



Differential diagnosis of icterus

Katalin Keltai, MD



What is icterus?



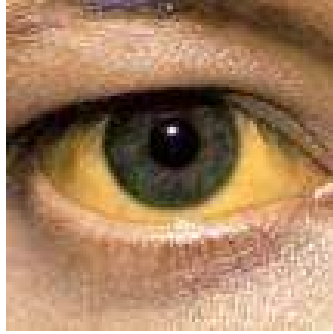
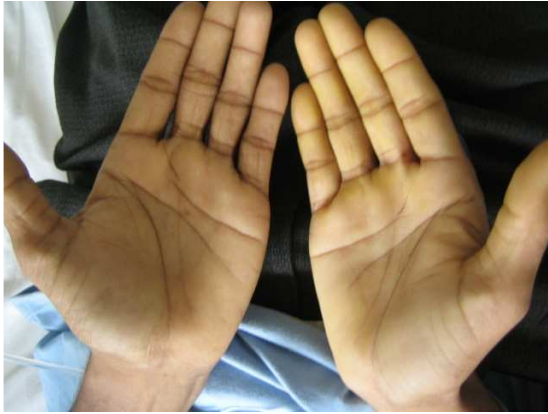
Icterus nigrogularis

= ORIOLE

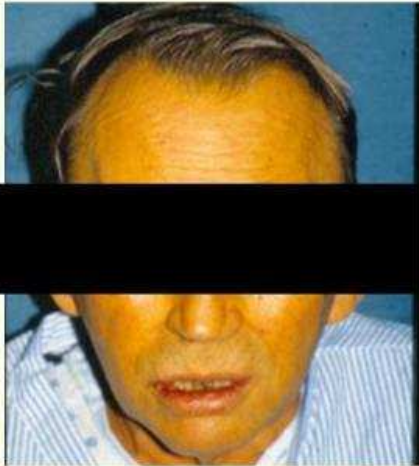
DEFINITION: Bile or liver problem causing yellowness

- A yellow discoloration of the skin, mucous membranes, or sclera of the eyes, **jaundice** indicates excessive levels of conjugated or unconjugated bilirubin in the blood.
- In fair-skinned patients, it's most noticeable on the face, trunk, and sclera; in dark-skinned patients, on the hard palate, sclera, and conjunctiva.

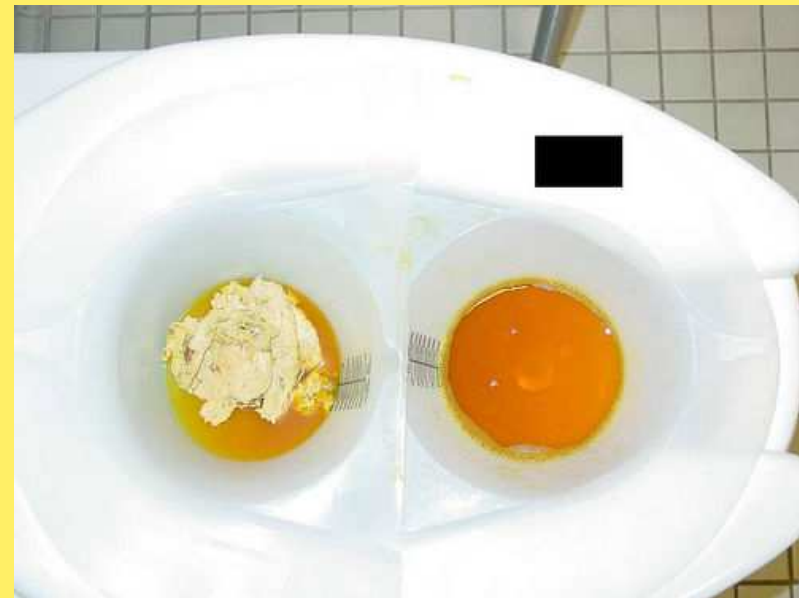




Jaundice



Jaundice is most apparent in **natural sunlight**. In fact, it may be undetectable in artificial or poor light. It's commonly accompanied by **pruritus** (because bile pigment damages sensory nerves), **dark urine**, and **clay-colored stools**.



- Jaundice develops from hyperbilirubinemia and may not be noticed until the bilirubin exceeds 50 $\mu\text{mol/L}$.
 - Scleral elastin has a high affinity for bilirubin, and with a white background, it is a sensitive indicator of jaundice.
 - Biliary obstruction gives a **greenish skin** tint due to accumulation of biliverdin.
 - Hemolysis gives a **lemon-yellow** tint when observed in natural light.
 - An **orange-yellow** color is more consistent with hepatocellular disease.
 - Pseudojaundice may be found in black patients with pigmented sclera, with carotinemia, with uremia (a sallow yellowish pallor), and with quinacrine (a yellow-green color).
- Dark urine with green foam confirms a conjugated hyperbilirubinemia and excludes hemolysis or a conjugating defect. Unconjugated bilirubin is tightly bound to albumin, which prevents glomerular filtration.



Hyperbilirubinemia is due to

- increased production of bilirubin
- impaired transport of bilirubin to the liver for excretion
- and decreased excretion of bilirubin.

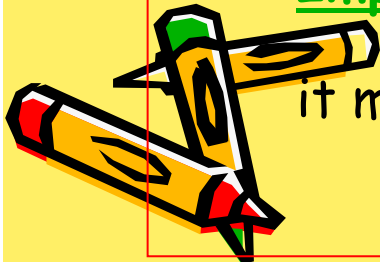
- Increased production.

- release of hemoglobin from the red cells and its subsequent breakdown.

- Common hereditary hemolytic anemias include the hemoglobinopathies and abnormalities of RBC membranes and enzymes.
- Common acquired abnormalities include mechanical trauma, antibody mediated damage, and other toxic or physical insults. Thus, the **hemolytic anemias** are the principal cause of this category of jaundice. These include:
 - hereditary spherocytosis
 - Cooley anemia
 - Septicemia
 - autoimmune hemolytic anemia
 - malaria.

- Impaired transport

CHF is the principal cause of this form of jaundice, but it must be advanced enough to cause cardiac cirrhosis.



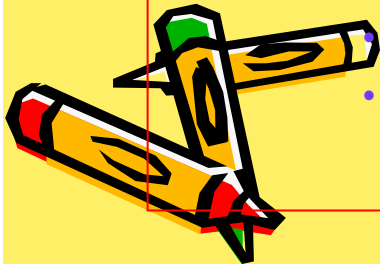
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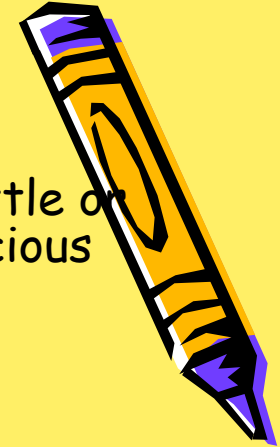
- Decreased excretion

This group of causes of jaundice is divided into conditions

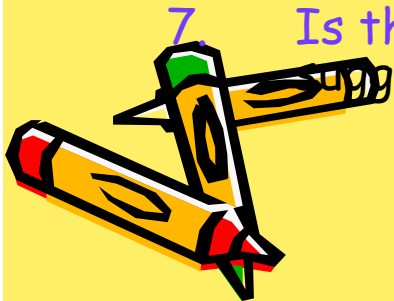
- in which the liver is **unable to transform** unconjugated bilirubin to the conjugated form
 - Gilbert disease
 - infectious hepatitis
 - cirrhosis
- conditions in which the liver **cannot transfer** the conjugated bilirubin into the bile ducts
 - Dubin-Johnson syndrome
 - Rotor syndrome
- and conditions that **obstruct the bile ducts**
 - common duct stones
 - Cholangitis
 - chlorpromazine toxicity
 - carcinomas of the pancreas and ampulla of Vater.



IMPORTANT QUESTIONS TO RAISE



1. **Is the jaundice associated with hepatomegaly?** There is little or no hepatomegaly associated with hemolytic anemias, pernicious anemia, Gilbert's disease, and Dubin-Johnson syndrome.
2. **Is the hepatomegaly massive?** Massive hepatomegaly is associated with Gaucher's disease.
3. **Is there associated fever, right upper quadrant pain, or a tender liver?** These findings would suggest viral hepatitis, cholecystitis, infectious mononucleosis, leptospirosis, ascending cholangitis, hepatic vein thrombosis, and toxic hepatitis.
4. **Is the gallbladder enlarged?** The finding of an enlarged gallbladder with the jaundice suggests obstructive jaundice, carcinoma of the pancreas, carcinoma of the bowel ducts, or ampulla of Vater.
5. **Is there skin pigmentation?** The presence of skin pigmentation that is not bilirubin suggests hemochromatosis.
6. **Is there splenomegaly?** The presence of significant splenomegaly suggests infectious mononucleosis, cirrhosis of the liver, hemolytic anemia, Gaucher's disease, kala azar, or agnogenic myeloid metaplasia.
7. **Is there edema and ascites?** The presence of edema and ascites suggests alcoholic cirrhosis.



DIAGNOSTIC WORKUP

History

- Begin by asking the patient when he first noticed the jaundice.
- Does he also have pruritus, clay-colored stools, or dark urine?
- Ask about past episodes or a family history of jaundice. Does he have nonspecific signs or symptoms, such as fatigue, a fever, or chills; GI signs or symptoms, such as anorexia, abdominal pain, nausea, weight loss, or vomiting; or cardiopulmonary symptoms, such as shortness of breath or palpitations?
- Ask about alcohol use and a history of cancer or liver or gallbladder disease.
- Has the patient lost weight recently?
- Obtain a drug history.
- Ask about a history of hepatitis, gallstones, or liver or pancreatic disease.



DIAGNOSTIC WORKUP

Physical examination

- Perform the physical examination in a room with **natural light**. Jaundice is best seen in the periphery of ocular conjunctivae and oral mucous membranes
- Make sure that the orange-yellow hue is jaundice and not due to hypercarotenemia, which is more prominent on the **palms and soles** and doesn't affect the **sclera**.
- Inspect the patient's skin for texture and dryness and for hyperpigmentation and xanthomas.
- Look for **spider angiomas or petechiae, clubbed fingers, testicular atrophy, palmar erythema and gynecomastia**.
- If the patient has heart failure, auscultate for arrhythmias, murmurs, and gallops as well as crackles and abnormal bowel sounds.
- Palpate the lymph nodes for swelling and the abdomen for **tenderness, pain, and swelling**.
- Palpate and percuss the liver and spleen for enlargement, and test for ascites with the **shifting dullness and fluid wave techniques**.
- Obtain baseline data on the patient's **mental status**: Slight changes in **sensorium** may be an early sign of deteriorating hepatic function.



DIAGNOSTIC WORKUP

Lab and imaging

- Basic workup includes a **CBC** (hemolytic anemia, infection), **sedimentation rate**, **reticulocyte count**, red cell fragility test, **urinalysis**, **chemistry panel**, **VDRL test**, **ECG**, a **chest x-ray**, and **flat plate of the abdomen**.
- If infectious hepatitis is suspected, a hepatitis profile, febrile agglutinins, Monospot test, cytomegalic virus antibody titer, and leptospirosis antibody titer should be done.
- If lupoid hepatitis is suspected, a test for antinuclear antibodies and a smooth muscle antibody should be done.



DIAGNOSTIC WORKUP

Lab and imaging

- If hemochromatosis is suspected, a serum iron, iron-binding capacity, and ferritin should be done.
- If hemolytic anemia is suspected, serum haptoglobins, hemoglobin electrophoresis, and sickle cell preparations may be done.
- If obstructive jaundice is suspected, then gallbladder **ultrasound** should be done to rule out gallstones, and a **CT scan** of the abdomen may be done to look for GI neoplasm. An **upper GI series** may assist in finding a primary neoplasm in the GI tract.
- **Magnetic resonance cholangiopancreatography** is **useful** for common duct stone.



DIAGNOSTIC WORKUP

Lab and imaging

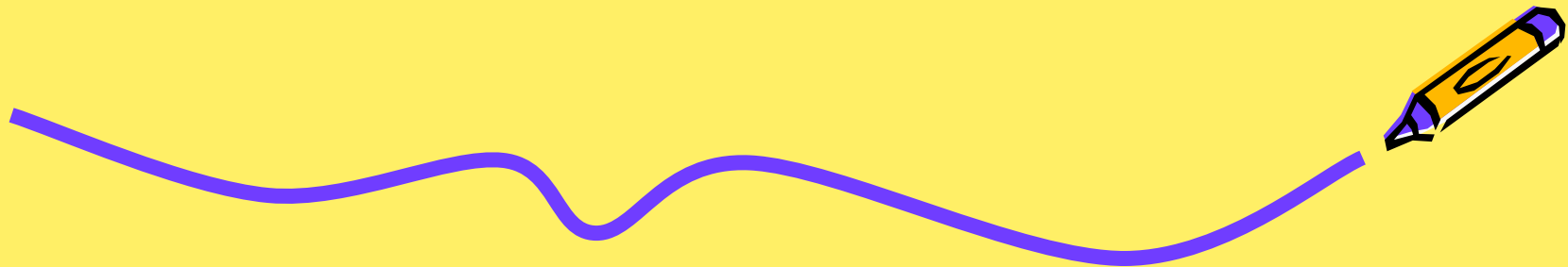
- ERCP or percutaneous transhepatic cholangiography will assist in determining whether there is definitely obstructive jaundice and whether it is due to a surgically resectable lesion.
- Peritoneoscopy can also be helpful.
- An exploratory laparotomy will probably be necessary regardless of whether one performs the above tests.
- Cholangiopancreatography and endoscopic ultrasonography are two newer methods that may be used to evaluate the biliary tree and pancreatic ducts, especially when a neoplasm is suspected.
- Hepatocellular jaundice will often require a needle biopsy of the liver to pin down the diagnosis.
- Antimitochondrial antibodies will need to be ordered to screen for biliary cirrhosis.
- Alpha 1-fetoprotein will help diagnose hepatocellular cancer.



By the time you have reached this point, you have gone to considerable expense in the diagnostic workup. It would be much more prudent to ask for a gastroenterology consultation before ordering all these expensive diagnostic tests.



DIFFERENTIAL DIAGNOSIS



- **Viral hepatitis**

- Fatigue, anorexia, fever, nausea, vomiting, dark urine, light-colored (acholic) loose stools, RUQ pain, hepatomegaly, and/or pruritis

- **Alcoholic hepatitis**

- Associated with fever, leukocytosis, and AST:ALT ratio >2

- **Nonalcoholic steatohepatitis or nonalcoholic fatty liver disease**

- Associated with obesity, diabetes, hyperlipidemia and medications



Cholelithiasis

- commonly causes jaundice and biliary colic
- It's characterized by severe, steady pain in the right upper quadrant or epigastrium that radiates to the right scapula or shoulder and intensifies over several hours.
- Accompanying signs and symptoms include nausea and vomiting, tachycardia, and restlessness. Occlusion of the common bile duct causes a fever, chills, jaundice, clay-colored stools, and abdominal tenderness.
- After consuming a fatty meal, the patient may experience vague epigastric fullness and dyspepsia.



Cholecystitis

- produces nonobstructive jaundice in about 25% of patients
 - RUQ pain, fever, leukocytosis
 - 4F Female, fertile, fat, forty
 - Murphy's sign: Pain upon palpation of the gallbladder while taking a deep breath
 - Biliary colic typically peaks abruptly, persisting for 2 to 4 hours. The pain then localizes to the right upper quadrant and becomes constant. Local inflammation or passage of stones to the common bile duct causes jaundice.
 - Other findings include nausea, vomiting (usually indicating the presence of a stone), a fever, profuse diaphoresis, chills and, possibly, abdominal distention and rigidity.



Cirrhosis (Laënnec's; alcohol)

Mild to moderate jaundice with pruritus usually signals hepatocellular necrosis or progressive hepatic insufficiency

- Common early findings:

ascites

weakness

leg edema

nausea and vomiting

diarrhea or constipation

anorexia, weight loss

right upper quadrant pain.

Massive hematemesis and other bleeding tendencies may also occur.

- Other findings:

enlarged liver and parotid gland

clubbed fingers

Dupuytren's contracture

mental changes

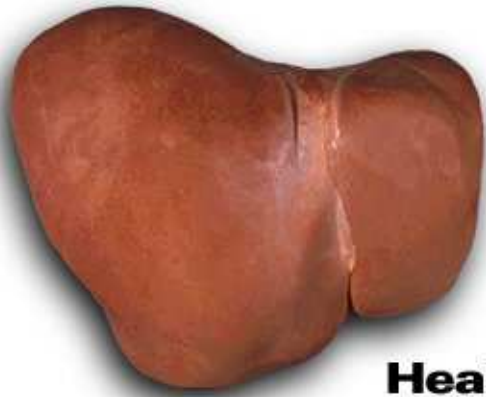
asterixis

fetor hepaticus

spider angiomas, and palmar erythema

Males may exhibit gynecomastia, scanty chest and axillary hair, and testicular atrophy; females may experience menstrual irregularities.

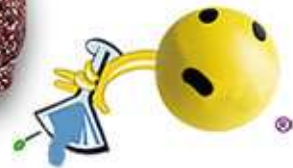




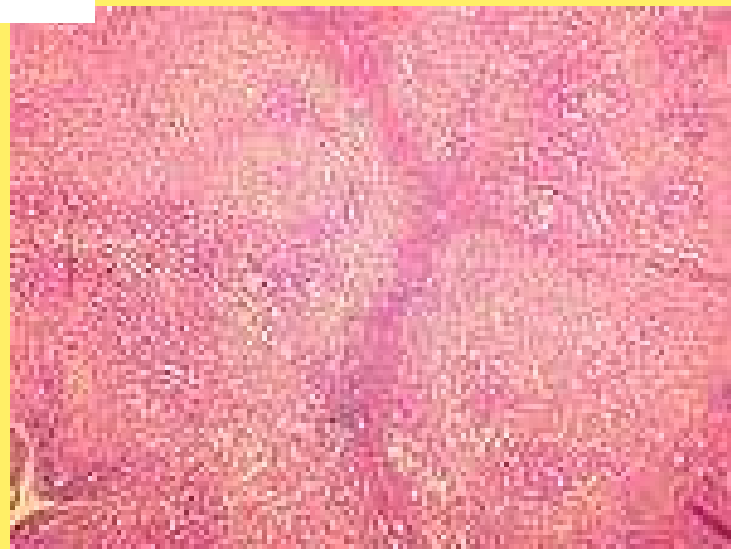
Healthy



Cirrhosis



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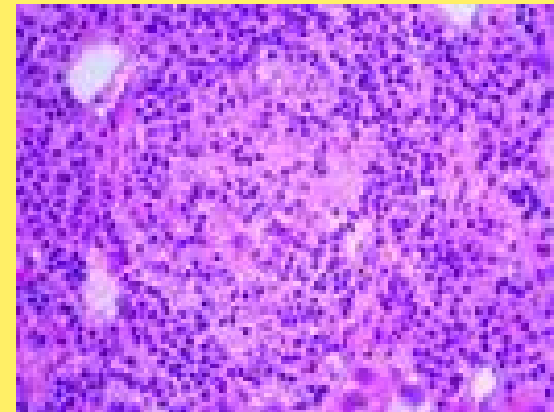
Primary biliary cirrhosis

fluctuating jaundice may appear years after the onset of other signs and symptoms:

- pruritus that worsens at bedtime (commonly the first sign),
- weakness, fatigue, weight loss
- vague abdominal pain
- itching may lead to skin excoriation

Associated findings

- hyperpigmentation
- indications of malabsorption
 - nocturnal diarrhea
 - Steatorrhea
 - Purpura
 - osteomalacia
- hematemesis from esophageal varices
- ascites
- edema
- xanthelasmas; (tendon) xanthomas on the palms, soles, and elbows
- Hepatomegaly and splenomegaly



Malignancy

- **Hepatic cancer** (primary liver cancer or another cancer that has metastasized to the liver) may cause jaundice by causing obstruction of the bile duct.
- Even advanced cancer causes nonspecific signs and symptoms, such as right upper quadrant discomfort and tenderness, nausea, weight loss, and a slight fever.
- Examination may reveal irregular, nodular, firm hepatomegaly; ascites; peripheral edema; a bruit heard over the liver; and a right upper quadrant mass.

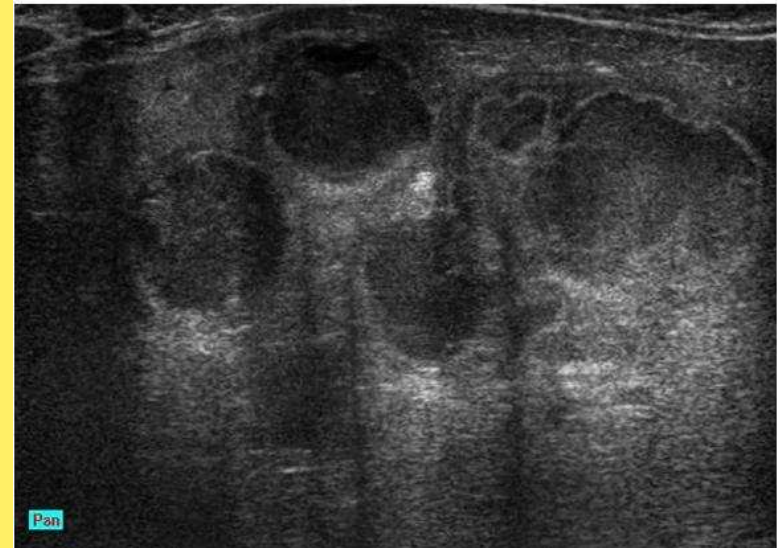


Malignancy

- **Cancer of the ampulla of Vater** initially produces fluctuating jaundice, mild abdominal pain, a recurrent fever, and chills. Occult bleeding may be its first sign. Other findings include weight loss, pruritus, and back pain.
- **Pancreatic cancer**, progressive jaundice — possibly with pruritus — may be the only sign. Related early findings are nonspecific, such as weight loss and back or abdominal pain. Other signs and symptoms include anorexia, nausea and vomiting, a fever, steatorrhea, fatigue, weakness, diarrhea, pruritus, and skin lesions (usually on the legs).
Courvoisier sign - painless palpable gall bladder with icterus (pancreas head cancer)



- **Liver infiltration**
 - Amyloidosis, lymphoma, sarcoidosis, tuberculosis
- **Sclerosing cholangitis**
 - It occurs with active inflammatory bowel disease. Inflammatory bowel disease is also associated with cholangiocarcinoma, cirrhosis, amyloidosis, and gallstones (with ileal Crohn disease), each of which could produce jaundice.



Drugs

- Estrogens produce **canalicular cholestasis**.
- Phenothiazines produce **ductular cholestasis**.
- Methyldopa causes **autoimmune hemolytic anemia**.
- Hepatotoxins
 - Niacin
 - Acetaminophen
 - Isoniazid
 - Phenytoin
 - Sulfonamides
 - Ketoconazole
 - erythromycin estolate
 - Chlorpromazine
 - Propylthiouracil
 - anabolic steroids
 - Valproate
 - Amiodarone
 - vitamin A and D (in high doses)
 - carbon tetrachloride
 - amanita mushrooms.



- **Heart failure**

- Jaundice due to liver dysfunction occurs in patients with severe right-sided heart failure
- Other effects include jugular vein distention, cyanosis, dependent edema of the legs and sacrum, steady weight gain, confusion, hepatomegaly, nausea and vomiting, abdominal discomfort, and anorexia due to visceral edema. Ascites is a late sign. Oliguria, marked weakness, and anxiety may also occur.

If left-sided heart failure develops first, other findings may include fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, tachypnea, arrhythmias, and tachycardia.

- **Hepatic abscess (amoebiasis, actinomycosis, listeriosis, tbc)**

- Multiple abscesses may cause jaundice, but the primary effects are a persistent fever with chills and sweating
- Other findings include steady, severe pain in the right upper quadrant or midepigastrium that may be referred to the shoulder; nausea and vomiting; anorexia; hepatomegaly; an elevated right hemidiaphragm; and ascites.



- **Postoperative**

Jaundice occurs by several mechanisms including hemolysis of transfused blood, reabsorption of a hematoma, hemoperitoneum, sepsis, hypotension, and biliary tract injury.

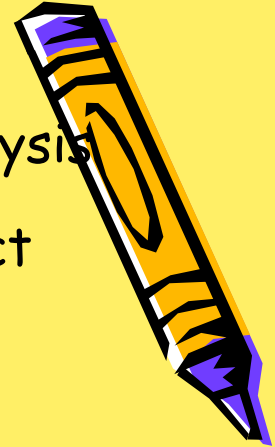
- **Pancreatitis (acute)**

- Edema of the head of the pancreas and obstruction of the common bile duct can cause jaundice; however, the primary symptom of acute pancreatitis is usually severe epigastric pain that commonly radiates to the back

- Lying with the knees flexed on the chest or sitting up and leaning forward brings relief. Early associated signs and symptoms include nausea, persistent vomiting, abdominal distention. Other findings include a fever, tachycardia, abdominal rigidity and tenderness, hypoactive bowel sounds, and crackles.

- Severe pancreatitis produces extreme restlessness; mottled skin; cold, diaphoretic extremities; paresthesia; and tetany — the last two being symptoms of hypocalcemia.

- Fulminant pancreatitis causes massive hemorrhage.



Sepsis

Prolonged hypotension results in liver dysfunction.

Total parenteral nutrition

usually requires at least 2 weeks of therapy

Intravascular hemolysis

haptoglobin decreased, LDH increased, Hb and hemosiderin in the urine

Gilbert's syndrome

-Decreased conjugation of bilirubin, especially with dehydration, fasting, infection



Sickle cell disease - hemolysis



Other findings include impaired growth and development, increased susceptibility to infection, life-threatening thrombotic complications and, commonly, leg ulcers, swollen (painful) joints, a fever, and chills. Bone aches and chest pain may also occur. Severe hemolysis may cause hematuria and pallor, chronic fatigue, weakness, dyspnea (or dyspnea on exertion), and tachycardia. The patient may also have splenomegaly.

During a sickle cell crisis, the patient may have severe bone, abdominal, thoracic, and muscular pain; a low-grade fever; and increased weakness, jaundice, and dyspnea.

- **Autoimmune hepatitis**

- May mimic viral hepatitis
- Females >> males, often 10-30 years old
- Associated with autoimmune disease (e.g., RA, UC, Sjögren's syndrome, thyroiditis)

- **Hepatic vein obstruction (Budd-Chiari)**

The presentation is acute, with severe abdominal pain, hepatomegaly, ascites, and jaundice. Oral contraceptives, paroxysmal nocturnal hemoglobinuria, and polycythemia predispose to its development.



- **Intrahepatic cholestasis of pregnancy**

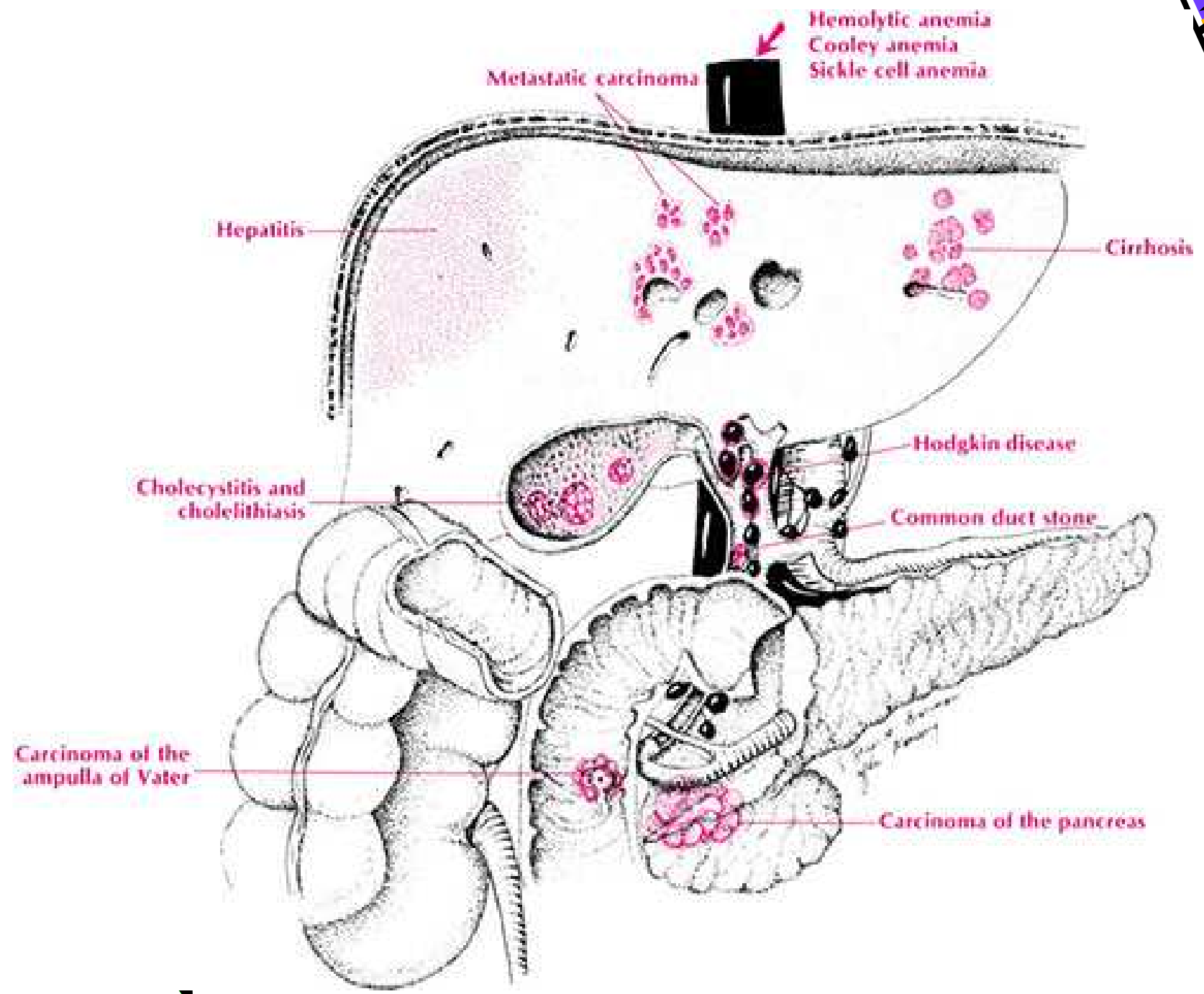
- Pruritus in third trimester
- Resolves after delivery

- **Hereditary cholestatic disorders** (e.g., Dubin-Johnson syndrome, Rotor syndrome)

- With Dubin-Johnson syndrome, which is a rare, chronic inherited syndrome, fluctuating jaundice that increases with stress is the major sign, appearing as late as age 40
- Related findings include slight hepatic enlargement and tenderness, upper abdominal pain, nausea, and vomiting.

- **Physiologic jaundice of newborn**





Hepatitis

Metastatic carcinoma

Hemolytic anemia
Cooley anemia
Sickle cell anemia

Cirrhosis

Cholecystitis and
cholelithiasis

Hodgkin disease

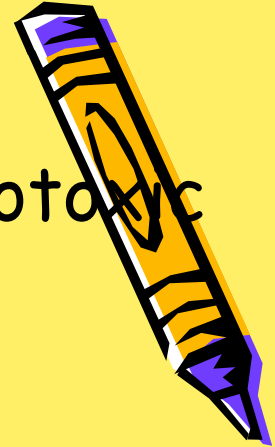
Common duct stone

Carcinoma of the
ampulla of Vater

Carcinoma of the pancreas

TREATMENT

- Discontinue and avoid potentially hepatotoxic medications
- Supportive care for viral hepatitis
- Rehydrate/refeed for Gilbert's syndrome
- Consider steroids in fulminant alcoholic hepatitis



• Cholecystectomy or ERCP with stone removal for obstructing gallstones

TREATMENT

- Treat underlying causes of hemolysis or other disorders
- Antibiotics for cholangitis, sepsis
- Hydroxyurea and folate for sickle cell disease, prevent crises by adequate hydration, vaccinating against diseases, and try to prevent other infections
- To help decrease pruritus, frequently bathe the patient; apply an antipruritic lotion, such as calamine; and administer diphenhydramine or hydroxyzine



**THANK YOU FOR YOUR
ATTENTION!**

