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Discovery of the Lipoproteins, Their Role in Fat Transport and Their Significance as Risk Factors FREE

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Abstract

The idea of a fat transport system in the plasma of mammals evolved slowly over three centuries. At the turn of this century, it was discovered that plasma globulins contained lecithin and that the digestion of plasma proteins with pepsin liberated small amounts of fat and cholesterol. The high density lipoprotein (HDL) was first isolated from horse serum in 1929 and the low density lipoprotein (LDL) in 1950. It was then shown that flotation of plasma in the ultracentrifuge revealed an array of lipoproteins that included VLDL, LDL and HDL and permitted quantitation. Subsequently, it was discovered that the free fatty acids (FFA) in plasma were bound to albumin and varied with feeding and fasting. From further studies, it was concluded that lipoprotein-bound triglycerides were delivered to adipose cells for uptake after meals; during fasting, the fat cells secreted FFA, which provided fuel for many tissues. The protein components of the lipoproteins (apopeptides) were characterized in the period from 1960 to 1970 and the

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to genetically altered or absent receptors explained dyslipidemias, which promoted atherosclerosis, xanthomatosis and Alzheimer's disease.

Keywords: [lipoproteins](#), [receptors](#), [atherosclerosis](#), [xanthomatosis](#), [Alzheimer's disease](#)

Topic: [atherosclerosis](#), [lipoproteins](#), [alzheimer's disease](#), [cholesterol](#), [high density lipoproteins](#), [lipoproteins](#), [vldl](#), [plasma](#), [low density lipoprotein receptor](#), [xanthomatosis](#)

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The first inkling that a fat transport system existed in the blood of animals can be traced to Boyle in 1665. He noted that after a fatty meal, the lacteals of animals appeared milky and subsequently this emulsion entered the blood stream by way of the thoracic duct. In 1774, Henson showed that this milky fluid contained fat, and in 1924, Gage and Fish showed that blood taken from humans after a fatty meal contained tiny particles about 1 μm in diameter, which they named chylomicrons. This postprandial lipemia lasted for several hours, but was absent from fasting blood specimens.

Cholesterol, a marker for all lipoproteins, was first discovered in bile and in gallstones by Poulletier de la Salle in 1769 ([Dam 1958](#)) and then rediscovered in 1815 by Chevreul, who named it “cholesterine.” Only later was cholesterol found in blood ([Boudet 1833](#)). In the early 19th century, biological chemists believed that the clear blood plasma from fasting animals contained only one soluble protein, albumin, and no fat.

In 1886, Kauder demonstrated that when blood plasma was treated with 50% saturated ammonium sulfate, a new class of proteins, the globulins, were precipitated, leaving the albumin in solution. About the turn of the century, [Haslam \(1913\)](#) and [Chick \(1914\)](#) in England independently found that these globulins contained small amounts of lecithin. In 1901, Nerking, working in Germany, showed that digestion of the proteins of horse plasma with pepsin and HCl liberated fat (in the amount of 250 mg/dL) that was not extractable by ethyl ether from the original sample. He concluded that plasma lipids were bound to protein, but did not attempt to isolate an intact lipoprotein.

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THE DISCOVERY OF PLASMA LIPOPROTEINS

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neutral 50% saturated ammonium sulfate extract of serum by lowering the pH to 3.8. This lipoprotein contained 59% protein and 41% lipid, which consisted of 18% cholesterol and 23% phospholipid and could be redissolved in water to form a clear solution. Later on it was shown that this lipoprotein was an α -globulin and had the same composition as the α -lipoprotein that we now recognize as HDL ([Table 1](#)).

Table 1

Composition of lipoproteins in blood plasma

Lipoprotein	Protein	Lipids ¹⁻¹ %			
	%	Total	CHOL	PL	TG
Chylomicron	1	99	4	7	88
VLDL	8	92	22	16	54
LDL	21	79	46	22	11
Lp(a)	36	64	37	18	9
HDL	50	50	20	26	4
FFA-albumin	99	1	0	0	0

F1-1 Cholesterol; PL, phospholipid; TG, triglyceride; FFA, free fatty acid.

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In 1941, Blix et al., in Upsala, observed upon electrophoresis of plasma that significant amounts of lipid were associated with both the α - and β -globulins. In 1947, in the same Swedish laboratory, Pederson was able to flotote a β -lipoprotein in the ultracentrifuge at the density of 45% saturated magnesium sulfate.

During World War II, [Cohn et al. \(1946\)](#) at the Harvard Medical School isolated a variety of proteins from human plasma for use in the war effort. Both albumin and γ -globulin were needed for the treatment of wounded soldiers. Their basic plan was to fractionate human plasma into five major protein families through the use of gradual changes in pH, ionic strength and ethanol concentration at low temperatures (0 to -5°C). As a by-product of this program, it was discovered that fractions III and IV in this orderly process contained the

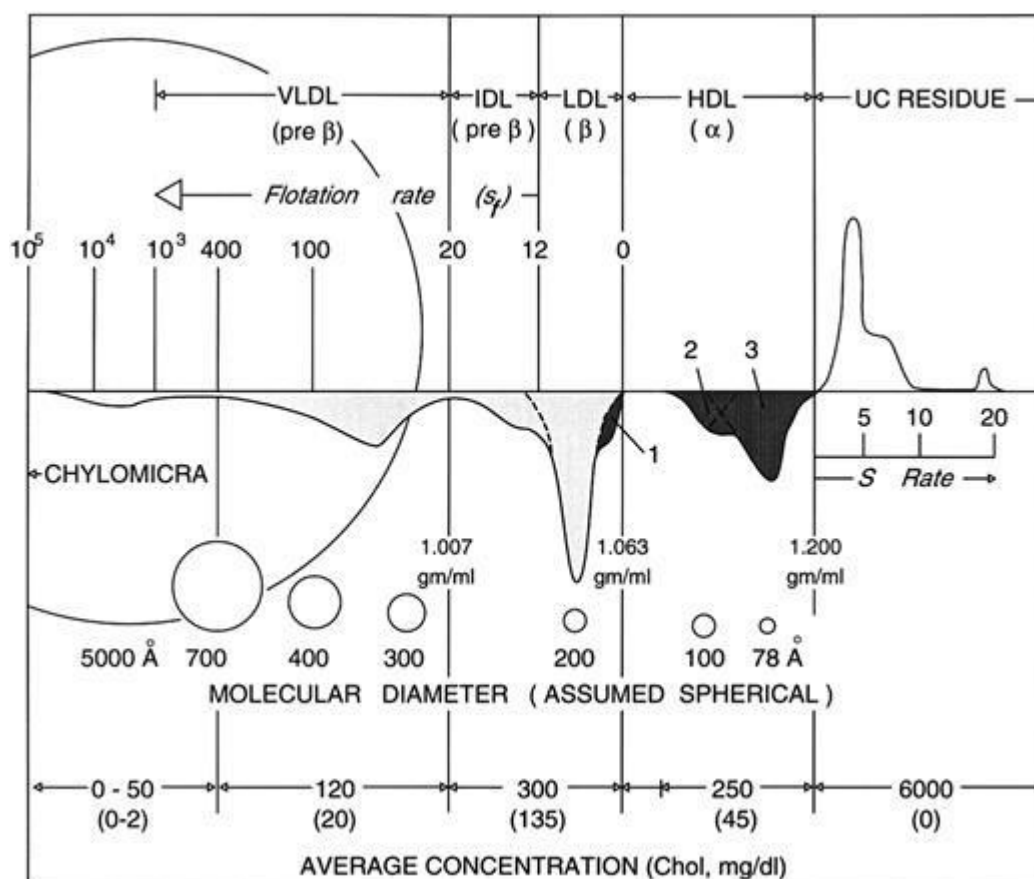
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this lipoprotein had 23% protein, 30% phospholipid, 8% free cholesterol and 39% cholesterol esters, very close to what we now accept as a consensus analysis for LDL ([Table 1](#)). Fraction IV was found to contain the high density α -lipoprotein, first isolated by Macheboeuf.

In 1949, Gofman et al. from the University of California at Berkeley proposed a new method for the quantitative measurement of serum lipoproteins using the ultracentrifuge. The low density lipoproteins were preparatively centrifuged in 1.7 mol/L NaCl ($d = 1.063$). Thereafter, the high density lipoproteins were preparatively centrifuged in D_2O containing sodium nitrate ($d = 1.21$). The concentrations of lipoproteins in each set were calculated from schlieren diagrams obtained in the analytical ultracentrifuge in runs of 30–60 min. [Figure 1](#) shows the typical patterns of VLDL, LDL and HDL from a healthy young adult. [Gofman et al. \(1950\)](#) were then able to associate certain lipoprotein fractions with atherosclerosis and xanthomatosis.

Figure 1



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Schematic presentation of the major lipoproteins in normal human plasma as measured by flotation in the ultracentrifuge at $200,000 \times g$ for 1 h. Flotation rates are measured in $-S$ (S_f) units. Each class of lipoproteins is

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bottom. Three subclasses of HDL are shown. HDL-1 (HDL_C) occurs only in hyperlipemic plasma. The nonlipid plasma proteins sediment at $d = 1.21$ and are shown at the right. The approximate diameter of each lipoprotein class is shown in angstroms ($1 \text{ \AA} = 0.1 \text{ nm}$). The plasma cholesterol accounted for by each class of lipoprotein is shown in parentheses, e.g., (45 mg/dL) equivalent to 1.16 M. Modified from [Fredrickson et al. \(1967\)](#).

Another lipoprotein, Lp(a), was discovered by K  re [Berg \(1963\)](#) in Norway in a immunochemical study designed to detect antigenic variations in human LDL. Lp(a) is a complex particle in human plasma that is assembled from one LDL molecule that carries all the lipid and one glycoprotein [apo(a)], which has a high degree of homology to plasminogen. Lp(a) provides some risk for atherosclerosis.

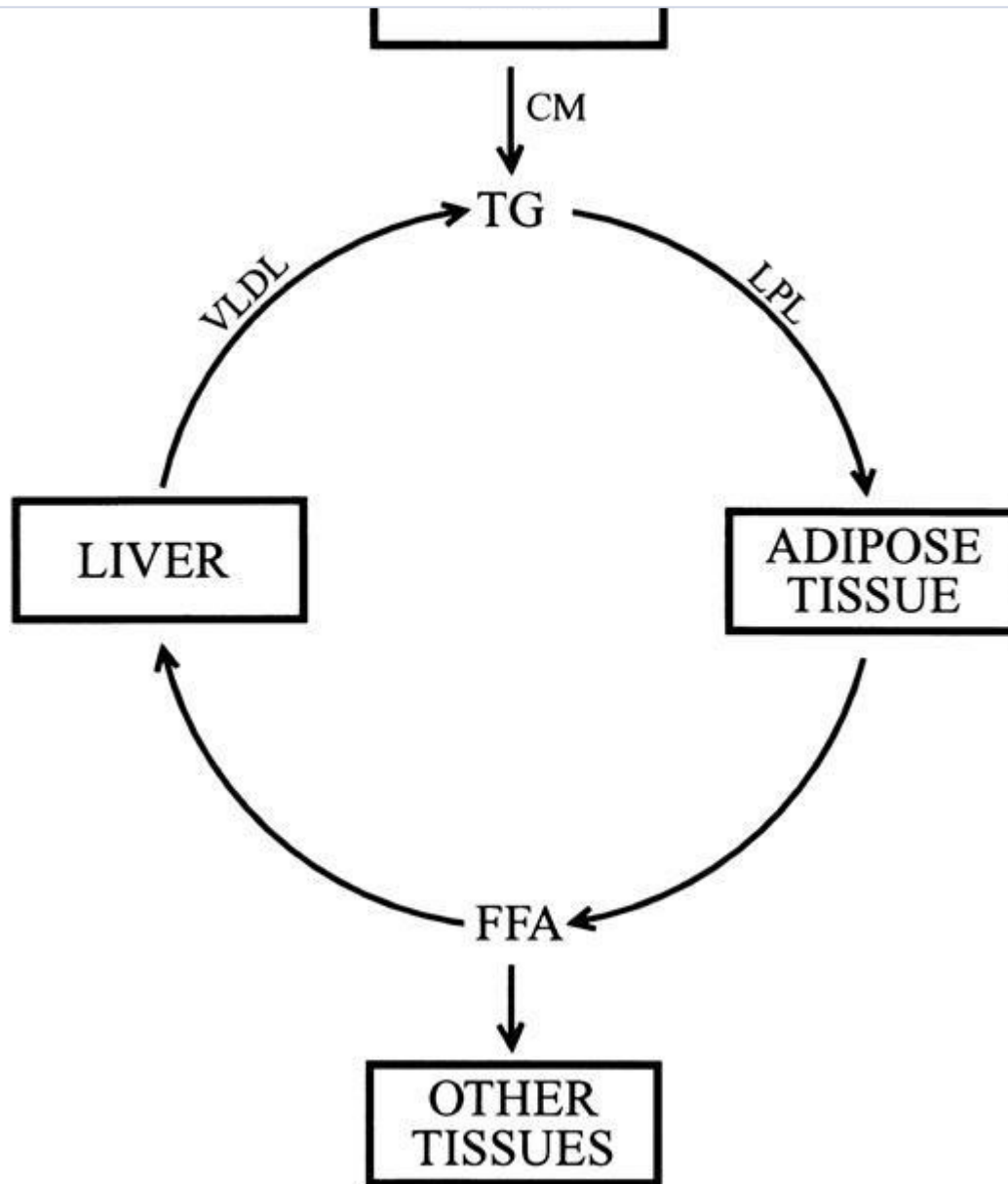
[Table 1](#) presents the overall composition of these lipoproteins. There is a wide variation in their composition, ranging from 1 to 99% for protein and, reciprocally, for lipid. [Figure 1](#) shows that all lipoproteins except free fatty acid (FFA)²-albumin are spheres that vary in diameter from 80    for HDL, to >5000    for chylomicrons. FFA were discovered in plasma by Szent-Gyorgi and Tominaga in 1924 and reinvestigated by [Dole \(1956\)](#) and [Gordon and Cherkes \(1956\)](#), who explored their physiologic significance and their binding to albumin.

A RUDIMENTARY VIEW OF FAT TRANSPORT (~1960)

In the 1960s, a more coherent view of fat transport began to emerge, aided by extensive reviews of a large body of evidence by [Fredrickson and Gordon \(1958\)](#) and [Olson and Vester \(1960\)](#). On the basis of physiologic studies of organ function and isotopic studies of lipoprotein turnover, it was concluded that triglycerides are transported by chylomicrons from the gut to adipose tissue, and by VLDL from the liver to adipose tissue. Both processes require lipoprotein lipase (LPL) and the local uptake of FFA by fat cells. [Sch  nheimer and Rittenberg \(1936\)](#) were the first to demonstrate a brisk turnover of adipose tissue lipid in mice fed deuterium-labeled precursors. It was then shown by study of A-V differences that fat transport from adipose tissue to liver and other tissues was accomplished by FFA bound to albumin. Isotopic studies showed that the turnover time of FFA in humans is about 3 min, which means that about 200 g of fatty acids (2–3 times the daily intake) is transported by human plasma each 24 h. ([Fig. 2](#)). Because the labeled FFA contributed <50% of the respiratory CO₂ over 24 h, it appeared that extensive recycling of FFA must occur.

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Figure 2

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The transport of lipid among the organs of the mammal. Plasma triglyceride (TG) arises from the gut via chylomicrons (CM) and the liver via VLDL. The TG content of both of the TG-rich lipoproteins is reduced by lipoprotein lipase attached to the endothelium of capillaries nourishing adipose tissue cells. The free fatty acids (FFA) generated are taken up locally by fat cells and synthesized into TG. The release of fatty acids by adipose tissue depends on the action of a hormone-sensitive lipase. These FFA enter the plasma and supply lipid fuel for all tissues.

[Skip to main content](#) THE CHARACTERIZATION OF THE LIPOPROTEIN APOPEPTIDES

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resulting peptides fractionated and studied to determine their size, shape and amino acid composition. At first, there were difficulties from the insolubility of some of the peptides and the denaturation and/or proteolysis of others during isolation. Nonetheless, by the mid-1970s, it became clear that there were four families of peptides associated with the major lipoproteins. (Jackson et al. 1976) The A-apopeptides were associated primarily with the α -lipoproteins (HDL); the B-apopeptides with β -lipoproteins and chylomicrons; the migratory C-apopeptides with all lipoproteins except LDL; and the E-apopeptide with VLDL, intermediate density lipoprotein (IDL) and HDL (Table 2). Most lipoprotein apopeptides are synthesized in the liver or the intestine, but one, apolipoprotein redundant E, is synthesized in all cells, except the gut.

Table 2

Human plasma apolipoproteins

Apolipoprotein	Molecular weight	Plasma level	Function
		(mg/dL)	
A-1	29,000	110 \pm 20	LCAT ²⁻¹ activator
A-II	17,500	40 \pm 10	HDL structure
B-100	549,000	90 \pm 10	VLDL, LDL
B-48	264,000	<5	Chylomicron
C-I	7000	6 \pm 2	LCAT activator
C-II	9000	4 \pm 2	LPL activator
C-III	9000	12 \pm 3	HDL structure
E	34,000	5 \pm 2	B-100 receptor

F2-1 LCAT, lecithin:cholesterol acyl transferase.

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Of particular importance for lipoprotein clearance are apo B-100 and apo E. Apo B-100, with 4536 amino acids and a molecular weight of 550 kDa is the largest protein known in mammals. Apo B-48, the form of apo B present in chylomicrons, is formed in the intestine

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Apoprotein E has three isoforms (E-2, E-3 and E-4), two of them (E-2 and E-4) resulting from mutations that change the properties and charge on the native peptide (Uterman et al. 1977). Apo E-2 binds to its receptors poorly and causes β -VLDL to accumulate in the plasma. Apo E-4 increases the plasma level of LDL and blocks cholesterol transport in neurons.

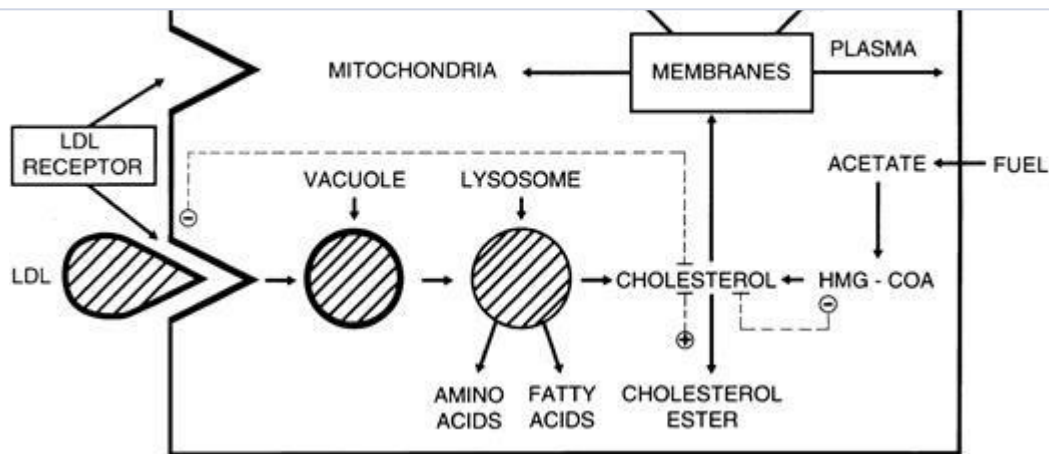
THE LDL RECEPTOR

In 1974, Michael Brown and Joseph Goldstein at the University of Texas demonstrated that fibroblasts cultured from normal humans bound ^{125}I -labeled LDL with high affinity and specificity and inhibited the activity of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase. Fibroblasts from patients with homozygous familial hypercholesterolemia showed no binding of LDL and no inhibition of endogenous cholesterol synthesis. Subsequently, these investigators ([Schneider et al. 1982](#)) purified the LDL receptor by affinity chromatography and determined that it is a cell surface glycoprotein of 839 amino acids that contains several domains. These include a ligand-binding domain for both B-100 and apo E, an epidermal growth factor domain, a glycoprotein domain, a membrane spanning domain and a cytoplasmic domain. The LDL receptor is located in coated pits in most cells.

The function of the LDL-receptor is the endocytosis of LDL ([Fig. 3](#)). The receptor binds and internalizes LDL, which then occupies a vacuole in the cell, ultimately merging with a lysosome. In the lysosome, both the apoprotein and lipids of LDL are degraded to monomers and released into the cytoplasm. The free cholesterol released has the following four effects: 1) incorporation into membranes; 2) inhibition of the synthesis of new LDL receptors; 3) inhibition of cholesterol synthesis by reducing the synthesis of HMG CoA reductase; and 4) promotion of the activity of acyl CoA:cholesterol acyltransferase (ACAT), which synthesizes cholesterol esters. These regulatory events are mediated by a sterol regulatory element binding protein, which monitors the free cholesterol concentration in the cell and adjusts the expression of the cholesterol regulatory genes ([Wang et al. 1994](#)). As free cholesterol levels rise, the expression of LDL receptors and HMG-reductase is inhibited and the activity of ACAT enhanced. The turnover of LDL receptors occurs partially as a result of recycling receptors that have undergone endocytosis and partially by new synthesis.

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Figure 3

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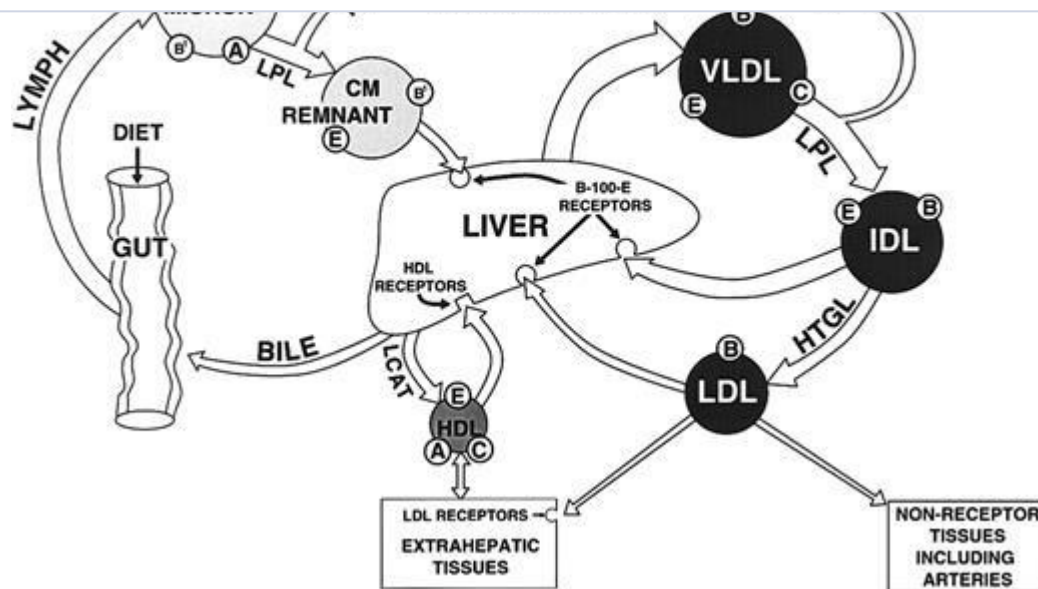
Sequential steps in the LDL-pathway for mammalian cells. The LDL receptor accomplishes the endocytosis of LDL by producing a vacuole, which merges with a lysosome which, in turn, digests the protein and lipids of LDL to produce monomers that diffuse into the cytoplasm. The increase in free cholesterol changes metabolic events indicated by + or -. The dark lines of LDL indicate protein; the diagonal lines indicate lipid. Modified from [Brown and Goldstein \(1979\)](#).

THE ROLE OF RECEPTOR MEDIATED EVENTS IN FAT TRANSPORT

Knowledge of the importance of lipoprotein receptors, which feature protein-protein interactions in the clearance of circulating lipoproteins, has modernized views of fat transport; the pathways are shown in [Figure 4](#). As noted earlier, chylomicrons arise in the gut during fat digestion, enter the thoracic duct and then the blood stream where they are attacked by LPL, which reduces their triglyceride content by 75% and produces a chylomicron remnant that is taken up by B-100-E receptors on hepatocytes. Within the liver, the chylomicron remnant is decomposed to its amino acids and component lipids. Cholesterol released from lysosomes in hepatocytes can be excreted into bile, converted into bile acids, incorporated into VLDL for secretion into the blood via the Golgi apparatus or esterified with long-chain fatty acids and stored in the hepatocyte.

Figure 4

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Receptor-mediated pathways of lipoprotein metabolism. Three major pathways are involved: chylomicrons, VLDL and HDL. Intermediate density lipoprotein (IDL) is the remnant of VLDL and is cleared by the liver. LDL, which contains only apolipoprotein B-100, is the final product of the pathway; most of it is returned to the liver. Some LDL is taken up by extrahepatic LDL receptors and some by a scavenger pathway. The apo-peptides contained in each lipoprotein are indicated. Three plasma enzymes essential for lipoprotein metabolism include LPL (lipoprotein lipase), LCAT (lecithin-cholesterol acyltransferase) and HTGL (hepatic triglyceride lipase.)

VLDL, the main secretory lipoprotein of the liver, contains cholesterol, phospholipid, triglyceride, newly synthesized B-100 and small amounts of E and C apo-peptides. Part of the triglyceride in the VLDL is hydrolyzed by LPL to form IDL, which may be considered the VLDL remnant and which is then taken up by the liver. The average turnover time for chylomicron triglycerides in the blood is 7 min, whereas that for VLDL triglycerides is about 20 min. Part of the IDL fraction is degraded by hepatic lipase to LDL, which then contains only apo B-100. LDL is the most prominent lipoprotein in human plasma, has a turnover time of about 3 d and is cleared principally by LDL-receptors.

A precursor of HDL containing A1-, A2- and A3-apo-peptides, phospholipids and free cholesterol is also synthesized in the liver and secreted into the blood. Apo A1, a co-factor for lecithin:cholesterol acyl transferase, stimulates this enzyme to transfer fatty acids from lecithin to cholesterol to form cholesterol ester, which enables HDL-3 to assume its spherical shape with a hydrophobic center and a more polar exterior. Cholesterol ester transferase protein further increases the cholesterol ester content of HDL-3 to form HDL-2 (See [Fig. 1](#)). HDL accomplishes reverse cholesterol transport from extrahepatic tissues to the liver.

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are beyond the scope of this review ([Breslow 1988](#)).

DISEASE STATES PROMOTED BY CHANGES IN LIPOPROTEINS

Three disease states that are known to be promoted by changes in plasma lipoprotein concentrations in individuals are as follows: 1) atherosclerosis; 2) xanthomatosis; and 3) Alzheimer's disease. Alterations in apo E structure relate to all three of these conditions.

Atherosclerosis.

The atheromatous plaque was first described by [Virchow \(1856\)](#) as the fundamental lesion of atherosclerosis. It is characterized by smooth muscle proliferation, accumulation of connective tissue fibers and matrix, and lipid accumulation. Usually there is a fibrous cap made up of collagen plus smooth muscle cells, and below that, a disorganized mass of lipids, cholesterol clefts, cell debris, fibrin and other plasma proteins. Calcification, ulceration and hemorrhage into the plaque may occur. [Thannhauser and Magendantz \(1938\)](#) were among the first to associate both atherosclerosis and xanthoma with high serum cholesterol levels. It is now known that high levels of LDL and/or β -VLDL increase the risk of atherosclerosis.

On the basis of Koch's postulates, the β -lipoproteins were considered to be the agent of atherosclerosis (in a framework of agent, host and environment) by [Olson \(1959\)](#) and, more recently, by [Brown and Goldstein \(1992\)](#). Cholesterol per se is not the agent because LDL, which contains cholesterol, is pro-atherogenic whereas HDL, which also contains cholesterol, is anti-atherogenic.

Xanthomatosis.

A xanthoma is a discrete, raised yellow lesion of the skin ([Addison and Gull, 1851](#)). Xanthomas are benign tumors characterized by collections of foamy histocytes. They occur in all races and both sexes in association with familial or acquired disorders leading to hyperlipidemia. High plasma levels of LDL and β -VLDL produce xanthomas of different types.

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Alzheimer's disease.

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play a major role in lipid transport in the central nervous system. Apo E plus a source of cholesterol promotes marked neuritic extension of the dorsal root ganglion cells in culture, and apo E levels dramatically increase after peripheral nerve injury.

Apo E-4, a mutant form of apo E-3, has been implicated in the pathogenesis of Alzheimer's disease. This disorder, which features memory loss, is associated with two characteristic neuropathologic lesions: extracellular neuritic plaques representing deposits of amyloid beta ($A\beta$) peptide and intracellular neurofibrillar tangles representing filaments of a microtubule-associated protein called tau. Binding of $A\beta_{42}$ to apo E-4, but not to apo E-3, leads to plaque formation. Apo E-3 also inhibits phosphorylation of tau, which tends to prevent the formation of neurofibrillar tangles, whereas apo E-4 does not affect the phosphorylation of tau ([Mahley et al. 1996](#)).

SUMMARY AND CONCLUSIONS

A century ago, knowledge about the relations of plasma proteins to lipids was fragmentary. [Nerking \(1901\)](#) observed that the digestion of plasma protein with pepsin liberated a mixture of free lipids, but the discovery of the lipoproteins responsible was delayed for many years. HDL was discovered in 1929 and LDL in 1950. From then on, many laboratories identified other lipoproteins, measured their concentration in plasma and studied their turnover in metabolism. On the basis of these studies, a view of fat transport involving triglyceride and FFA movements was formulated in the 1960s.

Not until 1974, however, when Brown and Goldstein discovered the LDL-receptor, was it realized that fat transport depended upon a series of receptor-mediated events. Most of the clinical hyperlipidemias have been found to be the result of genetic changes in lipoproteins, their receptors or the enzymes that mold lipoproteins in plasma. Finally, one isoform of apopeptide E has proven to play a role in Alzheimer's disease.

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Abbreviations

A β amyloid beta

ACAT acylCoA:cholesterol acyltransferase

apo apolipoprotein

FFA free fatty acid

HMG 3-hydroxy-3-methylglutaryl

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IDL intermediate density lipoprotein

Author notes

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