

Jaundice

Heme	<ul style="list-style-type: none"> ▶ From breakdown of senescent RBC's, hemolysis, etc...
<p style="text-align: center;">↓ <i>Heme Oxygenase</i></p> <p style="text-align: center;">Biliverdin IXa (+ CO + Fe²⁺)</p> <p style="text-align: center;">↓ <i>Biliverdin Reductase</i></p>	<ul style="list-style-type: none"> ▶ In macrophage ER of RES system, <i>Heme Oxygenase</i> converts Heme to biliverdin (The RES system is macrophages, spleen, kupfer cells) ▶ Contains NADPH-cytochrome c reductase ▶ In macrophage cytosol (still in the RES system!), <i>Biliverdin Reductase</i> converts Biliverdin to Bilirubin
Indirect (Unconjugated) Bilirubin Travels in blood bound to Albumin	<ul style="list-style-type: none"> ▶ Water-insoluble! (Lipid-soluble) ▶ Many factors affect binding affinity of bilirubin to albumin. This can be clinically important because free bilirubin is TOXIC (will cause kernicterus) <ul style="list-style-type: none"> ▶ ↓[albumin] or ↑[bilirubin] <i>increases</i> bilirubin-albumin binding affinity ▶ ↑[Cl⁻] <i>decreases</i> binding affinity (if someone is hyperchloremic they would be at a higher risk for having toxic free bilirubin floatin around)
Endocytosed ↓ into hepatocytes	<ul style="list-style-type: none"> ▶ In hepatocyte cytosol, bilirubin is bound to Lignadin (Y protein). No idea why this is important. Stupid useless detail. I just put it in here to highlight what's wrong with this course.
<p style="text-align: center;">⊗ ↓ UGTP1A1</p>	<ul style="list-style-type: none"> ▶ Ah, the famous UGTP1A, also known as UDP-glucuronyl transferase. Conjugates bilirubin with UDP-glucuronic acid to make bilirubin glucuronide → now it's water soluble and can happily go to the GB. ▶ ↑ activity in women (i.e. women are less jaundiced) ▶ ↓ supply of NAD⁺ (ethanol, fasting) → ↓ UDP-glucuronic acid ▶ Glucuronisation of lots of acetaminophen → ↓ UDP-glucuronic acid
Direct (Conjugated) Bilirubin	<ul style="list-style-type: none"> ▶ Water-soluble bile pigment
<p style="text-align: center;">⊕ ↓ released into canaliculi</p>	<ul style="list-style-type: none"> ▶ Transport protein: cMOAT (canalicular multispecific organic anion transporter) rate limiting step in bilirubin metabolism
<p style="text-align: center;">↓ stored in gallbladder</p>	
<p style="text-align: center;">↓ released into gut</p>	
<p style="text-align: center;">↓ reduced by bacteria</p>	
Urobilinogen	<ul style="list-style-type: none"> ▶ Excreted in feces. That's why crap is brown. ▶ 20% reabsorbed into liver (enterohepatic circulation)

Hereditary problems leading to an **INDIRECT** hyperbilirubinemia (Defect @ ⊗)

All are UGTP1A1 defects! Just depends on degree...

1) **Crigler Najjar**

- ▶ Type I: UGTP1A1 totally broken
you're completely screwed! severe, fatal!
- ▶ Type II: ↓ UGTP1A1 (about 10% of normal)
hyperbilirubinemia, but normal lifespan

2) **Gilbert**

- ▶ Totally benign!
- ▶ ↓ UGTP1A1 (about 30% of normal)
- ▶ With stress or fasting (which normally depletes UDP-glucuronic acid in liver), transient indirect (unconjugated) jaundice
- ▶ Yes, it really is that easy!

Hereditary problems leading to a **DIRECT** hyperbilirubinemia (Defect @ ⊕)

All are problems with hepatocyte storage of conjugated bilirubin

Easy to remember: **D**ubin-Johnson and **R**otor spells "DR"

1) **Dubin-Johnson**

- ▶ Due to point mutation in **cMOAT**
- ▶ Benign, but the liver is black
- ▶ Can't release bilirubin-glucuronide into bile canaliculi

2) **Rotor**

- ▶ Similar to D-J, but liver isn't black
- ▶ Benign!
- ▶ Who cares?

Acute Liver Injury

Interpretation of Lab values

Indirect vs. Direct bilirubin

▶ Predominantly INDIRECT

As far as my limited knowledge goes, only three things give you an INDIRECT hyperbilirubinemia:

- 1) hemolytic anemia or related things
- 2) crigler-najjar
- 3) gilbert

▶ Predominantly DIRECT

Everything else (i.e. problems with the LIVER or obstruction)

▶ MIXED

Viral hepatitis, because the virus also causes a defect in the uptake of bilirubin

ALT/AST

▶ Technically these are NOT liver function tests

- ▶ A true "LFT" would be things like Albumin, PT, PTT (clotting factors are synthesized in the liver), etc
- ▶ But everyone calls them "LFT's" anyway
- ▶ Instead, they measure damage to hepatocytes (necrosis)

▶ If ALT ≈ AST

- ▶ Hepatocyte necrosis not due to alcohol
- ▶ If > 1,000 → ischemia, acute hepatitis, drug-induced hepatotoxicity

▶ If AST is twice as big as ALT

- ▶ **Alcoholic hepatitis**
- ▶ Usually less than 500

Other markers of liver "function"

▶ GGT (γ -glutamyltransferase)

- ▶ Measures induction of P450 system
- ▶ Technically should be ↑ in chronic alcoholism but practically no one measures it

▶ Alkaline phosphatase

- ▶ Produced by biliary canaliculi in liver (also produced in many other places in body)
- ▶ ↑ implies cholestasis (biliary obstruction)

The Liver detoxifies drugs

▶ Increasing water solubility

1) Phase 1: P450!

- ▶ Generally (not always) adds a hydroxyl group to make things a little more water soluble

Once drugs/hormones/whatever are more soluble, down the toilet bowl it goes...

- ▶ Transfers electrons to perform:

aliphatic/aromatic hydroxylation, O-, N-, or S-dealkylation, or dehalogenation

- ▶ Varies greatly in activity, can be induced/repressed by drugs

we know all of this already, leave us alone!

2) Phase 2:

- ▶ Makes things more water soluble by adding a large water-soluble group to the drug (typically after it has undergone a phase 1 reaction already)

▶ Glutathione important in "disarming" free radicals

- ▶ Acetylcysteine (contains glutathione) is the antidote to acetaminophen poisoning

Mechanism of Acetaminophen poisoning

Three things can happen to Acetaminophen in the liver:

- 1) Converted to Glucuronate by UDP-glucuronosyl-transferase → inert

- ▶ Is this the same UGT involved in bilirubin metabolism? If it looks like it and smells like it...

- 2) Converted by Sulfotransferase → inert

3) Converted to NAPQI by CYP2E1

- ▶ VERY BAD!!! Will bind covalently to cell proteins and may cause you to be on the liver transplant waiting list.

- ▶ BUT! **Glutathione-S-transferase** to the rescue!

▶ If there is sufficient **GSH (reduced glutathione)** then NAPQI is converted to Mercapturic acid, a harmless little fellow.

- ▶ If 2E1 is induced by chronic alcoholism, rifampin, barbiturates, etc, then there is a greater potential for liver damage.

Hepatitis

The following page is taken directly from my "Micro Memorizer" which covers the exact same material that was presented in class, plus a little bit we were never taught but that I learned from Q Bank (what the elusive "window period" is)

Acute Liver Injury

Clinical Hepatitis

Incubation: no symptoms

Preicteric:

Initially: **nonspecific malaise**, fever.

Later: nausea, taste change, **RUQ pain**.

↑ AST/ALT

Icteric: ~ 25%

Jaundice, ↑↑ AST/ALT, ↑ bilirubin

Fever uncommon

Convalescence +/- Chronicity

Sometimes, you see **immune complex disease** in preicteric or chronic phase: PA, glomerulonephritis, etc.

Sometimes, you see **fulminant hepatitis**: Liver failure with encephalopathy

Hepatitis A, E

Short (~4 week) incubation, **no chronicity**

Serology: **IgM anti-HAV/HEV**

HEV only: 40% mortality in pregnancy

HAV only: Inactivated vaccine available.

Immune-globulin can also be used for prevention.

HAV: Picornavirus: SS linear, unenveloped RNA

HEV: Calcivirus: SS linear, unenveloped RNA

Fecal-oral transmission

("vowels hit your bowels")

Hepatitis B

Long incubation, ~10% chronicity, but **high chronicity for neonates**

Serology: **IgM anti-HBc for acute infection**

HBsAg: surface Ag

Appears during incubation phase.

Continued presence = chronicity.

HBcAg: core Ag

HBeAg: core Ag, **infectivity**

IgG anti-HBs: provides immunity induced by vaccination or infection

IgG anti-HBc: persists for life

anti-HBe: reduction in infectivity

Treatment: Interferon- α

antiretrovirals (Lamivudine, Adefovir) for fulminant infection

Vaccine: Recombinant vaccine is envelope protein expressed in yeast.

HBV: DS, partially circular, enveloped DNA Not a retrovirus but has RT.

Blood & sexual transmission.

Hepatitis D

Requires HBV

Chronic infections common

RNA satellite virus (defective)

Hepatitis C

Medium incubation, **high chronicity**

Serology: anti-HCV not reliable

Treatment: Interferon- α , Ribavirin

Flavivirus: SS linear enveloped RNA

Blood transmission (much less sexual).

HBV Window Period

Antibodies to HBsAg are made in enough concentration to precipitate Ag out of circulation.

Called "equivalence zone" of Ab/Ag precipitation titration: no HBsAG or HBsAb in circulation

Prozone: antigen excess.

Postzone: antibody excess. HBsAb(+) and HBsAg(-)

During the window period, HBcAb is positive

Acute Liver Injury

Various cells that live in the liver

Kupffer cells

- ▶ phagocytes
- ▶ live in sinusoids

Stellate/Ito cells

- ▶ live in space of Disse
- ▶ become myofibroblasts in response to injury

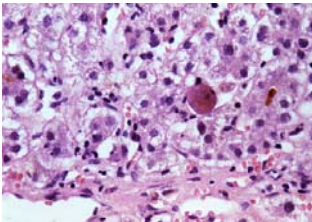
Hepatocyte response to injury

Reversible

- ▶ swelling
- ▶ steatosis → implies metabolic injury
- ▶ Mallory's hyaline
 - ▶ collapse of organelles and cytoskeletal proteins
 - ▶ rosy, dense, twisted appearance
 - ▶ associated with, but not specific to, EtOH
- ▶ pigments
 - ▶ cholestasis → bile pigment
 - ▶ wear and tear → lipofuscin
 - ▶ excess iron → hemosiderin
stains blue with prussian blue

Irreversible

- ▶ apoptosis



acidophilic body = Councilman body = apoptotic body

flushed away and broken down in spleen

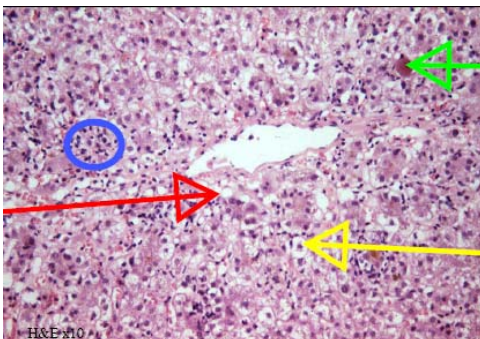
- ▶ necrosis

Overview of Common patterns of injury

1) Hepatitis

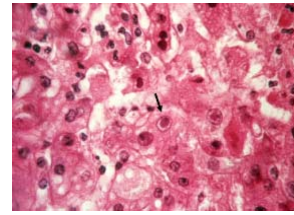
Acute

HBV



- ▶ apoptotic cells (green arrow)
- ▶ lymphocytic, inflammatory infiltrate (blue circle)
- ▶ disruption of lobular architecture/swelling (yellow arrow)
- ▶ steatosis (red arrow)

Herpes Hepatitis

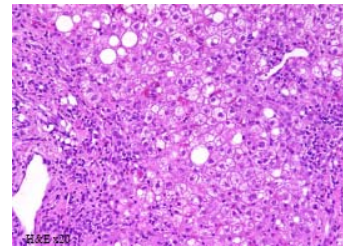


- ▶ inclusions in hepatocytes
- ▶ RARE in immunocompetent

All acute hepatitis look roughly the same, regardless of etiology

Chronic

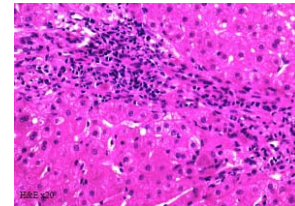
HCV



- ▶ portal tract expansion (bile duct damage)
- ▶ lymphoid aggregate
- ▶ fibrous tissue

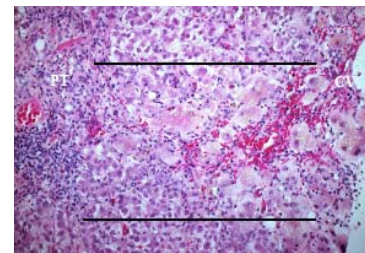
2) Nonspecific patterns of necrosis

- ▶ focal necrosis
 - ▶ limited to scattered cells within the lobule
- ▶ interface hepatitis = piecemeal necrosis



- ▶ necrosis/inflammation limited to interface between periportal parenchyma & inflamed portal tracts
- ▶ cells spill out into parenchyma
- ▶ commonly seen in chronic HCV infection

- ▶ bridging necrosis



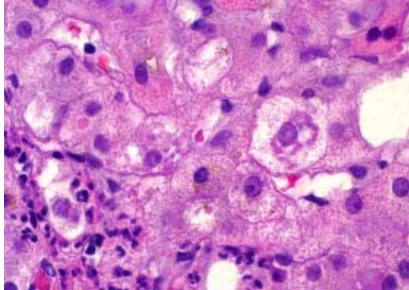
- ▶ necrosis of contiguous hepatocytes
- ▶ "collapse" of parenchyma between portal triad & central vein
- ▶ don't confuse with "bridging fibrosis"!
- ▶ massive necrosis
 - ▶ usually liver failure

Acute Liver Injury

3) Steatosis

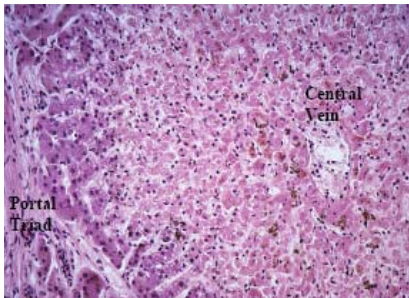
- ▶ metabolic problem
 - ▶ EtOH
 - ▶ obesity
 - ▶ diabetes, etc
- ▶ not much inflammation

4) NASH = *Nonalcoholic steatohepatitis*



- ▶ steatosis
- ▶ multifocal parenchymal inflammation (poly's)
- ▶ mallory hyaline
- ▶ apoptosis & ballooning degeneration (swelling)
- ▶ associated with diabetes, obesity
- ▶ "NASH" is a pathological term. "NAFL (non-alcoholic fatty liver) is the clinical term
- ▶ predisposes to cirrhosis (30%)
- ▶ ↑ susceptibility to HCV infection

5) Zone 3 Necrosis



- ▶ acetaminophen toxicity
- ▶ ischemic injury
- ▶ CCl₄ toxicity

Chronic Liver Injury

Cirrhosis

What is it?

- ▶ A diffuse, final-common pathway of liver injury

What are its features?

- ▶ ↑ collagen and GAG deposition
- ▶ ↑ interconnecting fibrous septa
- ▶ ↑ collagen in space of Disse
- ▶ formation of regenerative nodules by alternating death and regeneration of hepatocytes

Why is it dangerous?

- ▶ ↓ liver function → ↑ bleeding, encephalopathy, etc
- ▶ portal HTN → varices (hemoptysis), ascites
- ▶ can progress to hepatocellular carcinoma due to continued regeneration

What is its pathogenesis?

- 1) hepatocyte injury/death (drugs, virus, free-radical, etc)
- 2) immune recruitment (poly's & macrophages) → cytokine release from kupffer cells & h-cytes
- 3) activation/transformation of hepatic stellate cells
- 4) vicious cycle since ↑ collagen restricts blood supply to viable hepatocytes
- 5) return to #1 above

Viral

- ▶ HCV >> HBV

- ▶ Pathology of chronic viral hepatitis

Robbins says:

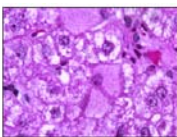
- ▶ Chronic hepatitis is characterized by necrosis of hepatocytes at the interface between portal triad and the liver lobule. This eventually leads to bridging necrosis, and finally, to cirrhosis with portal bridging fibrosis and nodular regeneration.

Banner says:

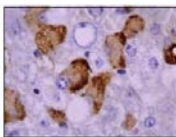
- ▶ portal inflammation with piecemeal necrosis
- ▶ spotty lobular inflammation (CD8+ cells)
- ▶ mild micro and macro vesicular steatosis

- ▶ Specific pathological features:

- ▶ chronic HCV
 - ▶ steatosis, lymphoid aggregates
- ▶ chronic HBV



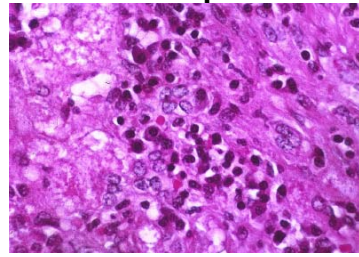
H & E stain



Immunostain for HBsAg

- ▶ ground glass inclusions (cytoplasmic HBsAg)

Autoimmune hepatitis



- ▶ specific pathological features:

- ▶ severe inflammation
- ▶ plasma cells

Alcohol

- ▶ Metabolic effects of EtOH

- ▶ ↑ NADH

- ▶ Pathogenesis

Alcohol dehydrogenase and aldehyde dehydrogenase both ↑ NADH

Acetate (product of EtOH degradation) is metabolized in the TCA cycle to yield 3 more NAHD

- ▶ Consequences of ↑ NADH

↑ TGL synthesis → fatty liver

↓ FA oxidation → fatty liver

hyperuricemia

↑ ketones (β-hydroxybutyrate)

↓ gluconeogenesis since pyruvate is shunted into lactate, not oxaloacetate

- ▶ ↑ CYP2E1 and sER hypertrophy

- ▶ more potential for toxic drug interactions

- ▶ ↑ reactive oxygen species

- ▶ Direct effects of EtOH

- ▶ acetaldehyde (intermediate product in metabolism of EtOH) can bind covalently to structural proteins, causing all sorts of problems

- ▶ disordered bile synthesis → cholestasis

- ▶ damaged tubulin

- ▶ damaged calmodulin

- ▶ formation of "neo-antigens" from damaged proteins which can be targets of immune response

- ▶ EtOH is mitochondrial poison

- ▶ Cellular response to EtOH injury

- ▶ Kupffer cells are the main "directors" of cytokines in response to injury:

- ▶ TNFα and TGFβ cause the HEPATOCYTE to ↑ collagen synthesis and also cause hepatocyte necrosis

- ▶ IL-1 and TNFα cause the ITO cell to undergo proliferation and transformation to collagen-synthesizing cell

- ▶ TGF-β directly stimulates the myofibroblasts that the ITO cells turned into

- ▶ TNFα calls in more PMN's to amplify the process

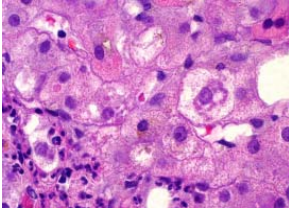
Chronic Liver Injury

▶ Clinical Syndromes of EtOH abuse

1) Fatty liver

- ▶ all heavy drinkers will get this (90-100%)
- ▶ completely reversible with abstinence & good diet
- ▶ occurs first in zone 3

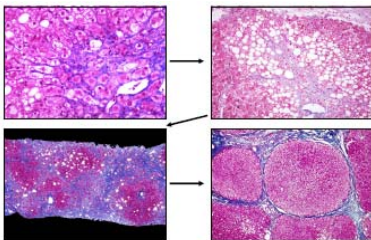
2) Alcoholic hepatitis



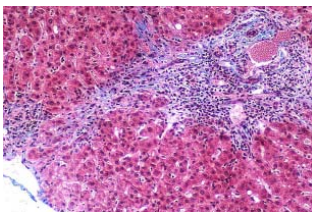
- ▶ 10-35% of heavy drinkers will get this, dose-dependent
- ▶ most patients who develop alcoholic hepatitis probably do not become symptomatic enough to reach a clinical threshold of disease
- ▶ occurs first in zone 3
- ▶ abstinence and perhaps corticosteroid therapy could cause reversal
- ▶ pathology: hepatocyte swelling, neutrophils, perisinusoidal fibrosis in zone 3

3) Alcoholic cirrhosis

- ▶ 8-20% of heavy drinkers will get this
- ▶ Pathogenesis:



- ▶ Stage 1: ↑ fibrosis in portal tracts (periportal)
- ▶ Stage 2: septal fibrosis



- ▶ Stage 3: bridging fibrosis (above): linking of fibrous septa between lobules

▶ Establishing a diagnosis between the three syndromes

- ▶ requires history, PE, labs, AND liver biopsy
- ▶ Liver biopsy needed to
 - ▶ differentiate alcoholic from non-alcoholic liver disease
 - ▶ establish the stage of alcoholic liver disease
 - ▶ evaluate possible progression to cirrhosis (zone 3 sclerosis ↑ risk of cirrhosis development)

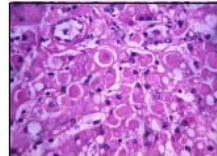
▶ Laboratory tests that imply poor prognosis

- ▶ serum bilirubin > 8
- ▶ PT > 6 secs over control
- ▶ albumin < 2.5

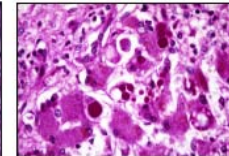
▶ Clinical management of alcoholic liver disease

- ▶ Fatty liver
 - ▶ Dietary management only:
 - ▶ must abstain from alcohol!
 - ▶ Eat 1.5 g/Kg of protein
 - ▶ vitamins
- ▶ Alcoholic hepatitis
 - ▶ Dietary management (see above)
 - ▶ prednisone in severe disease
 - ▶ Maddrey discriminant function determines severity of disease
 - ▶ H₂ blocker/PPI to ↓ risk of GI bleed
- ▶ Cirrhosis
 - ▶ colchicine inhibits fibrogenesis
 - ▶ β blocker for portal hypertension and to ↓ risk of varices rupture

α-1-antitrypsin deficiency



H&E stain

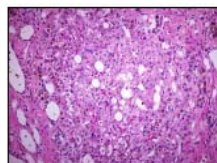


PAS with diastase stain

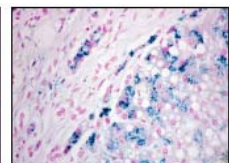
▶ PAS-positive, diastase-resistant cytoplasmic inclusions

▶ also causes pan-lobular pulmonary emphysema

Hemochromatosis



H&E stain



Prussian Blue stain

▶ deposition of hemosiderin (prussian blue)

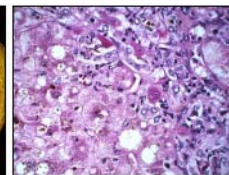
▶ cirrhosis

▶ pancreatic fibrosis

Wilson's disease

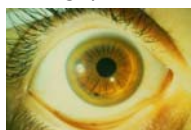


Gross Specimen



H&E x40

▶ histologically looks like acute hepatitis (w/ fatty change) or chronic hepatitis



Kaiser-Fleischer!

Chronic Liver Injury

Primary Biliary Cirrhosis

What is it?

- ▶ nonsuppurative inflammatory reaction of medium intrahepatic bile ducts
- ▶ affects middle-aged women

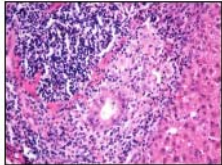
▶ *clinical features*

- ▶ xanthomas (cholesterol retention)
- ▶ jaundice late in course
- ▶ hepatomegaly

▶ *pathology*



Gross Specimen



H&E x20

- ▶ initially: lymphocytes, macrophages, plasma cells in portal tracts
- ▶ later: secondary hepatic damage → cirrhosis

Major Complications of Cirrhosis

1) *Portal HTN*

varices

large risk of rupture → massive bleeding
may be made worse by ↓ in liver function

hypersplenism

hyperfunctioning spleen → cytopenia

contributes to ascites

2) *sodium and water retention due to ↓ effective circulating volume*

also contributes to ascites

edema

3) *functional renal failure also due to ↓ ECV*

4) *porto-systemic encephalopathy*

neurotoxins (ammonia, etc) get shunted to brain
via varices

Liver Cancer

Hepatocellular Adenoma

What is it?

- ▶ Benign neoplasm composed of hepatocytes

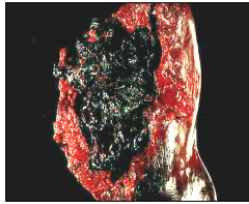
Risk Factors

- ▶ Most typical: young woman on OCP's
 - ▶ Often regress when OCP's discontinued
- ▶ Androgens (anabolic steroids)
- ▶ Tyrosinemia
- ▶ Glycogen storage disease (Type I = von Gierke)

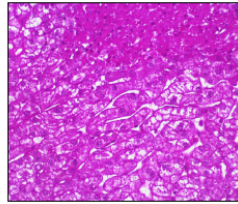
Clinical

- ▶ pain, mass, **rupture!**

Morphology



Resected adenoma
With rupture



H&E stain x20

- ▶ gross: pale, yellow-tan
- ▶ cells resemble normal hepatocytes
 - ▶ may have variation in cell/nuclear size
- ▶ ↑ glycogen
- ▶ no portal tracts → instead have prominent arteries & veins

Focal Nodular Hyperplasia

What is it?

- ▶ Benign mass of hepatocytes, bile ducts, vessels, and fibrosis in abnormal proportions, with a central scar

Risk Factors

- ▶ Adults: F>M (2:1)
- ▶ unproven association with OCP

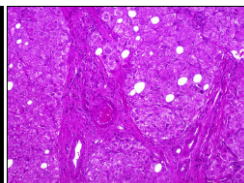
Clinical

- ▶ can be asymptomatic or have abdominal pain
- ▶ malignant potential controversial

Morphology



Gross Specimen



H&E x10

- ▶ gross: central scar radiates to periphery
- ▶ essentially normal hepatocyte parenchyma
- ▶ radiating septa have intense lymphocytic infiltrates and exuberant bile duct proliferation
- ▶ nodules of hepatocytes separated by fibrous bands

Hepatocellular Carcinoma

What is it?

- ▶ most common visceral malignant tumor

Risk Factors

- ▶ HBV, HBV, HBV, HBV, HBV, and a little Aflatoxin (from *Aspergillus flavus*)
 - ▶ HBV vaccine is a tumor vaccine!
 - ▶ HBV infection 200x relative risk
 - ▶ HBV DNA integrated into genome (even though Robbins says the main mechanism of transformation is continued cycles of restoration and repair):
 - ▶ ↑ proto-oncogene
 - ▶ ↓ p53 tumor suppressor gene
 - ▶ HBV-X factor stimulates growth (activates IGF)
 - ▶ chronic cell injury & repair → ↑ malignancy!
- ▶ Risk even greater with HBV & cirrhosis
- ▶ Arises from cirrhotic livers 85% in western countries

▶ the rate is lower in eastern countries because they have more vertical transmission in 3rd world

▶ If a mother passes HBV to the baby, there is a very HIGH chance that the baby will be a chronic carrier

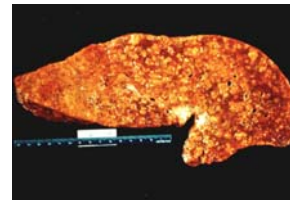
▶ Since the newborn doesn't have a good immune system yet, baby will not mount an immune attack against the virus so it will live there happily their whole life (but still ↑ risk of HCC)

Morphology

Grossly, can look:



- ▶ unifocal: one large mass (above)



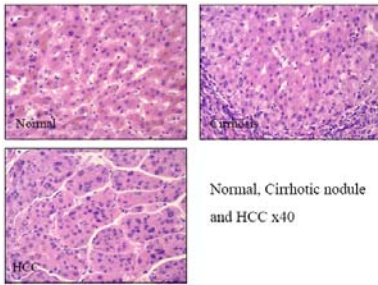
- ▶ multifocal: widely distributed nodules of various sizes (above)



- ▶ diffusely infiltrative (above)
all are paler than surrounding liver
can be green (if well-differentiated → bile)

Liver Cancer

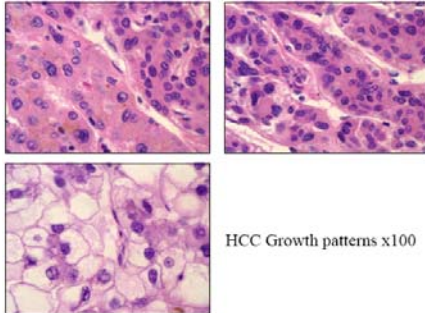
HCC Microscopic:



Normal, Cirrhotic nodule and HCC x40

(top left: normal; bottom left: HCC; top right: cirrhosis)

- ▶ can range from differentiated to anaplastic



HCC Growth patterns x100

- ▶ can be in multiple patterns
 - ▶ trabecular
 - ▶ acinar, pseudoglandular
 - ▶ poorly differentiated → pleomorphic

Behavior

- ▶ **strong** propensity for VEIN invasion, even though it's a carcinoma
 - ▶ in contrast, most carcinomas (except RCC) spread first through lymphatics
 - ▶ mass can extend snakelike into IVC
- ▶ capsule invasion, "drop" metastases
- ▶ can extend to porta-hepatis lymph nodes
- ▶ systemic mets to lung, bone, adrenal

Clinically

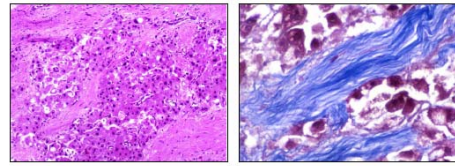
- ▶ anorexia, pain, malaise, "fullness", "mass" feeling
- ▶ **α-fetoprotein > 400 in about 70%**
- ▶ tender hepatomegaly
- ▶ bruit (hypervascular tumor)
- ▶ ascites
- ▶ fever possible

Paraneoplastic syndromes

- ▶ hypoglycemia (makes insulin-like factors)
- ▶ ↑ cholesterol
- ▶ ↑ Ca⁺⁺ (makes PTH-related peptide)
- ▶ gynecomastia (hyperestrogenism)

Fibrolamellar Carcinoma (HCC variant)

- ▶ Usually well-differentiated, better prognosis
- ▶ NOT associated w/ HBV or cirrhosis



H&E stain

Trichrome stain

- ▶ nests and cords of malignant cells in normal liver separated by dense bundles of collagen

Cholangiocarcinoma

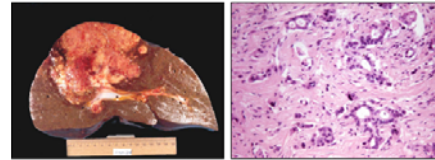
What is it?

- ▶ Malignant cells with origin from bile ducts.
- ▶ can be inside or outside of liver

Risk Factors

- ▶ liver fluke (*Opisthorchis sinensis*)
- ▶ inflammatory bowel disease (UC)
- ▶ Caroli's disease (congenital fibropolycystic disease of the biliary system)

Morphology:



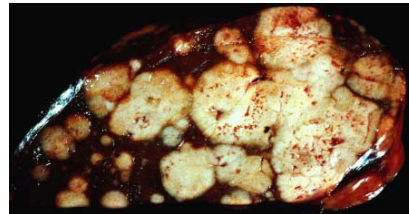
Gross specimen

H&E stain x40

- ▶ tubular glandular structures embedded in dense sclerotic stroma
- ▶ rarely bile stained (differentiated duct epithelium don't synthesize bile → hepatocytes do!)

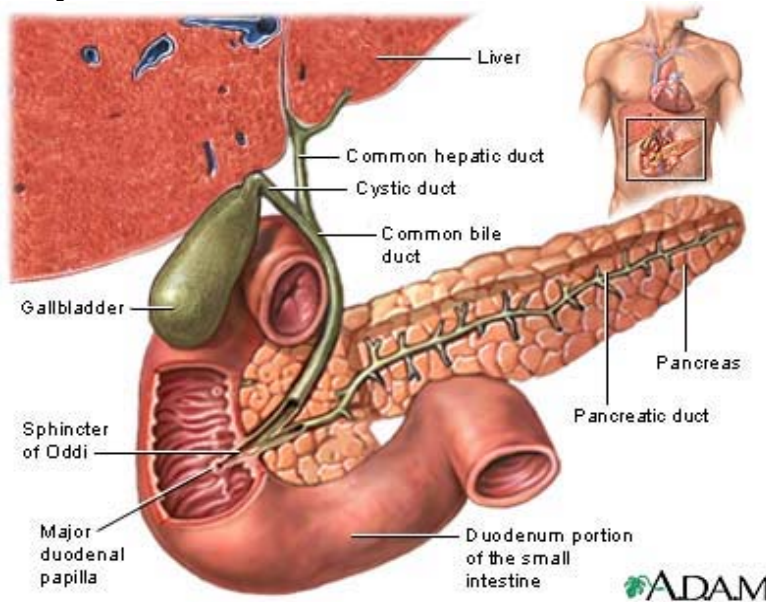
What's the most common cancer of the liver?

Metastasis!



From where? Lung! Then colon. Then probably breast.

Gallbladder/Duct Anatomy



If you understand a few simple anatomical relationships then you can figure out just about all gall bladder disease presentations. Can you imagine learning cardiology without knowing the anatomy? Of course not! Most of this is obvious, but bear with me, it's important! You must learn the freakin' ducts!

- ▶ Bile is MADE in hepatocytes and travels OUT of the liver via the **common hepatic duct**
- ▶ Bile can choose to travel INTO the gallbladder via the **cystic duct**. How it does this I have no idea because it looks like an "uphill" journey. Maybe the GB relaxes creating a negative pressure, sucking bile into it. But whatever – somehow bile makes it into the gall bladder.
- ▶ Bile flow in the **cystic duct** can be bidirectional, depending on if the GB is squeezing or not. Bile can flow out of the GB, down the **cystic duct**, merge into the **common bile duct**, through the **sphincter of oddi**, and into the **duodenum**.
- ▶ Notice that the common bile duct travels right through the **head of the pancreas!**

Just by understand the flow of bile you can answer many questions by thinking of the anatomy:

- ▶ What will happen to the flow of bile if there is a gallstone or obstruction in the **cystic duct?**

Not much!!!!!!

There will NOT be any obstruction. Whatever bile is in the GB will just stay there. New bile made by the hepatocytes will just flow right into the duodenum.

Will there be jaundice? NO!!! Sorry for all the exclamations marks, but I just discovered the secret of the stabucks "short" cappuccino.

- ▶ What will happen to the flow of bile if there is a gallstone or obstruction in the **common hepatic duct?**

You will get **OBSTRUCTIVE JAUNDICE!** I wondered, "what does that mean?" You may be wondering the same thing. Read on for the answer...

- ▶ What does pancreatitis have to do with gallstones?

I will repeat (because it's important): the common bile duct travels right through the stinking **head of the pancreas!**

Oh, and look above where the awesome Dr. Oddi found a little sphincter to make himself immortal! Right in the pancreas!

Imagine you have a shiny black or yellow stone just waiting to become infected, causing a nasty buildup of crap right there. Your pancreas don't like to be rubbed that way!

- ▶ Now do you understand (like I just did) why a cancer of the head of the pancreas can cause obstructive jaundice?

You should.

Gallbladder/Pancreas

Obstructive Jaundice

Only caused by two types of disease! It's easy!
Something is blocking the flow of bile, either **INSIDE**
or **OUTSIDE** of the liver.

1) Blockage of common bile duct (Extrahepatic obstruction)

▶ **choledocholithiasis**: gallstone in common bile duct

What could be more simple? Read below for the details of how stones are formed.

Would present clinically with COLICKY pain due to obstruction of a hollow organ. Note that the common bile duct doesn't peristaltic, but the GB squeezes every now and then, and the ↑ pressure causes pain.

↳ note that "cholelithiasis" simply means a gallstone in the gall bladder

▶ **primary sclerosing cholangitis (PSC)**

Associated with IBD (UC > CD)

fibrosis of **both** extrahepatic and intrahepatic bile ducts

I guess nothing ever fits perfectly into any category.

↑ risk of **cholangiocarcinoma**

▶ **pancreatic carcinoma (of the head)**

Remind yourself of the anatomy again

Would cause *Courvoisier's sign*: painless palpable gallbladder

Probably from backup of bile

▶ **cholangiocarcinoma**

Cancer of the bile ducts

Would also cause *Courvoisier's sign*: painless palpable gallbladder

Either from backup of bile or actual palpable mass?

Risk factors:

primary sclerosing cholangitis
Opisthorchis sinensis

▶ **Choledochal cyst**

▶ rare congenital anomaly

▶ embryological remnant becomes symptomatic in childhood

2) Intrahepatic problems with bile flow (Intrahepatic obstruction)

▶ **primary biliary cirrhosis (PBC)**

don't confuse with primary sclerosing cholangitis (PSC) like I always do!

▶ PBC is a problem with the bile duct epithelium IN THE LIVER → they express abnormal antigens that are the target of CD8+ T cells

▶ **can progress to cirrhosis → portal HTN, etc**

▶ jaundice only occurs LATE in the disease when most of bile ducts have been destroyed

▶ anti-mitochondrial antibody (probably not on our exam but it's in every board review book)

pathology:

▶ **granulomatous destruction of bile ducts in portal triads**

▶ diffusely nodular, grossly green liver

▶ fibrous bridging between portal areas

▶ prominent bile stasis

Common clinical presentation of obstructive jaundice (and how to interpret those darn labs): Note that the general presentation is the same regardless of it's intrahepatic or extrahepatic obstruction.

▶ **Jaundice due to hyperbilirubinemia (direct)**

▶ **↑↑ Alkaline phosphatase and GGT**

Alk-phos is made by the bile canaliculi epithelium. If they get irritated it leaks out into the circulation.

Alk-phos is made by other organs (placenta, blastic bone) → check GGT to see if the alk-phos is coming from the liver.

▶ **Pruritus due to bile salts in skin**

Apparently it takes a while for the bile salts to get into the skin, so you would not see pruritus in an acute obstruction

▶ **hypercholesterolemia**

because the liver has no way to get rid of cholesterol: remember, it cannot be metabolized, it can only be excreted in the bile

▶ **light stools**

urobilin gives stools their color

▶ **malabsorption**

you need bile salts to absorb fat

what vitamins could you get deficient in?

ADEK!

Carcinoma of the gallbladder

▶ **epidemiology**

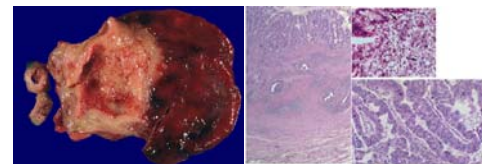
▶ associated w/gallstones (90%)

▶ F:M 2:1

▶ IBD, polyposis syndromes, porcelain gallbladder

▶ 1% 5 year survival

▶ **pathology**



▶ most (95%) adenocarcinoma

▶ mucin producing

▶ 5% squamous

▶ **Don't confuse with cholangiocarcinoma!**

▶ Cholangiocarcinoma is a cancer of the biliary tract, NOT the gallbladder.

▶ totally different risk factors!

▶ gallbladder carcinoma → gallstones

▶ cholangiocarcinoma → *Opisthorchis sinensis* and primary sclerosing cholangitis

▶ totally different presentation!

▶ gallbladder carcinoma: NO OBSTRUCTIVE JAUNDICE

Gallbladder/Pancreas

Pathogenesis of gallstones

1) supersaturation of bile

- ▶ bile MUST become supersaturated with either cholesterol or bilirubin
- ▶ **cholesterol stones** (yellow)
 - risk factors: fat, fertile, forty, female, ↑ TGL's (and being native american)
 - ↑ secretion of cholesterol (↑ estrogen) or ↓ secretion of bile salts (ileal disease)

▶ pigment (bilirubin) stones (black)

- risk factors: anything causing ↑ hemolysis!!
- the macrophages in the RES system chew on the heme and convert it to biliverdin then bilirubin. Pretty cool how it all ties together when you think about it, isn't it?
- totally different risk factors from cholesterol stones!

2) crystal formation

- biliary proteins play a role in forming a nucleus for the crystal to grow on

3) crystal entrapment in mucus

- gallbladder sludge forms when crystals get stuck in mucus

honey, what's for dinner? "I'm pan-roasting a nutmeg liver with caseous necrosis soufflé and for desert we'll have gallbladder sludge sundae with strawberry cervix sauce!"

4) stasis

- poor GB motility → can be due to fasting, SC injury, etc

Presentations of Gallstone disease

1) Asymptomatic cholelithiasis

- ▶ no need to treat (but ↑ risk of GB cancer)

2) Biliary colic

- ▶ gallstones transiently obstruct cystic duct
- ▶ RUQ pain (may radiate to back), nausea, vomiting
- ▶ NO Jaundice! But you already knew this already!!
- ▶ Must be treated!

▶ surgically

cholecystectomy: take the disgusting thing out

▶ medically

chenodeoxycholic acid (not very effective)
(should ↓ cholesterol saturation of bile)

3) Cholecystitis (can be acute or chronic)

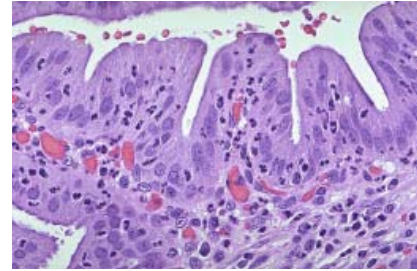
- ▶ inflammation/infection of impacted stone in cystic duct
- ▶ begins as biliary colic, but can progress to systemic signs of inflammation (fever, etc)
- ▶ localized tender pain in RUQ
- ▶ Is there jaundice? I shouldn't have to answer this by now – it's in the cystic duct!

- ▶ therapy: surgery only

▶ complications:

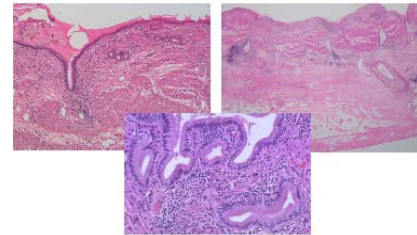
- ▶ perforation, abscess
- ▶ ascending cholangitis
- ▶ pancreatitis

▶ acute pathology



edema, congestion, hemorrhage, mucosal ulcers w/necrosis & poly's

▶ chronic pathology



▶ fibrosis, chronic inflammation

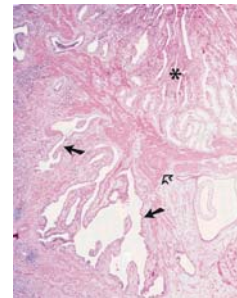
▶ epithelium can be atrophic, metaplastic, regenerative

▶ prominent sinuses

deeply invaginating mucosa without muscular coat

▶ complications of chronic cholecystitis

▶ adenomyoma



▶ exaggerated diverticular admixed w/SM proliferation

▶ forms a mass (fundus) or can be diffuse (adenomyosis)

▶ porcelain gallbladder



▶ end-stage chronic cholecystitis

▶ diffuse fibrosis and dystrophic calcification of gallbladder wall (muscle & lamina propria)

▶ ↑ risk of GB carcinoma

▶ hydrops of gallbladder

▶ atrophic, chronically obstructed gallbladder

▶ contains only clear secretions

Gallbladder/Pancreas

4) Ascending Cholangitis

- ▶ infection caused by backup due to obstruction of extra-hepatic biliary system
- ▶ presents as OBSTRUCTIVE JAUNDICE + systemic inflammation (fever, probably leukocytosis, etc)
- ▶ Based on the obstructive jaundice presentation & labs (which you now know so well), the only way to differentiate between this disease and parenchymal liver disease is by imaging studies. I'm not sure how true that is because this is an ACUTE INFECTION and should present with prominent fever, etc...
- ▶ Emergency, must be drained.
Can be performed by ERCP

5) Gallstone Pancreatitis

How to diagnose GB/pancreas disease

First diagnostic test to workup GB disease:

Ultrasound!

First diagnostic test to workup pancreatic disease:

CT! The pancreas is retroperitoneal – you won't be able to see anything on US!

The deal about ERCP

Only used if there is very high suspicion of a specific illness (i.e. gallstones)

Invasive test, but can intervene therapeutically

Forget oral cholecystography

maybe when these notes were written in 1820 people still used this

Mostly useless GB trivia

Histology of the GB

Rokitansky-Aschoff sinuses

- ▶ protrusions of GB luminal epithelium into the muscularis propria layer
- ▶ due to gallstones

GB has no submucosa or muscularis mucosa

Bile composition

▶ Cholesterol

- ▶ present in extremely high concentrations in bile due to equiosmolar micelles

▶ bile salts

- ▶ cholesterol conjugated with a polar structure (glycine or taurine)
- ▶ most abundant organic component of bile
- ▶ act as detergents, can form micelles

▶ phospholipids

▶ bilirubin (only a minor component despite all the fuss)

▶ mucin, IgA, etc

Bile flow and recirculation

▶ **motilin**

- ▶ promotes relaxation of GB and contraction of sphincter of oddi
- ▶ cases bile to flow "upstream" into the GB
- ▶ released between meals

Bile concentration in the GB

- ▶ during storage, mucosal epithelium of GB actively absorbs electrolytes → water follows
- ▶ bile salts and lipid remain in lumen and become very concentrated
- ▶ as they are concentrated, they form micelles to remain isoosmotic (pretty clever of them!)

▶ **cholecystokinin (CCK)**

- ▶ stimulates gallbladder contraction and sphincter of Oddi relaxation
- ▶ bile flows into duodenum
- ▶ released post-prandially

Entero-hepatic recirculation of bile salts

- ▶ In distal ileum, most bile salts are reabsorbed actively
- ▶ the remainder are deconjugated by colonic anaerobes and some are partially reabsorbed in the colon
- ▶ bile salts absorbed from ileum or colon → liver via portal circulation

Gallbladder/Pancreas

Pancreatic secretion of juice

▶ **cholecystokinin**

- ▶ stimulated by fats and proteins in duodenum
- ▶ released from neuroendocrine cells in duodenum
- ▶ CCK stimulates pancreas to secrete digestive enzymes

▶ **secretin**

- ▶ stimulated by acid in the duodenum
- ▶ also released from neuroendocrine cells in duodenum
- ▶ secretin stimulates secretion of Cl^- and bicarb

▶ "juice" composition

- ▶ both acinar and ductal cells secrete fresh-squeezed florida-fresh pancreatic juice
- ▶ flow of juice mediated by flow of Cl^- through the famous CFTR channel
 - ▶ in CF, the channel is defective, so the "juice" is very very thick → pancreatitis!
- ▶ water follows chloride paracellularly
- ▶ in the ducts, bicarb is exchanged for Cl^- → lots of bicarb in the juicy-juice

Protective mechanisms of the pancreas

- 1) Digestive enzymes kept separate in vesicles
- 2) Protease inhibitors inactivate "accidentally" activated proteases
- 3) all enzymes except amylase & lipase stored as pro-enzymes
- 4) acid pH of zymogens inactivates prematurely activated trypsin
- 5) ↓ $[\text{Ca}^{2+}]$ inhibits trypsin activation

Etiologies of pancreatitis

1) ductal theory

- permeability of main pancreatic duct increased
 - ▶ pancreatic enzymes can escape the duct and chew on the pancreas
 - ▶ can be caused by bile reflux (i.e. gallstones), alcohol, and ↑ $[\text{Ca}^{2+}]$

2) acinar cell theory

- acinar cells directly damaged by alcohol, drugs, infections, etc

3) blood vessel theory

- ischemia causes pancreatitis
- release and activation of proteases
- seen in severe shock

4) A "new" theory

- inspired by hereditary pancreatitis
 - ▶ cationic trypsinogen gene (chrom 7)
 - ▶ trypsin cannot be inactivated once it's activated

Acute Pancreatitis

Clinical

- ▶ abdominal, pain, vomiting
- ▶ mid-epigastric pain, may radiate to mid back

Etiology

- ▶ **caused mostly by gallstones or alcohol**
- ▶ less often, caused by drugs, infections, etc

Ranson's criteria (or CT scan) used to determine severity

- age > 55
- WBC > 16K
- glucose > 200
- LDH > 350
- AST > 250

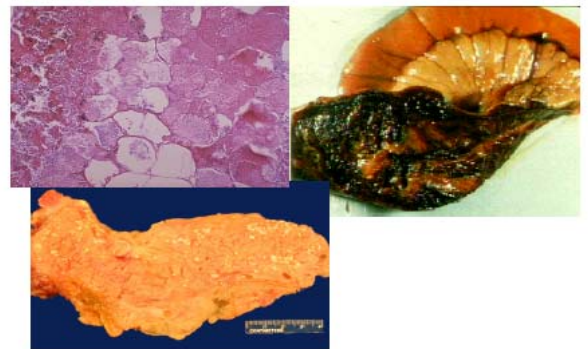
▶ **non-severe acute pancreatitis**

- less than 3 ranson's criteria

▶ **severe acute pancreatitis**

- more than 3 ranson's criteria

Pathology



Amylase and Lipase

- ▶ ↑ amylase and lipase signifies pancreatitis
- ▶ absolute value does NOT correlate with severity of injury
- ▶ may be normal in chronic pancreatitis and pancreatic cancer
- ▶ lipase is more SPECIFIC to the pancreas

Gallbladder/Pancreas

Chronic pancreatitis

Pathological features

- ▶ duct obstruction
- ▶ atrophy of acinar cells
- ▶ parenchymal fibrosis

Clinically

- ▶ recurrent or persistent pain but no inflammation
- ▶ exocrine insufficiency
 - ▶ diarrhea
 - ▶ steatorrhea
 - ▶ weight loss
- ▶ endocrine deficiency if long standing →DM

Etiology

- ▶ **EtOH most common etiology**
- ▶ hereditary pancreatitis
- ▶ CF
- ▶ congenital anomalies (pancreas divisum)

Pathology

- ▶ glands unevenly affected
- ▶ indurated
- ▶ nodules
- ▶ calculi (pathognomonic of chronic pancreatitis)
- ▶ bile duct dilatation
- ▶ can mimic carcinoma

Complications

- ▶ pseudocysts
 - extrapancreatic, turbid contents, not true cysts

Pancreatic Cancer

The basics:

- ▶ 3 categories recapitulating normal pancreatic components (ductal, endocrine, exocrine)
- ▶ most are malignant, but a few subtypes can be indolent
- ▶ tumor-produced products dominate clinical picture

1) Ductal tumors

▶ ductal adenocarcinoma

epidemiology

- ▶ ~90% of malignant exocrine pancreatic tumors
- ▶ M > F
- ▶ 3.5% 5-yr survival
- ▶ occur mostly in head of pancreas

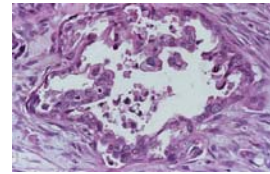
clinical picture

- ▶ abdominal pain, weight loss, jaundice (if in head of pancreas!)

gross features

- ▶ gray-white, infiltrative mass
- ▶ small lesions may be inapparent
- ▶ usually extends beyond pancreas to invade duodenum, bile duct, spleen, adrenal

microscopic features



- ▶ adenocarcinoma with irregular, small glands
- ▶ dense fibrotic stroma, perineural invasion
- ▶ aggressive, infiltrative growth pattern

▶ intraductal papillary mucinous neoplasm

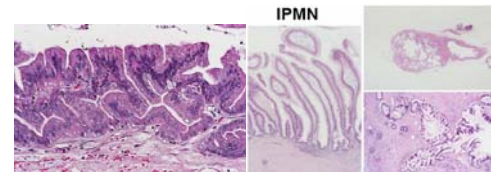
epidemiology

- ▶ **good prognosis! (>10 year survival)**
- ▶ complete resection usually curative
- ▶ M > F

clinical

- ▶ presents with symptoms of acute or chronic pancreatitis
- ▶ 50% develop pancreatic insufficiency
- ▶ 35% harbor invasive carcinoma

pathologic features



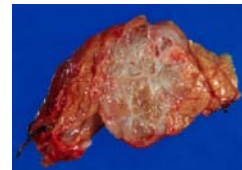
- ▶ papillary pattern, intraluminal MUCIN deposition
- ▶ intraductal proliferation of mucinous cells

▶ serous cystadenoma

epidemiology

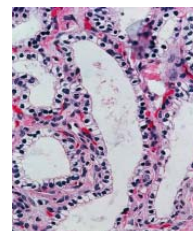
- ▶ 1-2% of exocrine tumors
- ▶ F > M (unlike the two above)
- ▶ associated with my favorite disease: VON HIPPEL LINDAU! Chromosome 3! RCC!!
- ▶ **most are benign**

gross characteristics



- ▶ well demarcated, solitary mass
- ▶ numerous cysts
- ▶ fibrous septae
- ▶ central stellate scar

microscopic features



- ▶ single layer of cuboidal cells
- ▶ clear cytoplasm
- ▶ small round nuclei

Gallbladder/Pancreas

2) Endocrine tumors

▶ pancreatic endocrine tumor

epidemiology

- ▶ 5-8% of pancreatic tumors
- ▶ most make hormones
- ▶ associated with MEN-1

clinical picture depends on hormones!

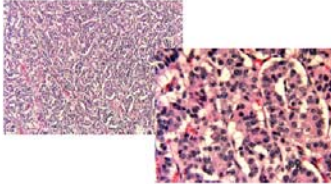
Zollinger-Ellison → **gastrin**

Hyperglycemia → **glucagon**

Hypoglycemia → **insulin**

Watery diarrhea, hypokalemia → **VIP**

microscopic features



(islet cell tumor above)

- ▶ round, uniform cells
- ▶ "salt and pepper" chromatin
- ▶ trabecular, gyriform, rosette-like patterns

biologic behavior

- ▶ malignant tumors tend to be larger
- ▶ **glucagonomas malignant**
- ▶ **insulinomas benign**
- ▶ can metastasize to liver, regional lymph nodes
- ▶ long-term survival DESPITE metastases

3) Exocrine tumors

▶ acinar cell carcinoma

epidemiology

- ▶ 1-2% of pancreatic tumors
- ▶ M > F

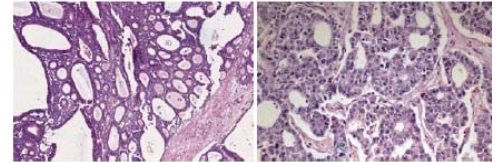
clinical picture

- ▶ disseminated fat necrosis and arthralgias
- ▶ uniformly malignant, poor prognosis

gross features

- ▶ large, solid tumors up to 30 cm
- ▶ has nodules like the pancreas
- ▶ fleshy, soft, tan-yellow
- ▶ absence of prominent stromal reaction

microscopic features



- ▶ nodules of cells, lacking desmoplastic stroma
- ▶ trabecular or solid growth pattern
- ▶ common vascular invasion
- ▶ polarized cells with granular cytoplasm
- ▶ prominent, single nucleoli
- ▶ PAS-D positive granules