Lecture 6:

Cholesterol (Ch. 9.1e, 9.2b, 19.7b,c) & Lipoproteins (Ch. 10.3*, 19.1, 19.7b,c)

Next lecture:
Fatty Acid Oxidation (Ch. 19.2), Ketone Bodies (Ch. 19.3) and Fatty Acid Biosynthesis (Ch. 19.4)

(Note: Only portions of these sections will be covered in lecture. The material will not necessarily be presented in the same order as in the text, but most can be found in the sections listed above.)

*New (review) reading assignment; not on syllabus.
Long-chain fatty acids can be esterified to cholesterol to form CHOLESTERYL ESTERS.

STEROIDS are derivatives of cyclopentanoperhydrophenanthrene (four fused, nonplanar rings)

OH makes it weakly amphipathic

Ring system makes it very RIGID.

Cholesterol is the most abundant steroid in animals; it is also classified as a STEROL because of the C3-OH. It is a major component of plasma membranes.
Cholesterol:

Many other important steroids are derived from cholesterol in animals, including...

- **STEROID HORMONES** (androgens, estrogens, progestins, glucocorticoids, and mineralocorticoids)

![Figure 9-11](image)

and...

- **BILE ACIDS** or **BILE SALTS** (detergent-like molecules that are secreted in bile from the gallbladder, and assist in the absorption of dietary lipids in the intestine; see Fig. 19-1).
Fig. 19-1: Structures of the major bile acids

R₁ = OH

R₂ = H  Cholic acid  Chenodeoxycholic acid
R₂ = NH–CH₂–COOH  Glycocholic acid  Glycochenodeoxycholic acid
R₂ = NH–CH₂–CH₂–SO₃H  Taurocholic acid  Taurochenodeoxycholic acid

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What happens to the cholesterol and other fatty acids that we eat? How do they get into our bloodstream? How can fatty acids (which are hydrophobic and thus only slightly soluble in aqueous solution) be transported in the blood (which is an aqueous solution/suspension)?

ANSWER(S) to the third question:

Some SIMPLE unesterified FAs are merely bound to serum albumin and other serum proteins, and are transported through the bloodstream by these proteins. However, PHOSPHOLIPIDS, TAGs, CHOLESTEROL and CHOLESTERYL ESTERS are all transported through the body in the form of LIPOPROTEINS.
LIPOPROTEIN structure & function

Are globular, micelle-like particles that consist of a nonpolar core of TAGs and cholesteryl esters, surrounded by an amphipathic monolayer of protein, phospholipid, and cholesterol that is about 20 Å thick. These lipids and proteins associate noncovalently.

Lipoproteins function in the blood plasma as transport vehicles for TAGs and cholesterol.
Lipoprotein Classification

5 broad categories on the basis of their functional & physical properties, primarily on their DENSITIES:

1) Chylomicrons: Transport dietary TAGs and cholesterol from the intestines to the liver

2) VLDL — very low density lipoprotein;
3) IDL — intermediate density lipoprotein;
4) LDL — low density lipoprotein:
   A group of related particles that transport endogenous TAGs and cholesterol from the liver to the tissues.

5) HDL — high density lipoprotein: Transport endogenous cholesterol from the tissues to the liver.
Only one B-100 protein per lipoprotein particle.
Fig. 19-5

Exogenous pathway
- Dietary fat
- Bile acids and cholesterol

Dietary cholesterol

Liver
- Remnant receptor

Chylomicrons
- Remnants

Intestine
- Capillaries
  - Lipoprotein lipase
  - Free fatty acids

Adipose tissue, muscle

Endogenous pathway
- LDL
- LDL receptors

Extrahepatic tissue
- HDL

VLDL
- IDL
- Capillaries
  - Lipoprotein lipase
  - Free fatty acids

Adipose tissue, muscle

What happens to the fatty acids that we eat? How do they get into our bloodstream?

Remember that lipids, such as this TAG, are not water soluble. However, most digestive enzymes are water soluble. Therefore, lipid (TAG) digestion takes place at lipid-water interfaces. These processes depend on the presence of bile acids, which are essentially digestive detergents — they have an emulsifying action on the fats in the intestine.
Digestion of TAGs in the Small Intestine:

**Pancreatic Lipase** catalyzes hydrolysis of TAGs at their C-1 & C-3 positions. The activity of PL is greatly increased at the lipid-water interface. Binding to the lipid-water interface requires a 1:1 binding PL to pancreatic **colipase**, a 90 residue protein (see Fig. 19-2 for the 3D structure of the complex).

Other **intestinal lipases** and **esterases** attack the C-2 position.
Phospholipids are degraded by phospholipase A$_2$, which has a hydrophobic channel that allows direct access of the substrate to the active site of the enzyme.

(b) Hypothetical structure of the complex

Figure 19-3b. Substrate binding to phospholipase A$_2$. Copyright 1999 John Wiley and Sons, Inc. All rights reserved.
The resulting mixture of fatty acids, monoacylglycerols, and diacylglycerols produced by pancreatic digestion is absorbed by cells of the mucosa of the small intestine:

Short-chain FAs (10 Cs or less) are absorbed directly into the villi of the intestinal mucosa.

Long-chain FAs are less soluble, and form micelles with bile acids. These micelles carry the FAs to the surface of the epithelial cells, and the FAs pass into these cells.
Inside the cells, the fatty acids form complexes with intestinal fatty acid-binding protein, a cytoplasmic protein that increases the effective solubility of the FAs, and protects the cell from their detergent-like effects.

The FAs then condense again with glycerol to form new TAGs inside the intestinal cells (remember: "you are what you eat!"). These TAGs aggregate into CHYLOMICRONS, which are transported to the lymphatic system and into the bloodstream.
Chylomicrons (and chylomicron remnants)

- Transport "exogenous" (dietary) TAGs & cholesterol from the intestines to the tissues.
- Are assembled in the intestinal mucosa
- Keep TAG & cholesterol suspended in aqueous solution
- Are released into the intestinal lymph (called "chyle"), which is then transported through the lymphatic vessels → large body veins → muscles & adipose tissues (have binding sites for the chylomicrons)
- There the fatty acids are hydrolyzed off the TAGs by lipoprotein lipase (an extracellular enzyme that is activated by apoprotein C-II).
- These tissues then take up the monoacylglycerol fatty acid free hydrolysis products. These FA products can then be oxidized for energy in a highly endergonic pathway known as $\beta$-oxidation.
- Chylomicrons shrink as TAGs are hydrolyzed, leaving cholesterol-enriched CHYLOMICRON REMNANTS.
- The remnants re-enter the circulation & get taken up by the LIVER, where the cholesterol is delivered.

So, the chylomicrons deliver TAGs (FAs) to muscle & adipose tissue and the chylomicron remnants deliver cholesterol to the liver.
VLDL, IDL, and LDL ("BAD Cholesterol")

• Are related particles (size/density) that transport endogenous (internally supplied) TAGs & cholesterol from the LIVER to the TISSUES

• TAGs made in the liver are packaged into VLDLs & released into the bloodstream.

• TAGs of VLDLs are hydrolyzed to free FAs & glycerol in adipose tissue & skeletal muscle by lipoprotein lipase, similar to those from chylomicrons.

• The remnants of VLDL are IDLs, then LDLs. In going from VLDL to LDLs, most all proteins are removed & most cholesterol is esterified by Lecithin-cholesterol acyl transferase (LCAT)
HDL ("GOOD cholesterol")

- Transports endogenous cholesterol & cholesteryl esters from the TISSUES to the LIVER.
- Are assembled in the plasma from components largely obtained through degradation of other lipoproteins.
- Circulating HDL probably acquires its cholesterol by extracting it from cell surface membranes using LCAT (lecithin:cholesterol acyltransferase), and then converting it to cholesteryl esters, which it transfers to VLDL (*in a poorly understood process).
- *Liver may also have a specific HDL receptor.
- Formation of bile acids (from cholesterol) in the liver provides the only (normal) route for cholesterol excretion: < 1 g/day of bile acids are metabolized in the large intestine by bacteria & then excreted by us humans.

* Potential paper topics?
Densities of lipoproteins depend on their relative amounts of protein (1.3-1.4 g/mL or g/cm$^{-3}$) and lipids (~ 0.8 g/mL).

(Demonstration)
In healthy organisms, an intricate balance is maintained between the biosynthesis, utilization, and transport of cholesterol, keeping its harmful deposition to a minimum.

The biosynthesis of cholesterol follows a lengthy pathway (covered in section 19-7a; you are not responsible for all of it). The rate-limiting step is catalyzed by HMG-CoA Reductase.
**LDL, HDL & heart disease:**

Michael Brown & Joseph Goldstein (UTSWMC - Dallas) — Nobel Prize

Showed that mammalian cells take up exogenous cholesterol through **ENDOCYTOSIS** (i.e., engulfing) of LDL particles in a **receptor-mediated process**:

**LDL and IDL** are sequestered by **LDL-RECEPTOR** a cell-surface, transmembrane glycoprotein that binds **apoprotein ApoB-100** (the major protein in LDL). The C-terminus of the LDL receptor is inside the cytosol, and is needed for clustering of the LDL receptor molecules into **CLATHRIN COATED PITS** (see also Fig. 10-23). These invaginate into the plasma membrane to form **coated vesicles**. Lysosomes degrade LDL, releasing cholesterol. Cholesterol **down-regulates** the synthesis of **HMG-CoA Reductase** and **LDL Receptor**, and **increases** synthesis of **ACAT** (esterifies cholesterol for storage).
Serum LDL level depends on rate that liver cells remove LDL from bloodstream (by RMA), which in turn depends on the number of functioning LDL receptors on liver cell surfaces.

High blood cholesterol (hypercholesterolemia) caused by two factors:

1) **Genetic disease** — Familial hypercholesterolemia (FH) - Dominant; causes deficiency of functional LDL receptors (several different mutations)

2) **Overconsumption of high cholesterol diet** — Cholesterol enters liver via chylomicron remnants & high cholesterol level causes LDL receptor synthesis to be lowered

Both cause liver to not take up LDL as well, and thus raise blood LDL levels. This causes deposition of cholesterol into cells and blood vessels, which leads to heart disease ('heart attacks') and stroke ('brain attacks').
Strategies to treat high "cholesterol" (usually LDL)
1) Ingest resins that bind bile acids so won't recycle into body
2) Treat patient with inhibitors of **HMG-CoA reductase** (the primary control site in cholesterol biosynthesis) to decrease rate of synthesis.

**HDL** - has essentially the opposite function of LDL
- removes cholesterol from tissues
- assembled in plasma
  →probably gets its cholesterol by extracting it from cell surface membranes using **LCAT (lecithin:cholesterol acyltransferase)**
- ACTS as a cholesterol scavenger
- HDL transfers some cholesterol esters to VLDL and LDL using **Cholesterol Ester Transfer Protein**
  ?? Liver may also take up HDL directly by specific HDL receptor??