ANSC/NUTR 618
LIPIDS & LIPID METABOLISM
The LDL Receptor, LDL Uptake, and the Free Cholesterol Pool

I. Michael Brown and Joseph Goldstein

A. Studied families with familial hypercholesterolemia.

B. Defined the relationship of the LDL receptor and control of cholesterol metabolism.

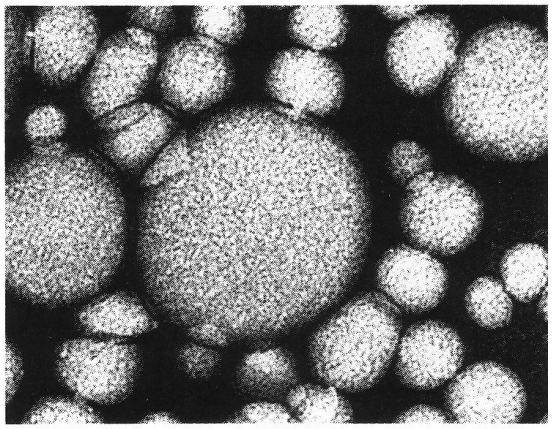
C. Were awarded the Nobel Prize in Science in 1985.

II. Source of LDL

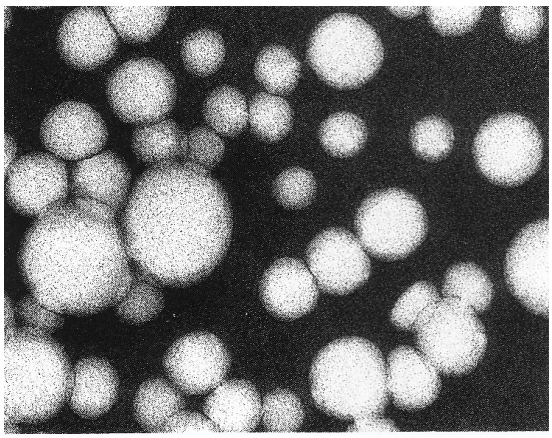
A. VLDL are synthesized in the liver and secreted with apoB_{100} and apoE.

B. Delipidation by LDL leads to the production of TAG-poor IDL (with apoE).

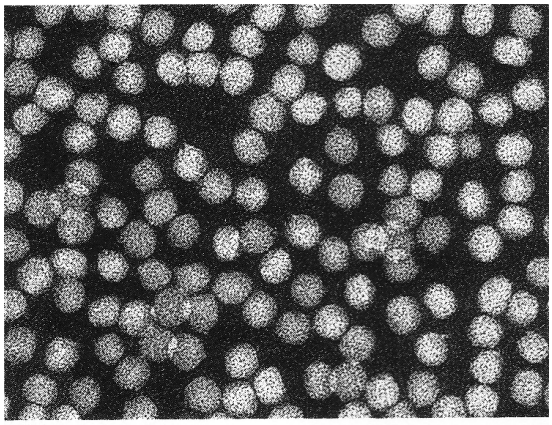
C. Loss of apoE leads to formation of LDL.



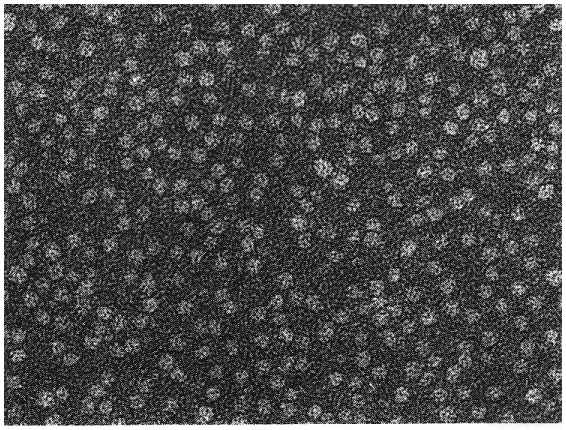
Chylomicrons (×60,000)



VLDL (×180,000)



LDL (×180,000)

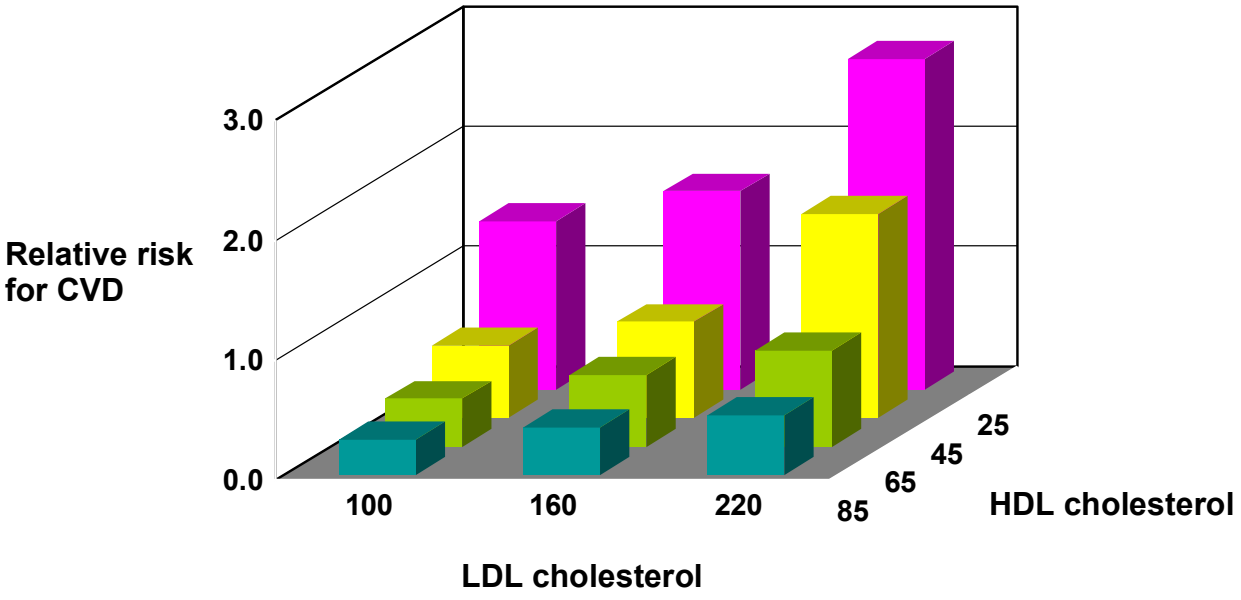


HDL (×180,000)

III. Relationship of LDL cholesterol and HDL cholesterol to risk for cardiovascular disease

A. Increasing LDL cholesterol can triple the relative risk for CVD.

B. Decreasing HDL cholesterol can increase the relative risk for CVD over 4-fold.



IV. The LDL receptor

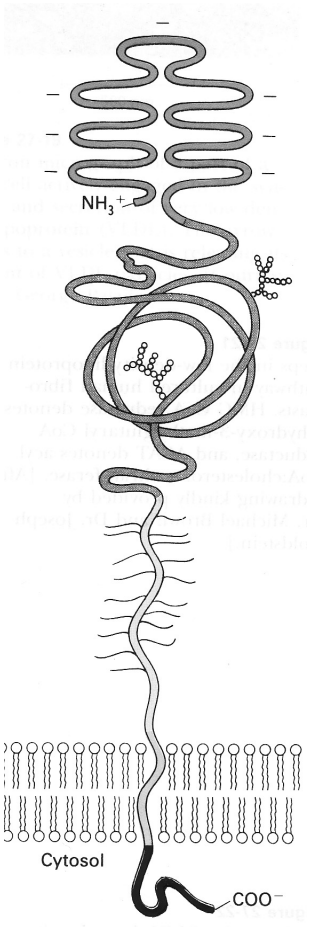
A. Located on many tissues (especially enriched in liver, adrenal glands, ovaries) in clathrin-coated pits.

B. Specifically designed to take up LDL particles.

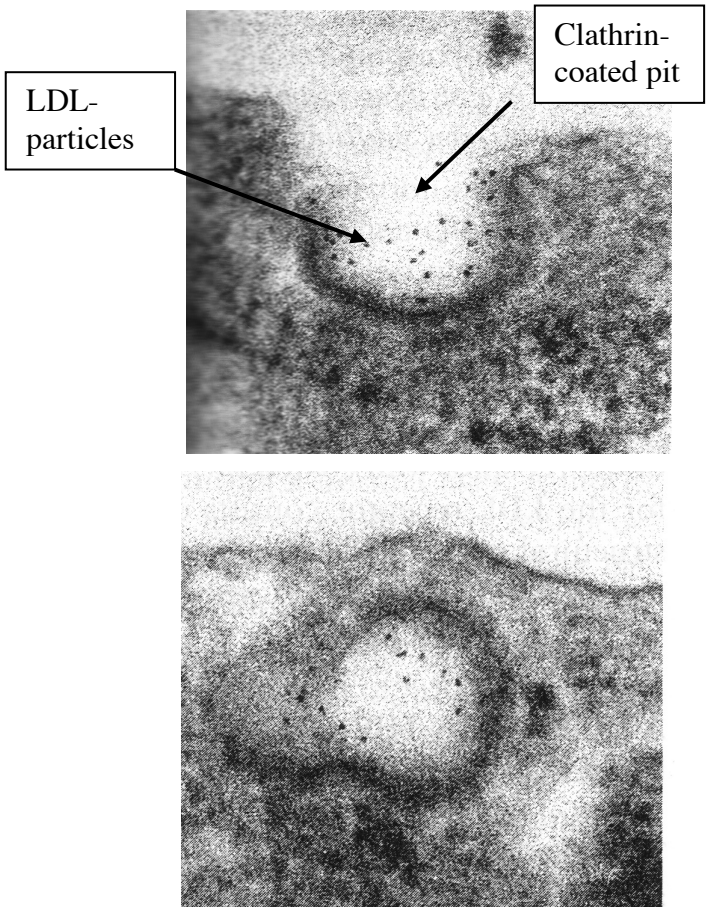
1. The LDL receptor has very high affinity for apoE, so apoE-containing particles (especially IDL) are taken up rapidly (half life approx. 3 *hours*).

2. The LDL receptor has lower affinity for $apoB_{100}$, so LDL particles (which contain no apoE) remain in circulation much longer (half life approx. 2 *days*).

3. The LDL receptor *does not* recognize $apoB_{48}$, so it does not take up chylomicron remnants.



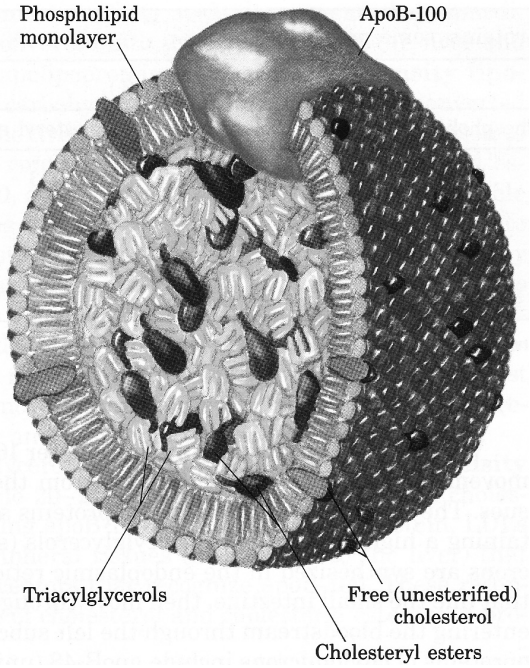
LDL receptor



Receptor-mediated endocytosis

C. The LDL receptor is missing in individuals with the genetic defect, familial hypercholesterolemia (**FH**).

1. FH heterozygote
   a. Have half the number of LDL receptors.
   b. Have twice the normal plasma LDL cholesterol (300 mg/dL). Normal is considered 175 mg/dL.
   c. Begin to have heart attack by age 35.
   d. For those over 60 who have heart attacks, one in 20 is FH heterozygous.
2. FH homozygote
   a. Have virtually no functional LDL-receptors (receptors are not synthesized or contain a point mutation).
   b. Have six times the normal LDL cholesterol (680 mg/dL).
   c. Heart attacks can occur by age 2 and are inevitable by age 20.
   d. LDL particles circulate about 2.5 times as long as in normal individuals.

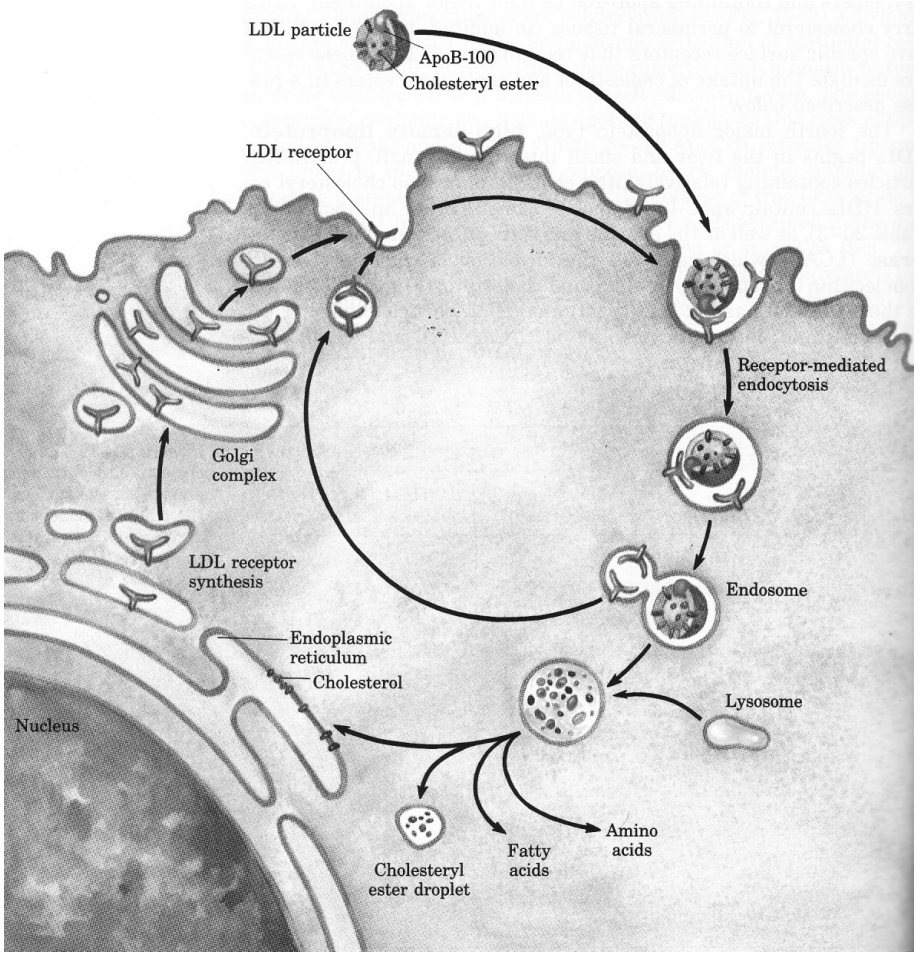


e. FH homozygote also produces about twice as much LDL cholesterol per day (due to an increased amount of conversion of IDL to LDL).

V. LDL uptake

A. Receptor-mediated endocytosis
   1. Circulating LDL is taken into a clathrin-coated pit containing LDL receptors.
   2. The coated pit invaginates and pinches off to form a coated vesicle.

B. Intracellular degradation of LDL
   1. Fusion of several vesicles → endosome.
   2. LDL dissociates from the receptor (which is recycled to the cell membrane).
   3. LDL is delivered to a lysosome, where $apoB_{100}$ is degraded and cholesterol ester is converted to free cholesterol and fatty acids.



VI. Regulation of the free cholesterol pool

A. Cholesterol synthesis

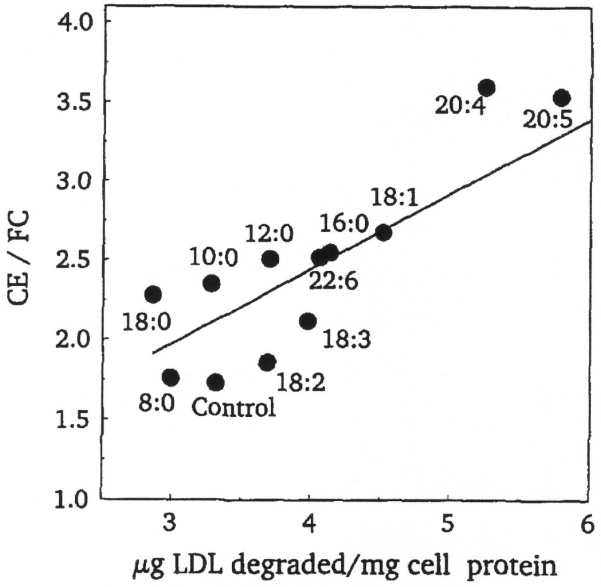
1. Free cholesterol is oxygenated to 25-hydroxy-cholesterol.
2. 25-hydroxy-cholesterol:
   a. Inhibits HMG-CoA reductase (decreases cholesterol synthesis).
   b. Inhibits LDL receptor gene transcription (decreases cholesterol uptake from the circulation).
3. Free cholesterol (and oleic acid?) activates acyl-coenzyme A:cholesterol acyltransferase (**ACAT**; this decreases the free cholesterol pool by converting cholesterol to cholesterol ester).
4. Mevalonate (the product of HMG-CoA reductase) inhibits HMG-CoA reductase.

B. ACAT and the regulation of the free cholesterol pool.

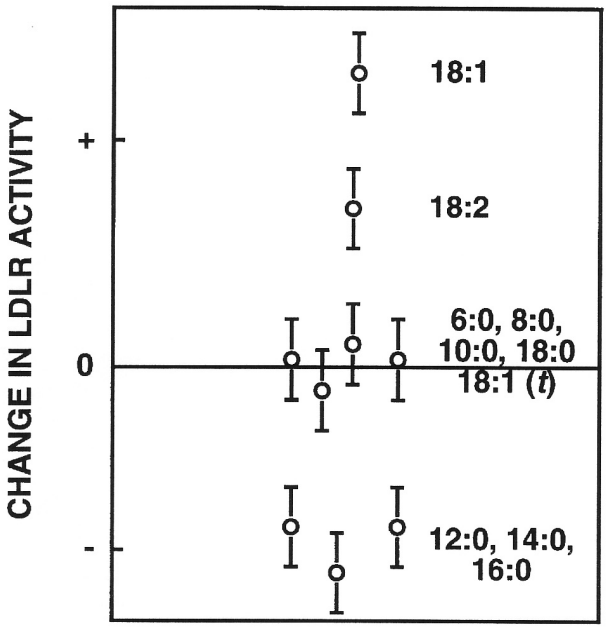
1. ACAT = acyl-coenzyme A:cholesterol acyltransferase

acyl-CoA + cholesterol → CoASH + cholesterol ester

2. Diets high in saturated fatty acids decrease apparent ACAT activity in hepatocytes.
3. Diets high in saturated fatty acids decrease the amount of LDL degraded in hepatocytes.
4. Diets high in 12:0, 14:0, and 16:0 reduce LDL-receptor activity.



Apparent ACAT activity (CE/FC) as a function of LDL degradation. CE = cholesterol ester; FC = free cholesterol.



Relative LDLR activity as influenced by dietary fatty acids. The graph implies differential effects of fatty acids on ACAT activity.

C. Decreasing cholesterol pool by exogenous means

1. Bile acid-binding resins, e.g., cholestyramine
   a. Bind bile acids and salts, causing excretion in the feces.
   b. Cause a net 10% reduction in LDL cholesterol in FH heterozygotes.
2. HMG-CoA reductase inhibitors (statins), e.g., compactin, mevinolin
   a. Inhibit cholesterol synthesis.
   b. Taken with resins cause 50% reduction in LDL cholesterol in FH heterozygotes.