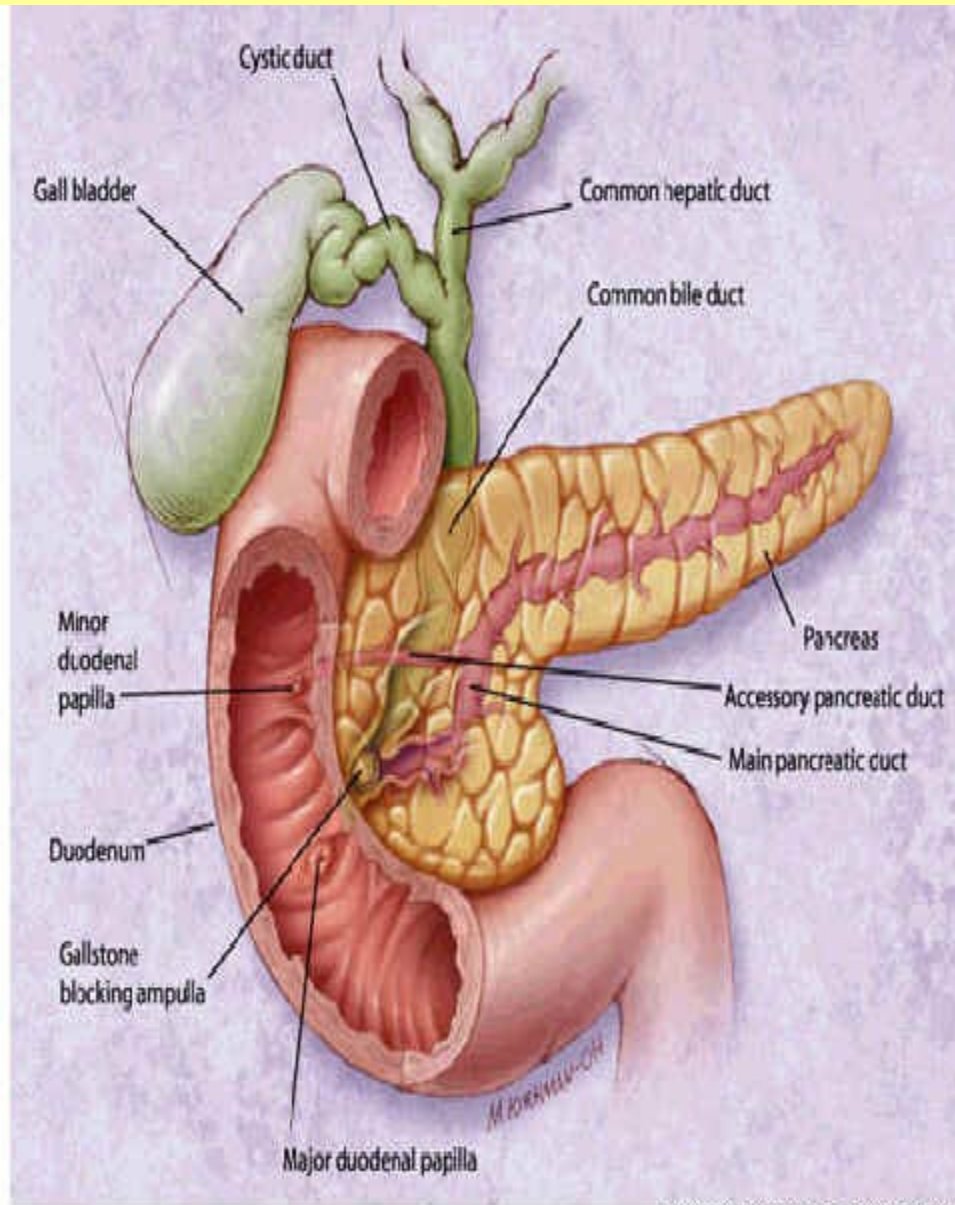


# Etiology of Posthepatic Jaundice

- Intrinsic to the ductal system:
  - Gallstones
  - Surgical strictures
  - Infection (cytomegalovirus, Cryptosporidium infection in patients with acquired immunodeficiency syndrome)
  - Intrahepatic malignancy
  - Cholangiocarcinoma: a rare tumor arising from the bile duct cells
  - Bile duct obstruction
  - Primary biliary cirrhosis
  
- Extrinsic to the ductal system:
  - Posthepatic malignancy (pancreas lymphoma)
  - Pancreatitis
  - pancreatic cancer

- **Bile Duct Occlusion causes problems with bile flow by extrahepatic cholestasis; there is blockage of bilirubin transport in the biliary tract.**
- **Occlusion of the bile duct (due to gallstone, primary biliary cirrhosis, pancreatic cancer, or whatever cause) prevents conjugated bilirubin from leaving the liver.**
- **Conjugated bilirubin increases in blood and may also appear in urine.**
- **Feces are light-colored.**

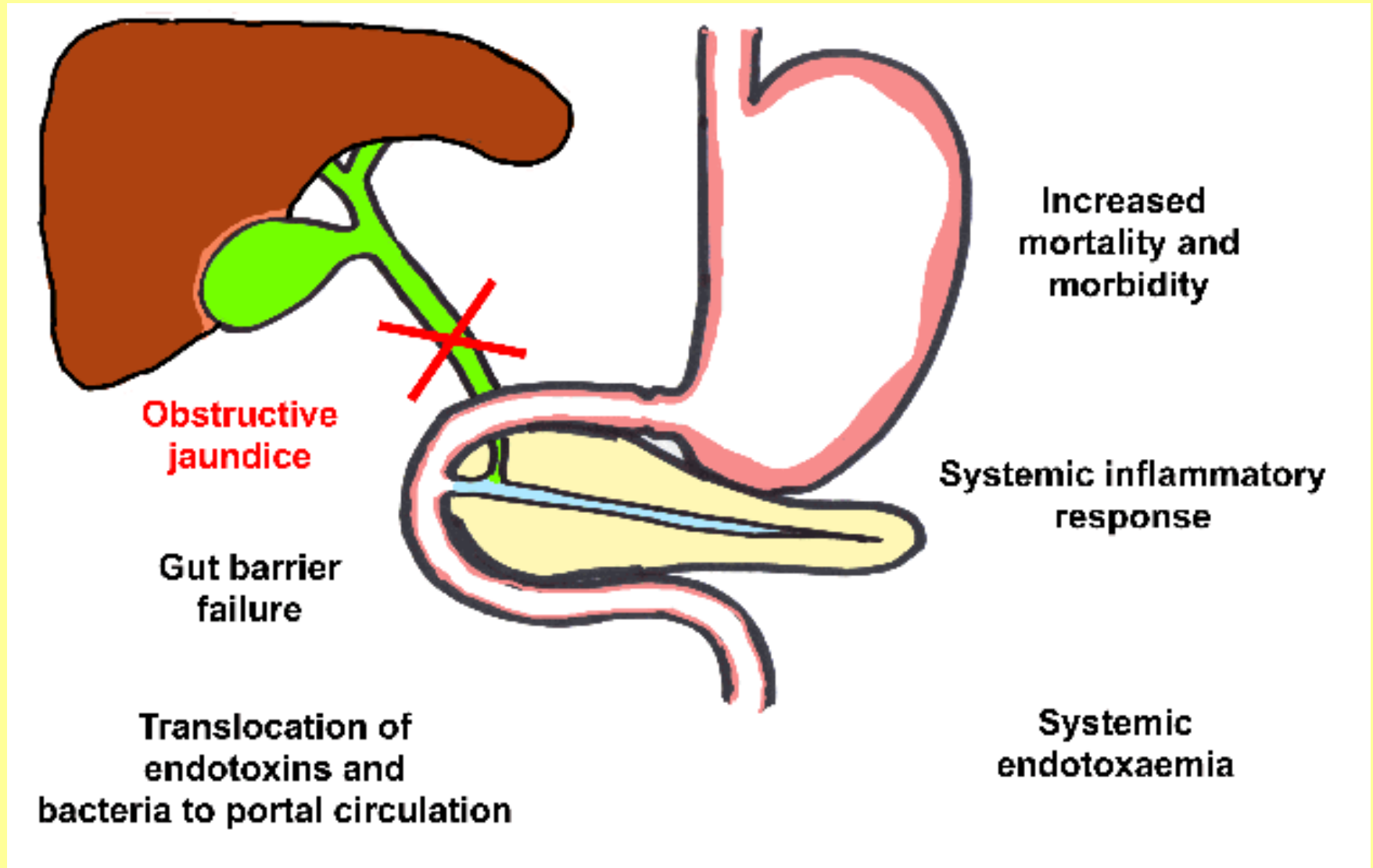
- Post Hepatic (Obstructive) Jaundice  
Obstruction to passage of conjugated bile
- **Conjugated bilirubin cannot pass into intestine**
- **instead enters the bloodstream**



# Why is gut barrier function important?

- In recent years, it has become clear that maintenance of the integrity of the gastrointestinal tract plays an important role in the critically ill patient.
- Breakdown of the barrier function of the gut in severe illness has been linked to multiple organ failure and the systemic inflammatory response syndrome (SIRS) and the gut has been referred to as "the motor of sepsis".

# Gut barrier function



- The barrier function of the gut has been shown to be defective in obstructive jaundice.
- Surgical intervention in jaundiced patients is associated with a high incidence of post-operative complications, multiple organ failure and a high post-operative mortality.
- It is thought that these complications result from failure of the gut barrier, allowing bacteria and endotoxins normally contained within the gut to cross into the circulation, activating a systemic inflammatory response which causes damage to multiple organs.
- Recent research group confirms that permeability of the gut barrier is increased in jaundiced patients and that this returns to normal when bile is returned to the gut by internal biliary drainage. Evidence of bacterial translocation and immune dysfunction in obstructive jaundice has also been demonstrated

## Patients with obstructive jaundice experience:

- GI pain
- Nausea
- **Stools that are a pale, clay color as there is no stercobilin in the faeces to give its normal color.**

The presence of pale stools suggests an obstructive or post-hepatic cause as normal feces get their colour from bile pigments.

- **Increased direct bilirubin due to increased conjugated bilirubin levels into the blood, and is excreted in the urine as urobilinogen.**

# Jaundice in pregnancy



- Most of the diseases discussed previously can affect women during pregnancy, but there are some additional causes of jaundice that are unique to pregnancy.
- Causes of jaundice specific to pregnancy include:
  - **Cholestasis of pregnancy**
  - **Pre-eclampsia**
  - **Acute fatty liver of pregnancy**

- **Cholestasis of pregnancy.**
- Cholestasis of pregnancy is an uncommon condition that occurs in pregnant women during the third trimester.
- **The cholestasis is often accompanied by itching but infrequently causes jaundice. The itching can be severe, but there is treatment (ursodeoxycholic acid or ursodiol).**
- **Pregnant women with cholestasis usually do well although they may be at greater risk for developing gallstones. More importantly, there appears to be an increased risk to the fetus for developmental abnormalities.**
- Cholestasis of pregnancy is more common in certain groups, particularly in Scandinavia and Chile, and tends to occur with each additional pregnancy.
- **There also is an association between cholestasis of pregnancy and cholestasis caused by oral estrogens, and it has been hypothesized that it is the increased estrogens during pregnancy that are responsible for the cholestasis of pregnancy**

- **Pre-eclampsia.**

- Pre-eclampsia, previously called toxemia of pregnancy, is a disease that occurs during the second half of pregnancy and involves several systems within the body, including the liver.
- It may result in high blood pressure, fluid retention, and damage to the kidneys as well as anemia and reduced numbers of platelets due to destruction of red blood cells and platelets.
- It often causes problems for the fetus.
- **Although the bilirubin level in the blood is elevated in pre-eclampsia, it usually is mildly elevated, and jaundice is uncommon.**
- Treatment of pre-eclampsia usually involves delivery of the fetus as soon as possible if the fetus is mature.

- **Acute fatty liver of pregnancy.**
- Acute fatty liver of pregnancy (AFLP) is a very serious complication of pregnancy of unclear cause that often is associated with pre-eclampsia.
- It occurs late in pregnancy and results in failure of the liver.
- It can almost always be reversed by immediate delivery of the fetus.
- There is an increased risk of infant death.
- **Jaundice is common, but does not always present in AFLP.**
- Treatment usually involves delivery of the fetus as soon as possible

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