Harvard-MIT Division of Health Sciences and Technology
HST.121: Gastroenterology, Fall 2005
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HST 121
Gastrointestinal Pathophysiology
Sections between Midterm and Final.

A few general comments...
1. Typically, the final exam is much more clinically oriented than the midterm exam. It is also longer and more difficult.
2. Therefore, make sure you study the minicases & clinics very thoroughly, and try to integrate this material with what you learned in the sections & labs.
3. The main subject of the post-midterm part of the course has been the liver, along with the pancreas and biliary tract. I recommend skimming/reading parts of Lippincott's Illustrated Review of Biochemistry (by Champe & Harvey) since much (if not most) of liver physiology is really biochemistry.
4. Please know and understand your classmate's questions. Dr. Carey may change these a bit, but many of these will be on the exam.
5. Email me if you have any questions (lynn_punnoose@student.med.harvard.edu).

Section 11: Lipids (Carey)

Focus on application of these ideas to biology (eg., plasma & intracellular membranes, lipoproteins).

1. You should know the basic categories of lipid systems (both single & mixed) and be able to give biological examples wherever possible. Important ones include:
□ *liquid crystals/mesophases* (lyotropic and thermotropic formation)
□ *micelles* include bile salts

□ *mixed liquid crystals* include cell and organelle membranes, biliary mixed vesicles
    □ these are *lamellar* liquid crystals, which means that the lipids can move freely only in the two dimensions within the plane of the lamella
□ *mixed micelles* include biliary mixed micelles
□ *stable emulsions* (dispersions of lipid in lipid) include plasma lipoproteins, dietary fat

2. Understand the difference in behavior between nonpolar and polar lipids. Basically:
□ nonpolar lipids form oils
□ polar lipids can interact with aqueous solvents in various ways:
□ insoluble, non-swelling: alone, form crystals or oil droplets; found in mixed micelles, membranes (cholesterol); function as emulsifiers
□ insoluble, swelling: form liquid crystals (phospholipids that make membranes), found as emulsifiers in lipoproteins
□ soluble: form micelles; example is bile salts

3. Know the *three "P" rules*.
□ Predictability rule: you can predict the physical form of a lipid in a biological system if you know how the lipid behaves in an aqueous system.
□ Predominance rule: the majority lipid will govern the behavior of the system
□ Phase rule: $F = C - P + 2$, where F=degrees of freedom (variance), C=number of components (order), P=number of phases.
□ Basically, if you have a system, you count up how many chemical constituents there are (C) and how many phases there are (liquid, gas, solid, liquid crystal, etc.). This tells you F, which is the number of variables you can change without changing the properties of the phases or constituents. The possibilities for F are temperature, pressure, and concentration.

4. Know the basics of examples of biologically relevant lipid systems.
□ Cholesteryl Esters: biological variations in temperature can change their phase from crystal to liquid crystal to oil. They are the major kind of cholesterol in blood.
□ Cholesterol/Water: think of gallstones and atherosclerosis
□ Phosphatidylcholine (lecithin)/Water: think of model membranes/vesicles
□ Bile Salt/Water: remember from above_forms micelles
□ Cholesterol/Lecithin/Water: cell membrane. *Note*: there is a small region of the system's phase diagram where the lamellar liquid crystalline phase can exist by itself. This establishes the boundaries for concentrations physically allowed within the cell membrane; ratio of 1:1 cholesterol:lecithin is upper limit.
□ Bile Salt/Lecithin/Cholesterol/Water: models both gallstones and fat digestion depending on which part of the system's phase diagram you look at.

5. Biomembranes: a few things to point out.

☐ Notice the amount of cholesterol in different membranes: mammalian plasma membranes contain up to 1:1 cholesterol:lecithin but organelles have little.

☐ Roles of lipids in membranes include:

  ☐ structure; eg., caveolae, which are plasma membrane domains of specific lipid composition

  ☐ second messengers; eg., IP_3, PIP_2, DAG

  ☐ anchors for membrane proteins

Different lipids are in inner/outer membrane leaflet. PS, PI, PE are inside; PC, glycosphingolipid, gangliosides are outside. When a cell (eg., RBC) is senescent, amino phospholipid flipase stops working, allowing PS to flip slowly from the inner to the outer leaflet, signalling for destruction.

6. Lipid movement

☐ across membranes

  ☐ as single molecules: rely on passive diffusion, facilitated diffusion, coupled transport, active transport. Eg: bile salt transporters in enterohepatic circulation (see Section 15)

  ☐ as aggregates: endocytosis (eg, LDL endocytosis) or scavenger receptors (eg, HDL internalization) play roles here.

☐ in liquid. Eg: lipids are carried inside lipoprotein emulsions in plasma (see section 19)

Section 12: Physiology & Biochemistry of Exocrine Pancreas (Freedman)

The exocrine pancreas secretes digestive enzymes, bicarbonate, mucin, and water into the duodenum.

  ☐ Acinar cell secretes zymogens and enzymes.

  ☐ Centroacinar and intralobular duct cells secrete bicarbonate and water.

  ☐ Interlobular and main duct cells secrete bicarbonate and mucin.

  ☐ Bicarbonate needed for zymogen solubility & apical membrane trafficking in acinar cell

1. What does the acinar cell secrete?

☐ Trypsinogen, chymotrypsinogen, proelastase, carboxypeptidases digest peptides.

☐ Amylase begins breakdown of amylose & amylopectin yielding maltose & maltotriose.

☐ DNAse, RNAse

☐ Elastase, collagenase, phospholipase

☐ Pancreatic Lipase, which requires colipase.

2. How is the pancreas protected from these destructive enzymes?

☐ Before secretion, enzymes are in membrane-bound compartments separate from lysosomal enzymes. Acidity of compartments inactivates trypsin.

☐ Enzymes are secreted as inactive precursors (zymogens) that require enterokinase, released from duodenal mucosa, as a trigger. Enterokinase needs Ca_{++}, which is lacking

in the pancreatic ducts.

☐ Trypsin inhibitors (PSTI) and degraders (mesotrypsin) are found in the pancreas. In the plasma, there are protease inhibitors like α_1 antiproteases & α_2 macroglobulin.

3. How is secretion regulated?

☐ Brain, food in stomach, chyme in duodenum cause duodenal mucosal endocrine cells to secrete *cholecystokinin (CCK)* and *secretin*.

☐ Feedback regulation of CCK: trypsin in duodenum degrades CCK-Releasing Factor when no food is present. If food is present, trypsin digests food, leaving CCK-RF intact to stimulate CCK release.

☐ CCK causes gallbladder to contract, sphincter of Oddi to relax, and acinar cell to secrete. Secretin stimulates ductal cells to secrete bicarbonate & water via CFTR.

☐ CCK acts by

    ☐ Stimulating cholinergic neurons in pancreas, leading to secretion

    ☐ CCK A & B receptors via G-protein, PLC, PKC signalling system.

☐ Somatostatin inhibits CCK and secretin release. Remember D-cell secretion of SS is stimulated by low pH in the stomach, which occurs when no food is present.

☐ Other hormones: bombesin, vasoactive intestinal peptide (VIP)

4. Dietary adaptation: high protein diet stimulates CCK, increases synthesis of proteases. High fat diet stimulates secretin, increases lipases. High glucose diet stimulates insulin, increases glycosidases.

    ☐ Hereditary pancreatitis (rare cause of pancreatis): normal autodigestion of trypsin at Arg 117 stopped by mutation to His 117.

Section 13: Pancreatitis (Hint: Dr. Apstein usually uses the SAME question each year)

Acute Pancreatitis

Inflammation occurs due to increased pancreatic duct permeability, acinar cell injury, ischemia.

Causes:

1. *Gallstones* most frequent cause.
2. Alcohol usually leads to multiple bouts of pancreatitis, therefore chronic pancreatitis
3. Other, including hypercalcemia, imuran, mumps, ductal obstruction, trauma, hypotension.

Pancreatic inflammation→necrosis in & around pancreas→abdominal pain radiating to back. Sometimes this produces pseudocysts (not lined by epithelium).

Systemic manifestations are life-threatening:

☐ vasodilation (kallikrein, bradykinin), blood vessel damage (elastase), capillary permeability

☐ DIC due to thrombin activation

☐ ARDS due to phospholipase A_2 digestion of lung surfactant

☐ local & distal fat necrosis

☐ overloaded plasma protease inhibitor mechanisms

Diagnosis/Prognosis:

1. Diagnosis is clinical, based on pain, systemic symptoms, ↑WBC, ↑ serum amylase/lipase.
2. Signs of worse prognosis: ecchymoses, Ranson's criteria, necrosis seen on CT scan.

Treatment: treat as "inside burn"
Mainly supportive: pain relief, IV fluids & nutrition.
Important to remove gallstone from common bile duct if pancreatitis is severe and unresponsive to supportive therapy.

Summary: clinical approach to acute pancreatitis

Figure removed due to copyright reasons.

Baron et al. (1999). NEJM 340: 1412

Chronic Pancreatitis
Main cause is *alcoholism* (at least 10 years of very heavy drinking).
Other causes include hereditary pancreatitis, cystic fibrosis.

Clinical features: pain, calcification, steatorrhea due to exogenous panceas failure (i.e. lack of secretion of digestive enzymes), diabetes (endogenous function), (the last 2 only in severe disease).

Diagnostic tests include Endoscopic Retrograde Cholangiopancreatography (ERCP), CT scan, secretin test. (ERCP is also used to remove gallstones from common bile duct.)

Section 14: Pathology of Pancreas & Biliary Tract (Glickman)

Pancreas (Exocrine) -
Structure:
☐ Multiple branching ducts terminated in acini where zymogens are secreted.
☐ Ducts join to form main pancreatic ducts that then join common bile duct at ampulla of Vater, where they empty into the duodenum.

▢ Flow past ampulla of Vater is regulated by sphincter of Oddi.
For function, see above.

Pathology:
▢ Cystic Fibrosis:
       ▢autosomal recessive genetic disorder; 5% carrier rate in whites
       ▢50% mortality by age 10, but some live to their 30's.
       ▢increased viscosity of of mucous secretions due to defect in a cAMP-activated
        chloride channel (cystic fibrosis transmembrane conductance regulator, or CFTR)
       ▢most common mutation is _F508, in which protein cannot be exported from ER
       ▢can lead to meconium ileus, gallstones, cholecystitis, biliary cirrhosis, pancreatic
        enzyme insufficiency, IDDM, pancreatitis.

▢ Pancreatitis (see above).

▢ Carcinoma:
       ▢majority arise from ductal epithelium & are adenocarcinoma
       ▢male smokers > 50 years old are at highest risk.
       ▢Clinically, presents as painless jaundice, palpable gallbladder (Courvousier sign),
        and migratory thrombophebitis (10% of the cases but classically described as
        Trousseau sign).
       ▢Prognosis is dismal: 5-year survival is 3%, accounting for 5% of cancer deaths in
        US
       ▢Surgical resection is sometimes possible (whipple's procedure), but very rarely
        achieves complete remission.
▢ Zollinger-Ellison syndrome (see midterm).

Biliary Tract

Structure and Function:
▢ Bile canaliculi in liver fuse to form (finally) common hepatic duct, which joins cystic
  duct from gallbladder to form common bile duct, which then joins pancreatic duct at
  ampulla of Vater.
▢ Bile passes through biliary tree, where exchange of inorganic & organic ions & water
  occurs and secretin-stimulated secretion of bicarbonate rich fluid occurs.
▢ Gallbladder is a hollow organ that stores bile and concentrates it by removing inorganic
  ions & water.
▢ CCK (see midterm) causes gallbladder contraction and sphincter of Oddi relaxation.

Pathology:
▢ Cholelithiasis (gallstones): very common, a whole spectrum of presentations as follows:
▢ Biliary colic: When gallstones temporarily obstruct the cystic duct or pass through into
  the common bile duct. Constant pain in RUQ or epigastrium, not colicky.
▢ Cholecystitis: inflammation of gallbladder, sterile or bacterial. Pain similar to biliary
  colic but more prolonged.
       ▢ Acute: almost always associated with gallstones; if not, often due to ischemia.
        Complications include necrosis and rupture/peritonitis.

□ Chronic: a pathologic diagnosis (i.e., NO symptoms), associated with gallstones 90% of the time. Inflammation→fibrosis, ulceration of mucosa, plasma-cell infiltrate.

□ Courvoisier's sign: palpable, acutely swollen gallbladder in the setting of Pancreatic CA.

□ Cholangitis: bacterial infection of the bile duct (due to stone, stent, catheter, acute pancreatitis, etc). Ascending cholangitis involves intrahepatic biliary tree, risk of sepsis and liver abscesses, rather than cholestasis.

□ Extrahepatic biliary atresia: found in 1/10,000 neonates; causes jaundice.

□ Primary biliary cirrhosis: anti-mitochondrial Ab

□ Primary sclerosing cholangitis: associated with ulcerative colitis.

□ Cancers: In gallbladder, carcinomas associated with gallstones. Rare in bile ducts.

Section 15: Biliary Secretion & Gallstone Formation (Carey)

Bile

Why do we have it?

□ For dispersion of dietary lipids in upper small intestine; this allows digestion & absorption.

□ For excretion of endogenous lipids, including bilirubin, cholesterol, and phosphatidylcholine.

What's in it?

□ bile salts

□ cholesterol

□ bilirubin

□ phosphatidylcholine (lecithin)

□ water (secreted passively by hepatocyte & ductal epithelium, absorbed in gallbladder)

□ bicarbonate (secreted with water by ductal epithelium via CFTR in response to secretin)

Bile salts:

1. In hepatocyte, cholesterol is converted to *primary bile acids* (cholate, chenodeoxycholate) by cholesterol 7α-hydroxylase (in ER; rate-limiting enzyme) & cholesterol 27 hydroxylase (mitochondrial).

2. Still in hepatocyte, bile acids are *conjugated* to glycine or taurine, making them more water soluble & better able to emulsify. They are now called *bile salts*.

3. Bile salts are secreted into canaliculus by special transporters:

□ Sister-to-P-glycoprotein=*bile salt* export pump (SPGP/BSEP, mutation in this gene causes type II PFIC)

□ Multiple-drug-resistance-related protein 2 (MRP2=cMOAT, mutations in this gene causes *Dubin-Johnson syndrome*).

4. Bile travels through bile ducts, is stored in gallbladder. Modifications mentioned above occur, as well as acidification in gallbladder.

5. In intestines:

□ normal bacterial flora of distal ileum, cecum, & colon modify bile salts:

□ remove 7α-hydroxy group, leading to *secondary bile salts*

□ other changes (e.g., sulfate addition) lead to *tertiary bile salts*

▢ hydrolyze amide linkage to glycine/taurine, leading to "unconjugated bile salts" or bile acids; this is called deconjugation

▢ mixed micelles (bile salts, cholesterol, lecithin) or vesicles form depending on whether bile is cholesterol-saturated. These emulsify dietary lipids, aiding dispersion/digestion.

▢ some bile is lost in the feces; this is the only mechanism of *cholesterol excretion*

▢ bile salts & acids are absorbed, mainly by $Na+$-coupled ileal bile-salt/acid transporter (IBAT) on apical membranes of distal ileal enterocytes (a.k.a: ASBT)

6. Bile salts/acids return to liver via portal venous system.
7. Hepatocytes take them up from the sinusoids by membrane transporters: $Na+$-taurocholate polypeptide (NTCP), Organic anion transport polypeptide (OATP). Very hydrophobic unconjugated bile acids can enter hepatocyte passively through membrane.
8. Once in hepatocyte, unconjugated bile acids are re-conjugated, but secondary/tertiary bile acids/salts cannot be re-converted to primary—they just get re-conjugated (if necessary).
9. Then bile salts can be secreted again. This is the enterohepatic circulation, and it occurs about ten times a day.

Summary of bile salt transporters:

Location	Process	Transporter
Distal ileum	Apical absorption (~90%)	Na+ coupled: ASBT
	Cytosolic transport	ILBP
	Basolateral release	MRP3
Jejunum, ileum	Apical absorption (~10%)	OATP3 (passive diffusion also)
Colon	Apical absorption (~10%)	Passive diffusion
Portal blood	Transport	50% bound to albumin, 50% to HDL
Hepatocytes	Basolateral entry	NTCP (80%)
		OATP's (20%)
	Release into bile	BSEP for monovalent salts (98%)
		MRP2 for divalent salts
	Out through lateral membrane	MRP1,6

Some transporters for other bile constituents

Molecule	Location	Transporter (function)
cholesterol	Canalicular membrane-hepatocyte	ABCG5, 8 (release into bile)
lecithin	"	MDR3 (release into bile)
Amino-phospholipid	"	FIC1 (release into bile)

Also understand ways in which enterohepatic circulation can go wrong

Gallstones
Epidemiology, etc.
▢ most expensive GI disease in US
▢ more common in Scandinavia/Northern Europe, with 2:1 female:male ratio for cholesterol stones
▢ epidemic prevalence (cholesterol stones) in Pima Indians; higher in women in 20s & 30s but equal in both sexes later on in life (the 4 "F": female, forty, fat, fertile)

☐ hemolytic anemias lead to increased risk of pigment gallstones

Types

☐ Pigment gallstones are made up of calcium bilirubinate and other calcium salts.
    ☐ Black stones are made of polymerized calcium bilirubinate and inorganic calcium salts (calcium phosphate/carbonate). Black stones form in gallbladder due to deranged physico-chemical factors: ↓solubilizers, ↑ calcium, ↑ anions, ↑ bile pH.
    ☐ Brown stones are made of free calcium bilirubinate salts and organic calcium salts (calcium palmitate/stearate). Brown stones form in bile ducts, often associated with infection that results from cholestasis due to chronic obstruction.
☐ Cholesterol gallstones can contain up to 50% calcium pigment salts, inorganic calcium salts. They form in the gallbladder.
1. Hepatic hyperproduction (active HMG-CoA reductase) & hypersecretion (sterol carrier protein 2) of cholesterol.
2. Cholesterol supersaturation of bile leads to biliary vesicles composed of 2:1 cholesterol:phospholipid.
3. Such vesicles nucleate cholesterol crystals.
4. Increased cholesterol causes gallbladder to absorb cholesterol.
5. This causes ↑NO, leading to inflammation & gallbladder hypomotility (CCK resistance). Also ↑mucin production.
6. Thus, cholesteryl esters accumulate in gallbladder wall (*strawberry gallbladder*), leading to stiffening & more permanent hypomotility (gallbladder failure).
7. Meanwhile, excess cholesterol precipitates in mucin gel, producing biliary sludge that may go on to form gallstones.

Sections 17: Imaging & Endoscopy (Schapiro)
These two sections give us a quick glimpse of the clinical-interventional side of gastroenterology; what can we *do* about things?

The details are not important right now. You should remember the pros & cons of imaging & endoscopy in general, with perhaps an example or two as well.
☐ Radiology is non-invasive but doesn't give access to inside of GI tract, as endoscopy does.
☐ Radiology is best for:
    ☐ quickly, cheaply defining obstruction, perforation, or calcification
    ☐ with barium contrast, measuring function
    ☐ visualization of the vascular tree (e.g., to identify site of active bleeding)
    ☐ diagnostic aspiration & therapeutic drainage of abscesses
    ☐ shock-wave lithotripsy
    ☐ gallbladder, biliary tree, pelvic organs: stones, cysts, masses, aneurysms (ultrasound)
    ☐ suspected pancreatitis, pancreatic cancer, hepatic metastases, abscesses (CT scan)
    ☐ differentiating cyst from vascular structure (MRI)
    ☐ some invasive procedures
        ☐ percutaneous transhepatic cholangiography (ultrasound or fluoroscopic guidance)
        ☐ transjugular intrahepatic portosystemic shunt (TIPS) (ultrasound and

fluoroscopic guidance)

☐ Endoscopy is best for:
- ☐ direct appraisal of area by looking at it and by cytology & biopsy
  - ☐ examples include biopsies of upper GI ulcers, polyps & thickened rugae, and of colonic polyps & tumors
  - ☐ routine colon screening in those at risk for cancer (e.g., people over 50 y.o., people with UC or Crohn's)
- ☐ obtaining very good radiologic images of certain areas:
  - ☐ in upper GI tract, ultrasound transducer coupled to endoscope tip allows more accurate pictures for staging of cancer, diagnosis of submucosal lesions, and visualization of small pancreatic lesions
  - ☐ endoscopic retrograde cholangiopancreatography (ERCP) allows high-quality radiographs of bile ducts & pancreatic ducts; useful in obstructive jaundice, recurrent pancreatitis
- ☐ therapeutic interventions in esophagus and stomach:
  - ☐ therapy of upper GI bleeding (due to ulcers, varices)
  - ☐ strictures (with expanding stents)
  - ☐ debride and stent esophageal tumors
  - ☐ anti-reflux procedures: radiofrequency burns, tightening LES with polymer injections
- ☐ therapeutic interventions in biliary tree (ERCP) and pancreas
  - ☐ removal of stones from bile duct—safe in pancreatitis
  - ☐ insertion of stents in bile duct obstructed due to malignancy, strictures
  - ☐ drainage of pancreatic cysts
- ☐ therapeutic interventions in intestines:
  - ☐ polypectomy & foreign object removal
- ☐ only major contraindications are perforation & active ischemia

Another new technique is laparoscopy, which is performed through two tiny incisions just below the umbilicus. It can be used for diagnosis (unexplained ascites, cancer staging, liver biopsy) and therapy (cholecystectomy).

Section 18: Pathology of the Liver (Glickman)

Dr. Glickman's notes describe many of the diseases we discuss in detail in subsequent lectures, and they correlate the clinical & etiologic picture with pathology. I suggest skimming these notes before beginning to study and then reading through them carefully later, as they come closest to a general chapter on hepatic diseases and will provide a well-organized picture of much of what we've learned about the liver.

Section 19: Structure, function and metabolism of plasma lipoproteins and mechanisms of lipid lowering (Cohen)

This section can be divided into two parts: understanding lipid transport in the body, and manipulating elements of this transport to lower lipid levels. Figures included are from Principles of Pharmacology, Chapter 22 (Golan et al., 2005).

Lipid transport: by (A) lipoproteins and (B) bile salts

A. lipoproteins: emulsions that transport lipids in plasma

1. structural information
-spherical particles with "hydrophilic monolayer surface," hydrophobic core
-classified according to type of lipid transported, type of apoproteins contained, site of origin
-contain proteins = apolipoproteins (aka apoproteins) that
        -stabilize lipoprotein particle
        -are amphiphilic and can be exchanged from one particle to another (except ApoB
         proteins)
        -act either to bind cell surface receptors or to activate enzymes

Figure removed due to copyright reasons.

2. transporting triglycerides (TG) to muscle and adipose tissue: ApoB (ApoB48, ApoB100) containing lipoproteins

-some elements of ApoB synthesis and secretion
        -ApoB gene transcribed in liver and intestine, but mRNA edited in intestine
        -editing by ApoB editing complex (chief component, apobec-1) produces a

shorter ApoB in intestine = ApoB48
-in both sites, co-translational modification by protein disulfide isomerase in
  ER→ disulfide bridges formed
        -ApoB48 is constitutively translated
-lipoprotein synthesis and secretion is a function of availability of TG and
microsomal transfer protein (MTP)
        -MTP subunits: M unit catalyzes intermembrane lipid transfer; P is PDI
        -MTP must bind apoB and transfer lipids to it (1 apoB per lipoprotein
          particle) for lipoprotein assembly = lipidation
        -secretion of lipoproteins is by exocytosis, with different pathways for
          chylomicrons and VLDL
-regulation of ApoB lipidation
        -if TG stores are low or MTP not present, both ApoB48 and ApoB100 are
          degraded
        -but during fasting, ApoB100 is still lipidated (in liver) with TG made
          available through lipolysis

-From intestine to peripheral tissues to liver: chylomicrons and chylymicron remnants

Figure removed due to copyright reasons.

Of note:
        -Lipoprotein lipase (LPL): hydrolyze TG→ MG + FA
                -can act only once lipoprotein gets ApoCII from HDL
                -expression is regulated
                        -much higher in muscle than fat tissue
                        -regulated by insulin (in fed state, insulin ↑, LPL transcription
                          stimulated in adipocytes; fasting, insulin ↓, LPL not released from
                          cells), so muscles get preferential access to lipids when fasting
                -many LPL molecules act on one lipoprotein particle

-heparin can displace LPL from cells because enzyme is anchored via sulfated proteoglycans

-Chylomicron remnants
    -once LPL acts, exchange ApoCII for ApoE from HDL
    -remnants taken up by liver
        - *sequestration by liver*: removal of remnants from plasma as they interact with heparan sulfate proteoglycans in Space of Disse
        -*processing by hepatic lipase*
        -*ApoE binds LDL-receptor*: redundancies built into this step include, LDL-receptor related protein (LRP); HSPG; HSPG +LRP→ all of which promote remnant uptake into liver

-From liver to peripheral tissues: VLDL, IDL, LDL: **figure is a little out of date**

Figure removed due to copyright reasons.

Of note:

- Lipoprotein lipase acts on VLDL also, once it gets ApoCII from HDL
- VLDL remnants **(slightly different processing than figure depicts)**
    -50% taken up by liver similarly to chylomicron remnants
    -other 50% again acted on by LPL to produce IDL

-The go-between and important player in reverse cholesterol transport to liver: HDL

Figure removed due to copyright reasons.

Of note:
-HDL formation
-ApoA1 in plasma interacts with ABCA1 on hepatocyte membrane: phospholipids and cholesterol released from cell → preβ HDL formed (equiv of nascent HDL in figure)
-plasma LCAT binds HDL and acts on lecithin and cholesterol on HDL surface→ resulting lysolecithin binds albumin in plasma and cholesteryl ester (CE) moves into HDL core→HDL bigger, now α-HDL (aka "HDL")
-cholesterol uptake by HDL
-HDL may bind SR-B1 on different cell types
-if favorable cholesterol concentration gradient, SR-B1 mediates cholesterol diffusion to HDL (it is bidirectional)
-Actions of LCAT promote favorable gradient: it keeps transforming surface cholesterol into CE, which moves into the core
-PLTP replenishes the lecithins necessary for this reaction by taking them from remnants of both VLDL and chylomicrons
-CETP then removes CE from HDL core to exchange for TG from remnants of both chylomicrons and VLDL→ these remnants thus help in reverse transport of cholesterol to liver!!
HDL transfer of cholesterol to liver
-hepatic lipase hydrolyzes TG and phospholipids of HDL
-SR-B1 on hepatocytes then can take up more of CE from HDL (no protein uptake)
-as HDL size diminishes, ApoA1 dissociates and is again free to interact with ABCA1 (for HDL formation)

Diseases:
-mutation in MTP→ abetalipoproteinemia
- hypolipidemia
-failure in chylomicron exocytosis→ Anderson's disease
-inactive ABCA1→ Tangier's disease
-low HDL levels

B. Bile salts and lipid transport

1. For synthesis and function, see section 15.
    a. bile salts are made from cholesterol (24 g secreted—NOT SYNTHESIZED—daily)
2. Cholesterol balance in body: cholesterol lost as both pure cholesterol and bile salts
    a. Calculating total pure cholesterol lost in feces:
        →average dietary intake of cholesterol: 0.4g/day PLUS 2g of pure cholesterol in biliary secretions
        → only 50% of this absorbed, so 1.2 g/day lost
    b. But also consider the 0.4g of cholesterol used to replenish lost bile salts (enterohepatic circulation only 95% efficient)
    c. body will synthesize cholesterol to equal loss of 1.6 g /day (but compensate for intake of 0.4 g/day)→ therefore 1.2g of cholesterol synthesized

Lipid lowering mechanisms: aim to reduce LDL levels

1. block cholesterol synthesis in hepatocytes: STATINS
    a. block HMG-CoA reductase, which stimulates LDL uptake from blood
    b. effects 50% reduction in LDL plasma levels
2. block bile salt re-absorption: bile salt sequestrants such as CHOLESTYRAMINE
    a. promotes increased cholesterol synthesis by hepatocytes→ requires more LDL uptake from plasma
    b. effects 20% reduction in plasma levels
3. block cholesterol absorption: plant sterols and ezetimibe
    a. plant sterols replace cholesterol in micelles that present to enterocytes; they are pumped out of enterocytes by ABCG5/8
    b. ezetimibe blocks NPC1L1 that takes up cholesterol from intestinal lumen
    c. both drugs cause decrease in CE formed by enterocytes and therefore, decrease in chylomicrons→less cholesterol available for liver to synthesize VLDL→ therefore, less LDL produced by body
    d. evidence for this mechanism of action comes from patients with familial hypercholesterolemia (no LDL receptors)
        - statins not effective because they require functional LDL receptors for effect
        -ezetimibe effective in these patients at reducing LDL levels
    e. ezetimibe can still not overcome compensatory cholesterol synthesis in hepatocytes
        - ezetimibe+statin very effective at blocking LDL synthesis, blocking cholesterol synthesis and stimulating LDL clearance
4. extra drugs
    a. niacin: mechanism not well understood
        -reduces VLDL synthesis (therefore, reduces LDL production) and increases HDL levels by decreasing ApoA1 clearance from plasma
    b. fibrates: actions hypothesized to involve PPAR-γ, but mechanisms poorly understood

-reduces VLDL levels in blood
    -increases LPL activity
    -reduces TG synthesis by liver and stimulates LDL affinity for LDL-
     receptor
-effect on HDL is HDL-concentration dependent
    -when HDL low, fibrates stimulate ApoA1 synthesis and increase
     HDL
    -conversely, brings HDL levels down if they are high

Section 20: Immunology of Liver (Wands – Bagel man)

This is basically a section on hepatitis. Most of you have heard about this already in microbiology.

Hepatitis B Virus and Hepatitis C Virus can be asymptomatic, lead to acute (ranging from mild to severe) hepatitis, lead to chronic hepatitis, or lead to a chronic carrier state. For both viruses, host autoimmune factors appear to play a role in the disease outcome.
□ HBV has an incubation period of about 60 days before acute illness, HCV about 50 days.
□ Transmission is through blood & sexual contact. HCV is infectious at lower titers than HBV.
□ Chronic hepatitis carries a high risk of cirrhosis and hepatocellular carcinoma (HCC).
□ Those who progress to chronic hepatitis lack a full cellular immune response to HBV & HCV proteins.

Hepatitis D Virus can infect only people already chronically infected with HBV.
□ Transmission is similar to HBV & HCV.
□ Infection with both HBV & HDV may cause liver disease to become more severe, increasing the risk of fulminant or chronic active hepatitis or cirrhosis. However, HCC risk is not increased by HDV infection.

Hepatitis A Virus is self-limited; there are no chronic carriers & no increased risk of cirrhosis or HCC.
□ Transmission is fecal-oral.
□ Disease is usually mild & may be asymptomatic. Occasionally, however, it may be fulminant.

Section 21: Jaundice and Disorders of Bilirubin Metabolism (Chung)
Lippincott's has concise sections on the degradation of heme and jaundice (pp. 261-264, Figures 23.7)

Heme (mainly from red blood cell hemoglobin but also from hemoproteins like cytochrome P-450 & catalase) is degraded in the reticuloendothelial system (including the liver).
1. Heme oxygenase & biliverdin reductase produce *unconjugated bilirubin*, which is relatively hydrophobic and must bind to albumin in order to be transported through the blood.
    □ Some drugs (e.g., analgesics) can displace the bilirubin from the albumin, leading to more unbound bilirubin that can cross the blood-brain barrier & cause

kernicterus.

2. Hepatocytes take up unconjugated bilirubin (& other organic anions) via a basolateral carrier called the Organic Anion Transport Polypeptide (OATP). Cytosolic proteins bind bilirubin.

3. In the ER, *conjugation* occurs: A specific isoform of UDP-glucuronosyltransferase (bilirubin glucuronyltransferase) catalyzes the conversion to bilirubin monoglucuronide (BMG) & then bilirubin diglucuronide (BDG). The second conversion is rate-limiting, so that normally there is 80% BDG in bile.

4. The conjugated bilirubin is then excreted into the bile via canalicular multi-organic anion transporter (cMOAT).

5. In the intestines, bilirubin is modified to urobilinogen & stercobilin by bacteria.

Clinical measurement of serum bilirubin:
☐ Direct reaction measures conjugated bilirubin. Indirect reaction (total - direct) measures unconjugated bilirubin.

Disorders fall into two categories: increased production & decreased excretion of bilirubin.
☐ Increased production: hemolysis (e.g., sickle cell disease, massive hematoma), ineffective erythropoiesis (e.g., pernicious anemia).
☐ Decreased excretion
      1. Impaired hepatic uptake (possibly occurs in Gilbert's syndrome)
      2. Impaired conjugation
            ☐ Neonatal jaundice (lack of mature UDP-glucuronosyltransferase, UGT, activity); treatment includes phototherapy, which makes unconjugated bilirubin watersoluble so that it is excreted into bile.
            ☐ Crigler-Najjar Syndrome Type I: No UDP-glucuronosyltransferase activity. Fatal kernicterus in infancy. Autosomal recessive with variable penetrance.
            ☐ Crigler-Najjar Syndrome Type II: Decreased UDP-glucuronosyltransferase activity leads to asymptomatic jaundice with 80% BMG. Treat with phenobarbital.
            ☐ Gilbert's Syndrome: Genetic changes in promotor sequence of gene for UDP- glucuronyltransferase. Mild decrease in UDP-glucuronosyltransferase activity. Usually asymptomatic with occasional mild jaundice.
      3. Impaired secretion
            ☐ Dubin- Johnson Syndrome: Defect in cMOAT leads to conjugated hyperbilirubinemia with asymptomatic jaundice. Brown pigment in centrilobular hepatocytes. Autosomal recessive.
            ☐ Rotor's Syndrome: a variant of DJS, similar defect, asymptomatic, unlike DJS, no abnormal hepatic pigmentation.
      4. Intrahepatic cholestasis
            ☐ some drugs (e.g., steroids) cause inflammation/damage of bile ducts
            ☐ primary biliary cirrhosis: inability to secrete bile salts, associated with hypercholesterolemia (but no excess risk of atherosclerosis), xanthomas
            ☐ cholestatic jaundice of pregnancy in 3rd trimester
            ☐ post-operative jaundice
      5. Extrahepatic cholestasis is obstruction of extrahepatic bile ducts (e.g., by gallstones, strictures, carcinoma of head of pancreas, congenital bile duct atresia)

6. Hepatocellular disease like hepatitis, cirrhosis affects several steps but not usually uptake or conjugation.

Section 22: Drug & Alcohol-Induced Liver Disease (R. Chung)

In this section, we learn about some ways that the liver's detoxification function can go awry.

Alcohol

Degradation in hepatocyte:
1. Alcohol dehydrogenase (cytosolic) breaks down 80% of ethanol, producing acetaldehyde & NADH. Activity of alcohol dehydrogenase is partly genetically determined.
2. Microsomal (ER) ethanol oxidizing system (MEOS): cytochrome P-450-2E1 produces acetaldehyde & NADPH. MEOS is induced by chronic alcohol consumption & some drugs.
3. Catalase (peroxisomal, mitochondrial) produces acetaldehyde and water, but its physiologic role is minimal.

Alcohol leads to centrilobular pattern of toxicity due to low oxygen tension & high alcohol dehydrogenase in this zone.

Mechanisms of damage:
- Increased NADH/NAD+ ratio
    - ↑ lactate leads to ↑uric acid, associated with gout
    - ↓ gluconeogenesis leads to hypoglycemia
    - fatty acids & fats accumulate

- Increased acetaldehyde
    - disrupts a number of pathways, leading to ballooning degeneration of hepatocytes
    - binds to cysteine & glutathione, depleting free-radical scavengers

Clinical manifestations:

- Fatty liver
    - most common abnormality, is reversible if alcohol intake stopped
    - hepatomegaly without elevation in liver function tests
    - pathology: macrovesicular ("signet ring") fat in hepatocytes

- Alcoholic hepatitis
    - occurs in 25% of alcoholics; symptoms/signs include weight loss, fever, fatigue, abdominal pain, nausea, jaundice, hepatomegaly, ascites, peripheral edema, encephalopathy
    - increased white cells, bilirubin, alkaline phosphatase, SGOT (AST) & SGPT (ALT)
    - pathology: necrosis with *PMN* infiltrate, pericentral fibrosis, Mallory bodies (alcoholic hyaline deposition)

⬜ Alcoholic cirrhosis
- ⬜ develops in 10-25% of alcoholics
- ⬜ symptoms/signs include malaise, fatigue, encephalopathy, portal hypertension, coagulopathy, ascites/edema, jaundice, splenomegaly, spider angiomata, asterixis
- ⬜ pathology: regenerative nodules entrapped by fibrous septae

Drugs

Mechanisms of injury:
1. Cytochrome P450 produces an electrophilic metabolite that injures the hepatocyte unless it binds to glutathione.
   - ⬜ Any induction of P450 (e.g., by alcohol) or depletion of glutathione (e.g., by acetaldehyde from alcohol degradation) will augment toxicity.
   - ⬜ Example is acetaminophen, most of which is excreted by urine, but a large dose causes metabolism via P450 & glutathione. Histological pattern is centrilobular necrosis.
   - ⬜ Treatment: N-acetyl cysteine restores glutathione levels within 24 hours.
2. Cytochrome P450 or other detoxification enzyme produces a free-radical metabolite, leading to lipid peroxidation & cell death.
   - ⬜ Again, glutathione can bind to the free-radical, so N-acetyl cysteine is effective.
   - ⬜ Example is carbon tetrachloride, which is modified to CCl_3 radical. Histology shows centrilobular necrosis.
3. Immunologic injury
   - ⬜ Example is halothane, which rarely leads to fever, rash, eosinophilia. P450 produces a metabolite (trifluoroacetate, or TFA) that reacts with cell proteins, rendering them antigenic. Histology shows viral hepatitis-like reaction.

Histopathological patterns of injury include zonal necrosis, viral hepatitis-like reactions, noninflammatory cholestasis (e.g., estrogens & anabolic steroids), inflammatory cholestasis, chronic hepatitis (due to long-term use of drug), fatty liver (macrovesicular, "signet ring", usually benign, e.g. ethanol, corticosteroids; microvesicular, usually sever hepatic failure, e.g., tetracycline), granulomas, tumors, vascular reactions (e.g., Budd-Chiari syndrome, which is hepatic vein thrombosis).

Section 23: Physiology and Biochemistry of the Liver (Ukomadu)

In this section, we learn about the structure of the liver, learn a lot about metabolism, and get a short introduction to detoxification.

Structure
Hepatic Lobule/Hepatic Acinus: a picture is worth 1000 words. See figure listed in section 22 and figures from p. 275, Wheater's Functional Histology, 4rth ed and Saunders Fig. 15-1.

⬜ Note zones of acinus:
- ⬜ periportal (zone 1), where ingested products absorbed in the gut first arrive and where arterial blood first arrives
- ⬜ intermediate (zone 2)
- ⬜ perivenular/pericentral/centrilobular (zone 3), which surrounds central (also called

hepatic) venules, and gets least exposure to ingested products and oxygen from arterioles
- □ contrast with historical/histological defintion of lobule (gave rise to "centrilobular")

□ Note cell types: again, a picture is best (figures from p. 278-9, Wheater's Functional Histology, 4rth ed and Saunders Fig. 15-8, 15-10).
- □ Parenchymal cells, which are the *hepatocytes*. These perform the liver's functions. Each hepatocyte faces at least 2 sinusoids (basolateral, 85-90% of surface), and 2 bile canaliculi (apical, 10-15% of surface).
- □ Endothelial cells: fenestrated; line sinusoids.
- □ Ito cells (lipocytes, stellate cells): located in Space of Disse; store lipids/fat-soluble vitamins (especially A); produce collagen in cirrhosis
- □ Kupffer cells: fixed macrophages located in sinusoid
- □ Pit cells: natural killer cells located in sinusoid

Metabolism

This is a huge subject, and most of it is covered in biochemistry. For this course, you just need the basics. I recommend the following pages in Lippincott's Review for a quick refresher:

□ Overall regulation of metabolism,
□ carbohydrate metabolism
□ amino acid & protein metabolism
□ lipid metabolism (especially fats)
- □ bile acids & salts
- □ fat-soluble vitamins

A few facts to point out:

In carbohydrate metabolism:
□ Glucokinase (converts glucose to G6P) prevents glucose exit from cell, & phosphatase (converts G6P to glucose) allows release of glucose into blood. Muscle has no phosphatase.
□ Remember glycolysis & the TCA cycle, and gluconeogenesis (principally from alanine).
□ Remember insulin & glucagon.
□ Understand principles behind glycogen storage diseases (classic simple boards question).

In protein/amino acid metabolism:
□ Most plasma proteins are synthesized in the liver, including albumin & most coagulation factors.
□ Amino acids are mainly degraded in the liver, where the urea cycle eliminates ammonia.
□ When liver is damaged, we see ↓ albumin, ↓ coagulation factors, ↑ammonia in blood (leading to encephalopathy and renal function tests that may hide renal dysfunction).
□ Deficiencies in urea cycle enzymes lead to hyperammonemia, lethargy & coma.
□ α_1-antitrypsin deficiency manifests itself in a higher risk of emphysema. In those with both mutant protein and delayed degradation in the ER, it also leads to liver disease (cirrhosis).

In lipid metabolism:
☐ Note that fatty acids undergo β-oxidation in the mitochondria (how do they enter?). This produces acetyl-CoA, which enters TCA cycle unless capacity of citrate synthase is exceeded. Then ketone bodies are produced.
☐ Know what LDL & HDL do. (LDL carries cholesterol to peripheral cells; HDL carries it from peripheral cells to the liver.)
☐ Rate limiting step of cholesterol synthesis is HMG-CoA reductase.
☐ Note cholesterol homeostasis: input, storage, output.
☐ For bile acids & salts, see section 15.
☐ Phospholipids are made in the ER and Golgi. They are secreted in bile.

Liver takes up hydrophobic compounds (unlike the kidney, which eliminates most hydrophilic ones).
☐ Basolateral transporters on hepatocytes take up compounds from sinusoids through *fenestrae* (why are these special?).
☐ Cytosolic binding proteins keep compounds from returning to plasma.
☐ Biochemical modifications (mainly in ER) make compounds more hydrophilic for secretion into bile.
☐ Rate limiting step is transport across apical membrane into bile canaliculus.
☐ Biliary duct epithelium absorbs/modifies some compounds.

Section 24: Pathophysiological Consequences of Cirrhosis (R. Chung)

This section could also be titled: why chronic liver disease is so devastating. We learn about the consequences of liver cirrhosis, which is the liver's response to a variety of chronic damaging processes, including alcohol, drugs, viruses, parasites, biliary cirrhosis, hemochromatosis, Wilson's disease, etc.

Portal Hypertension

Causes:
☐ Obstruction of portal vein/venules by:
   ☐ thrombosis of portal vein, such as post-surgery/trauma, hypercoagulable states, cancer
   ☐ schistosomiasis: parasite's eggs implant in portal venules, leading to portal hypertension, granuloma, fibrosis
☐ Obstruction of hepatic veins by:
   ☐ *Budd-Chiari syndrome*, which is hepatic vein thrombosis (from any cause) & causes portal hypertension, ascites, & tender hepatomegaly
      ☐ causes include: cancer, sepsis, pregnancy, hypercoagulable states (e.g., OCPs)
   ☐ severe right heart failure
☐ Cirrhosis
   ☐ regenerating nodules, swollen cells & scarring put pressure on sinusoids & hepatic venules
   ☐ also leads to arterio-venous & veno-venous channels

Consequences:

☐ Formation of collateral circulation from portal veins to vena caval system via:

  ☐ hemorrhoids

  ☐ caput medusa (spider pattern of veins around umbilicus)

  ☐ *esophageal varices*: we've learned about these already

      ☐ Very important; rupture is immediately life-threatening. PSPG>12mmHg likely to bleed.

      ☐ some methods of therapy: infusion of somatostatin to induce vasoconstriction, sclerotherapy (induced thrombosis), endoscopic ligation, creation of anastamoses (shunts) between portal system & other systemic veins to reduce pressure in esophageal veins→but this can lead to hepatic encephalopathy (see below)

☐ Congestive splenomegaly

☐ Estrogenic effects

☐ Ascites (not necessarily due to portal hypertension; can also be caused by peritoneal inflammation, right heart failure, pancreatitis)

  ☐ ascites compartment is not in equilibrium with other extracellular fluid Compartments

  ☐ diuresis must proceed slowly_maximum 900mL per day, overzealous diuresis may precipitate hepatic encephalopathy

☐ Hepatorenal syndrome is progressive renal failure in patient with liver disease.

  ☐ usually seen in end-stage liver disease

  ☐ high mortality (no treatment known) but kidney damage is potentially reversible

Hepatic Encephalopathy

1. Liver cannot detoxify noxious compounds because of ↓ hepatocyte function and portal blood shunting around liver parenchyma.

2. Potential toxic substances include: ammonia (from protein breakdown in intestines, often by gut bacteria), amines, short-chain fatty acids, inhibitory neurotransmitters (GABA) made by gut bacteria, false neurotransmitters. However, the exact mechanism is still unclear.

3. Clinically, you see **decrease in mental status/confusion**, and **asterixis** – rhythmic flapping of hands on wrist dorsiflexion.

4. Acute or Chronic Encephalopathy

  ☐ Acute: usually reversible, includes agitation, confusion, drowsiness, asterixis, fetor hepaticus, slow wave EEG.

  ☐ Chronic: usually in stable, long-term cirrhosis, but often not reversible (clear CNS pathology). Includes personality changes, dementia, memory loss, extrapyramidal signs.

5. Can be precipitated by: GI bleeding, azotemia, constipation (nitrogenous waste in GI tract), high protein meal, sedative drugs. In someone who is already borderline, decompensation can be triggered by: hyperkalemic alkalosis (diuresis), electrolyte imbalance, hypoxia, sepsis.

☐ Diagnosis by ↑ammonia levels in blood, EEG changes, perceptive tests.

☐ NOTE: ammonia levels, while usually correlating with the degree of encephalopathy do not cause it directly.

☐ Treatment includes removal of precipitating factors.

    ☐ Lower food sources of NH_3 – i.e. no more steak (meat is high in amino acids, which are the source of NH_3).

    ☐ Lactulose orally to acidify the gut lumen and trap NH3 as NH4+, which is excreted.

    ☐ Neomycine as a last resort – wipes out GI flora, thus reducing its ammonia production.