Pathophysiology of Lipid Disorders

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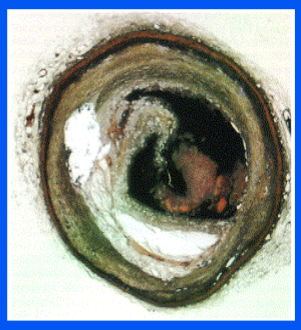
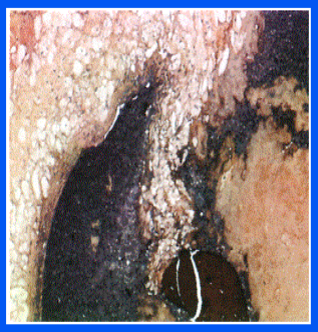
Ruptured Atherosclerotic Plaque



Epicardial Coronary Artery Section
Magnification × 30



Epicardial Coronary Artery Section
Magnification × 120

Reprinted with permission from Burke AP et al. *N Engl J Med.* 1997;336:1276–1282.

CHD in the United States

- CHD is the single largest killer of men and women
- 12 million have history of MI and/or angina
- Each year 1.1 million people have MI
  - 370,000 die of MI
  - 250,000 die within 1 hr
- By age 60, every 5th man and 17th woman develops CHD (1986 Framingham data)
- 1999 estimated direct and indirect costs of heart disease are $99.8 billion
- 53.3 million adults have elevated LDL-C and warrant intervention (1994 NHANES data)
  - 22.3 million qualify for drug therapy
  - 5.5 million actually receive drug therapy

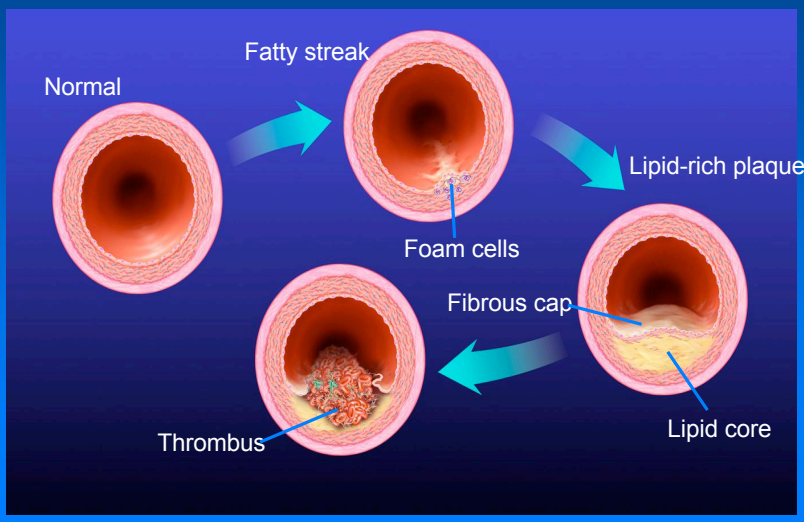
AHA. *1999 Heart and Stroke Statistical Update*; 1998.
National Center for Health Statistics. *National Health and Nutrition Examination Survey (III)*; 1994. (Data collected 1991-1994.)

101

Number of Adults (Millions) Who Need Lifestyle and Drug Treatment

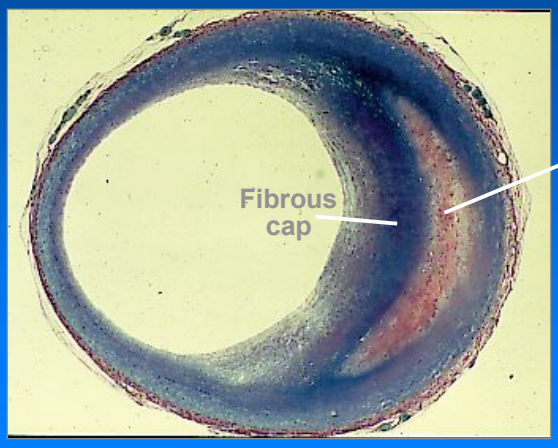
	Therapeutic Lifestyle Changes (TLC)		Drug	
CHD and CHD Risk Equivalents 10-year risk >20%	24.1	35	20.7	29
2+ Risk Factors 10-year risk 10–20%	10.9		8.3	
2+ Risk Factors 10-year risk <10%	14.6	30.2	2.8	7.5
0–1 Risk Factor	15.6		4.7	
Total	65.3M		36.5M	

Development of Atherosclerotic Plaques

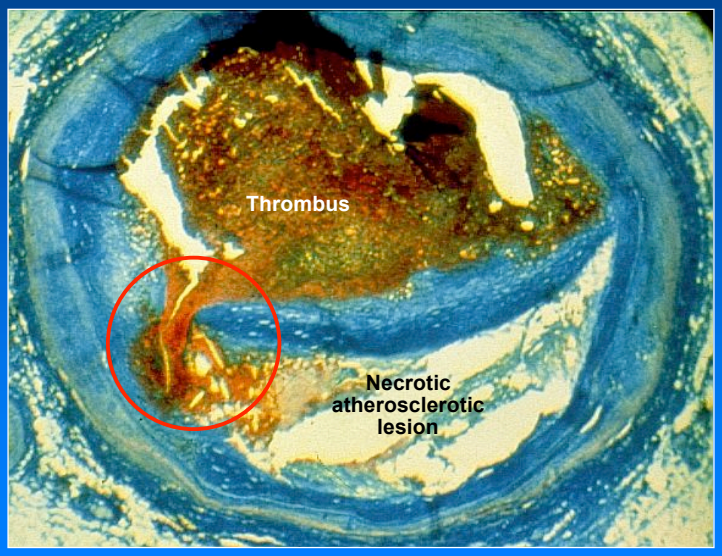


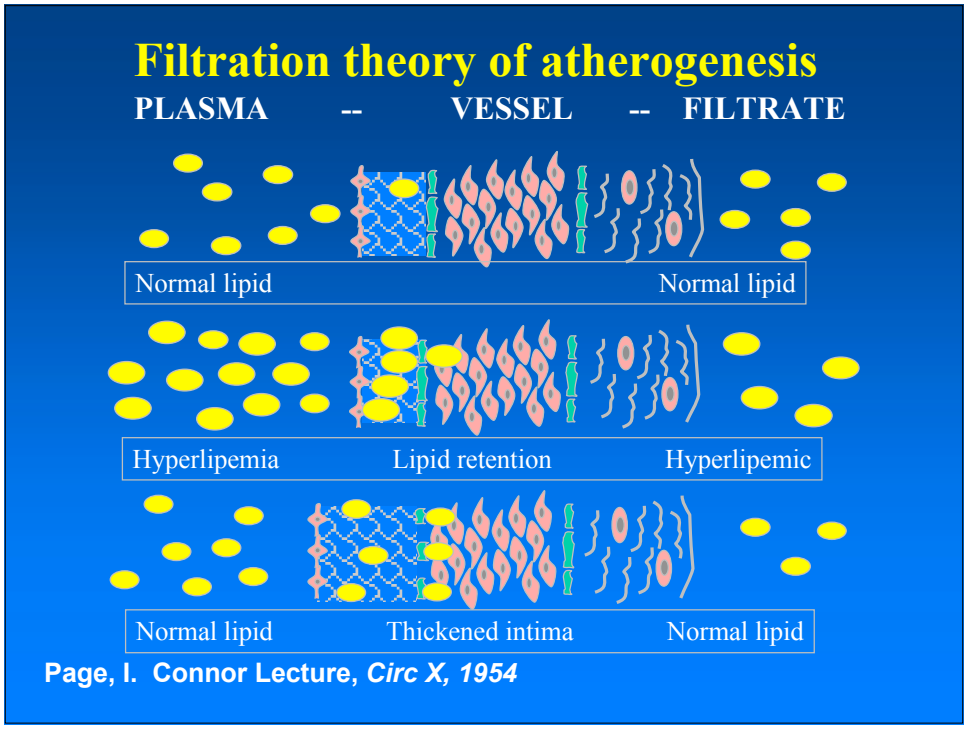
Unoccluded Coronary Artery

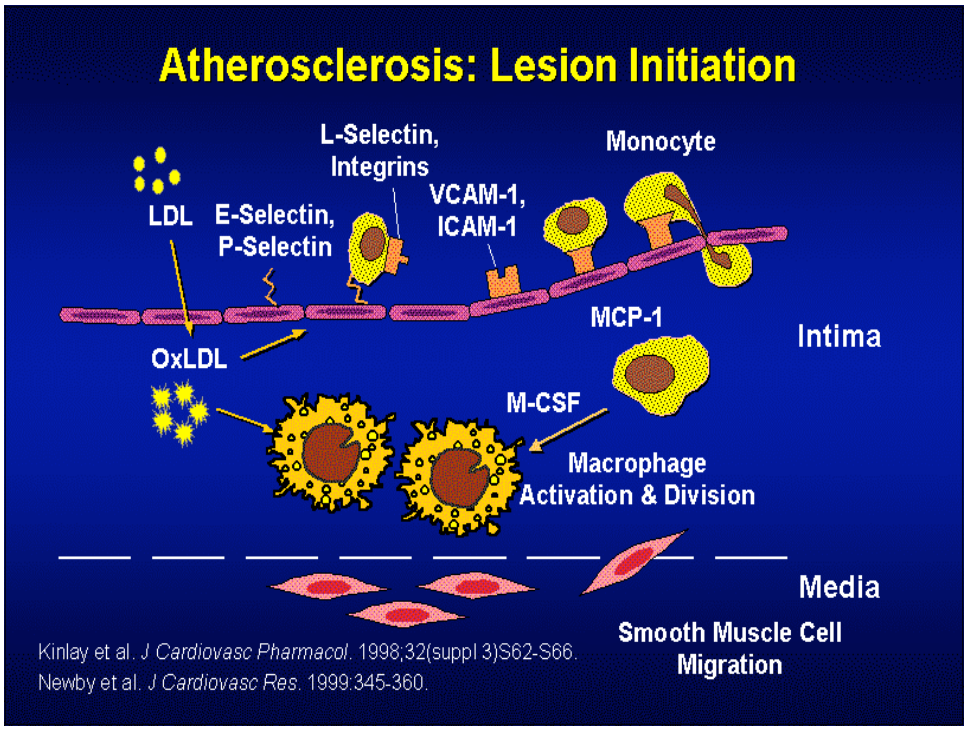
Fibrous Lesion with Necrotic Core



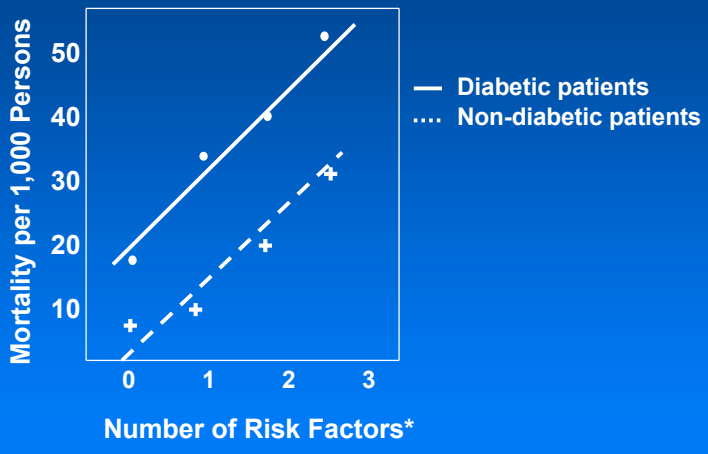
Occluded Coronary Artery




Filtration theory of atherogenesis
PLASMA -- VESSEL -- FILTRATE
Normal lipid
Normal lipid
Hyperlipemia
Lipid retention
Hyperlipemic
Normal lipid
Thickened intima
Normal lipid
Page, I. Connor Lecture, Circ X, 1954

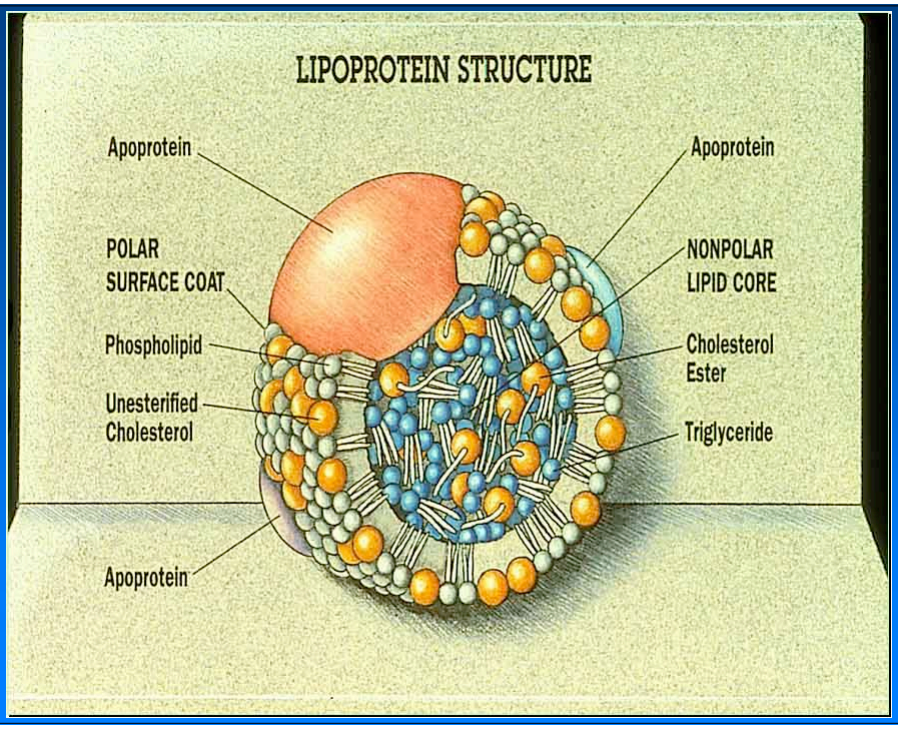

Atherosclerosis: Lesion Initiation
L-Selectin, Integrins
Monocyte
LDL
E-Selectin, P-Selectin
VCAM-1, ICAM-1
MCP-1
Intima
OxLDL
M-CSF
Macrophage Activation & Division
Media
Smooth Muscle Cell Migration
Kinlay et al. J Cardiovasc Pharmacol. 1998;32(suppl 3)S62-S66.
Newby et al. J Cardiovasc Res. 1999:345-360.

Impact of Diabetes on Cardiovascular Mortality



* Risk factors analyzed were: smoking, dyslipidemia and hypertension

Diabetes Care 12:573-579, 1989



Lipoprotein Lipid Composition

	Density	Cholesterol	Triglyceride	Phospholipid	Protein
CHY	0.98	5%	90%	4%	1%
VLDL	<1.006	13%	65%	12%	10%
IDL/LDL	1.006-1.063	43%	10%	22%	25%
HDL	1.063-1.210	18%	2%	30%	50%

Apolipoproteins

- Protein components of lipoprotein
- Functions include: serve as membrane stabilizers, cofactors for enzyme activation, interact with receptors to promote lipid metabolism
- Four major classes; A, B, C, and E

Classification & Location of Major Apolipoproteins

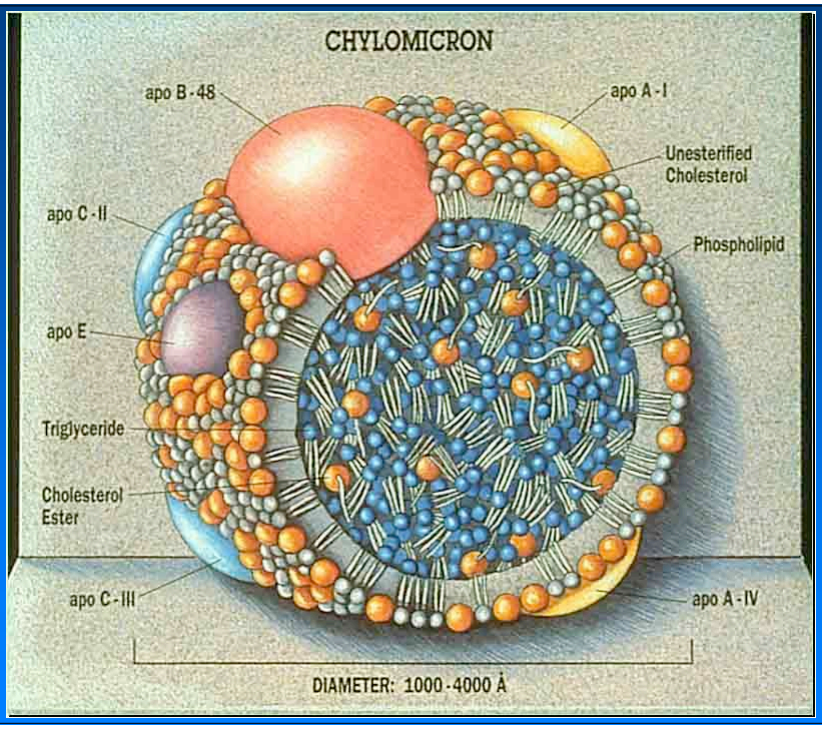
- Apo A-I, A-II, A-IV, AV
  - HDL, Chylomicron
- Apo A-IV
  - Chylomicron
- Apo B_{48}
  - Chylomicron
- Apo B_{100}
  - VLDL, LDL
- Apo C-I, C-II, C-III
  - Chylomicron, VLDL
- Apo E
  - Chylomicron, VLDL

Apolipoproteins

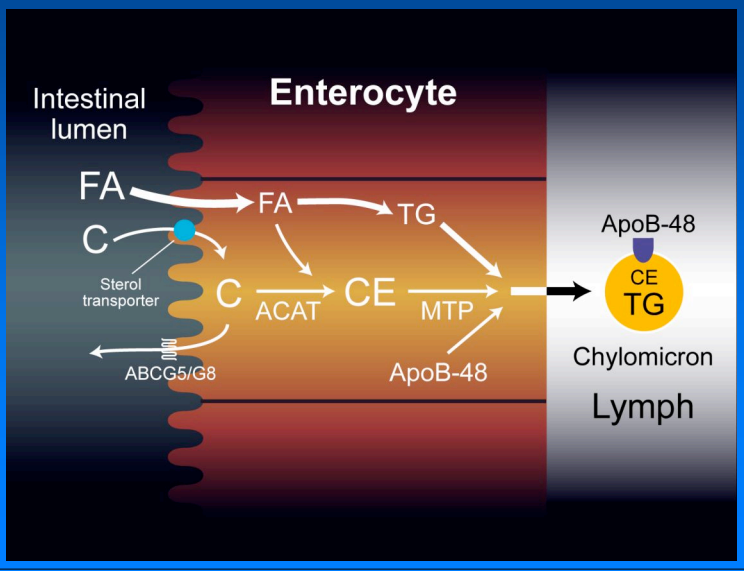
Apolipoprotein	MW (KDa)	Lipoproteins	Metabolic Function
Apo B100	540,000	VLDL, IDL LDL	**Essential structural protein Ligand for LDL receptor**
Apo B48	250,000	chylomicrons	**Essential structural protein**
Apo CI, CII, CIII	8-12,000	VLDL, IDL,, HDL chylomicrons	**CI inhibits remnant uptake, CII activate LPL, CIII inhibits LPL and remnant uptake**
Apo E	34,000	VLDL, IDL,HDL	**Ligand for LDL and LRP receptors**

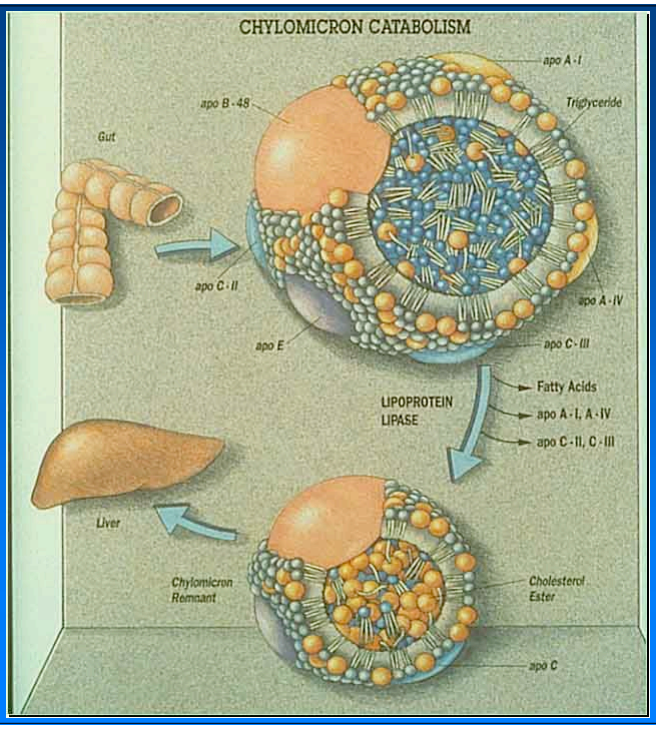
Apolipoproteins

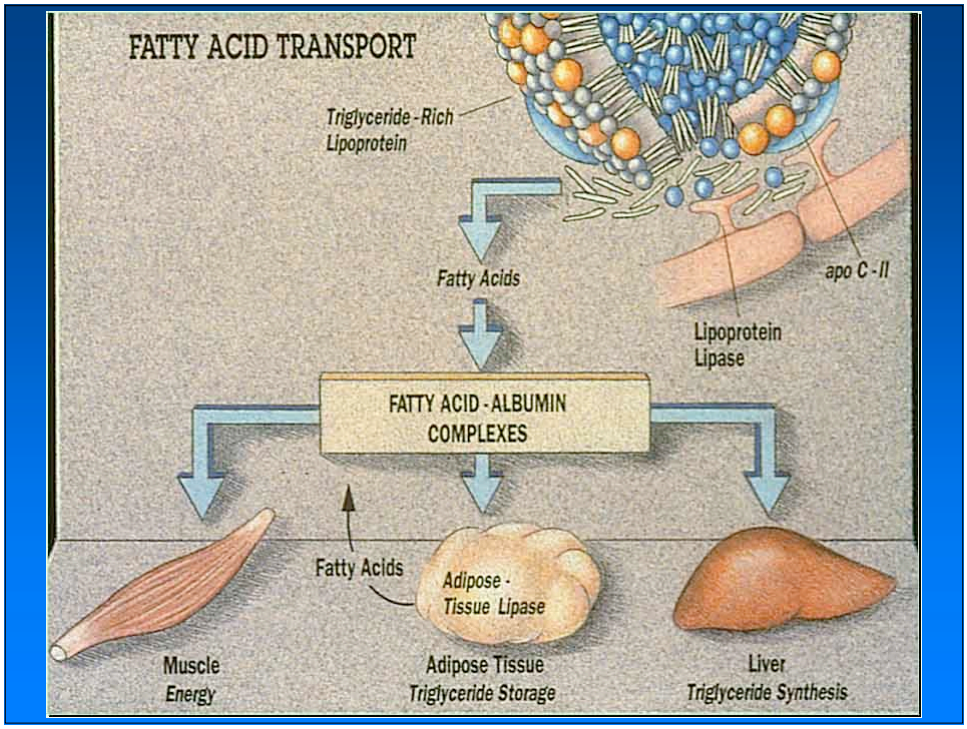
Apolipoprotein	MW (KDa)	Lipoproteins	Metabolic Function
Apo A-I	28	HDL, chylomicrons	**Structural component of HDL, LCAT activator**
Apo A-II	17	HDL, chylomicrons	**Unknown**
Apo A-V	40	HDL, chylomicrons	**Unknown, but strong Association with hiTG**
Apo (a)	400-800	Lp(a)	**Competitive inhibitor of plasminogen**

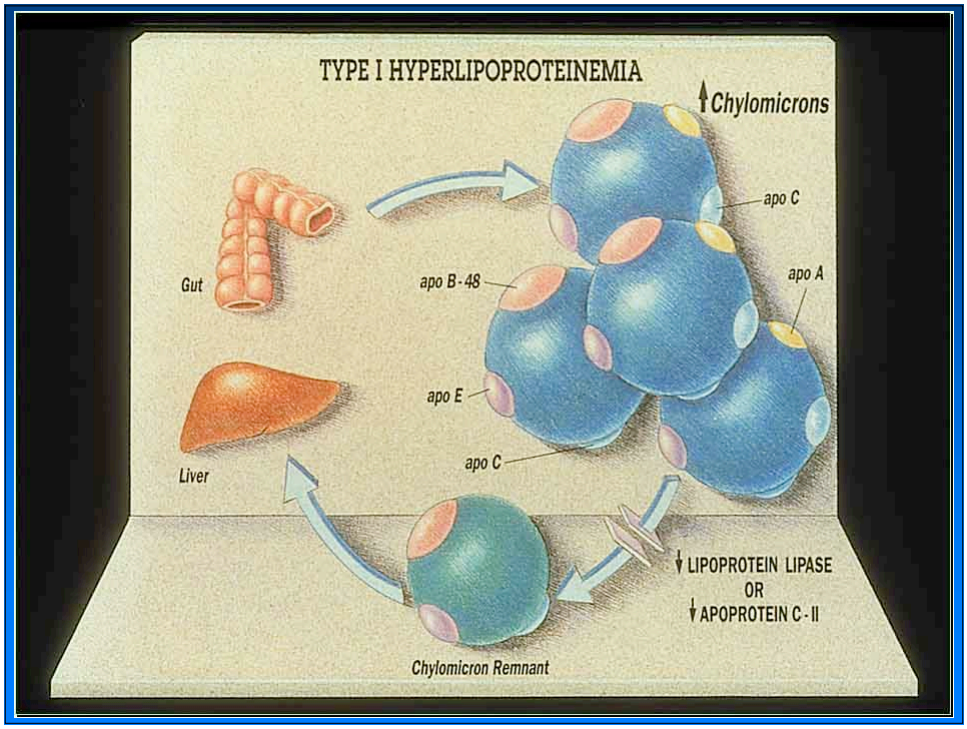


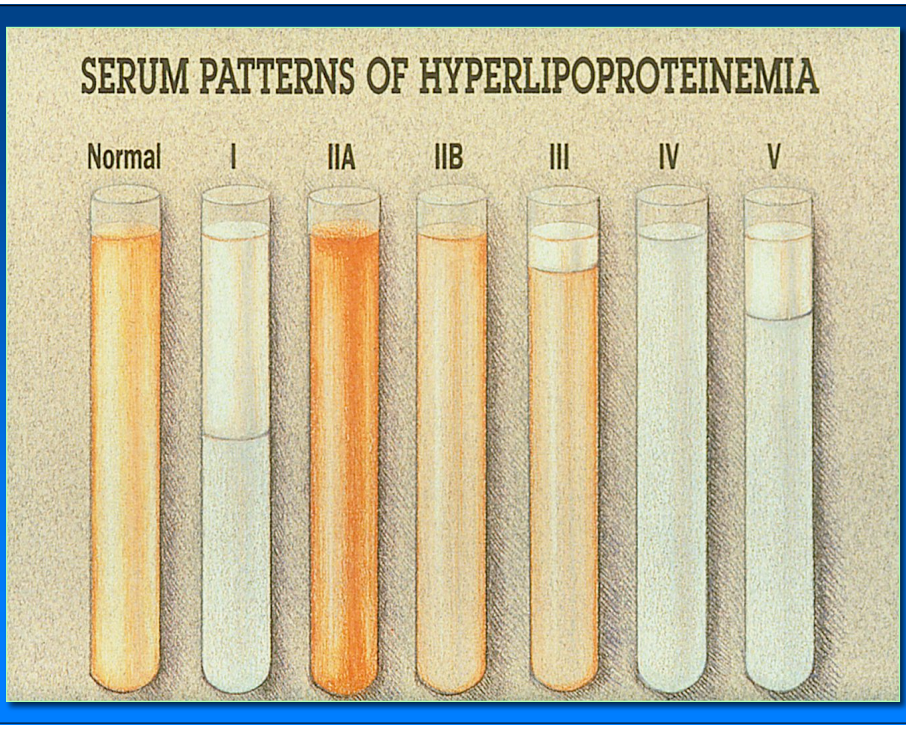
Transport of Intestinal Cholesterol






FATTY ACID TRANSPORT
Triglyceride-Rich Lipoprotein
Fatty Acids
apo C-II
Lipoprotein Lipase
FATTY ACID-ALBUMIN COMPLEXES
Fatty Acids
Adipose-Tissue Lipase
Muscle
Energy
Adipose Tissue
Triglyceride Storage
Liver
Triglyceride Synthesis

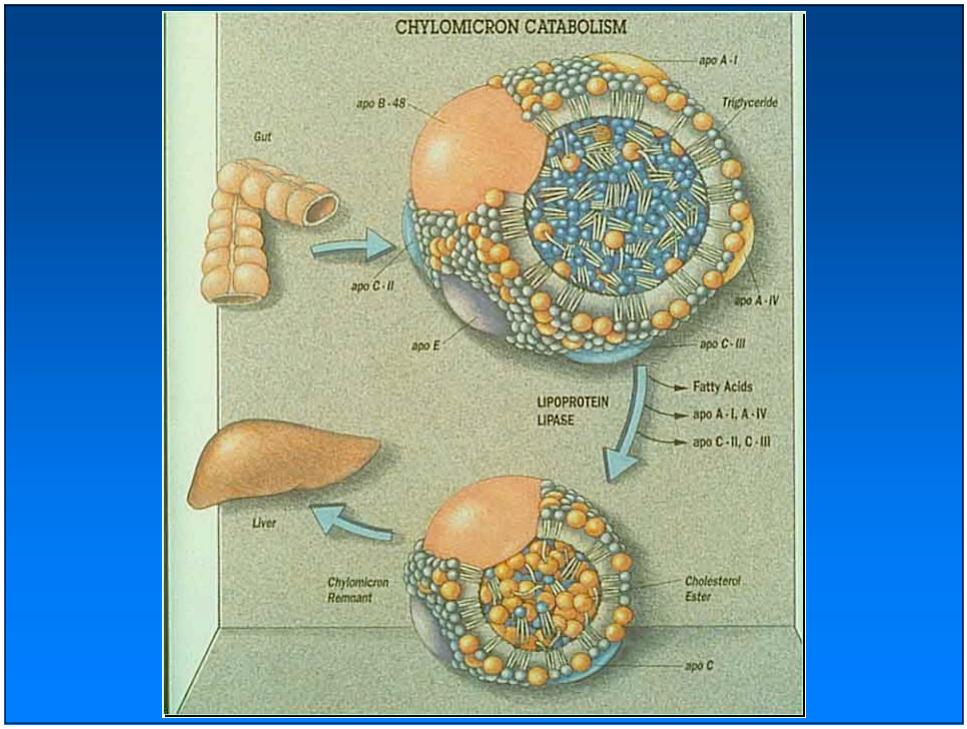

TYPE I HYPERLIPOPROTEINEMIA
Chylomicrons
apo C
apo A
apo B-48
apo E
apo C
Gut
Liver
LIPOPROTEIN LIPASE OR APOPROTEIN C-II
Chylomicron Remnant

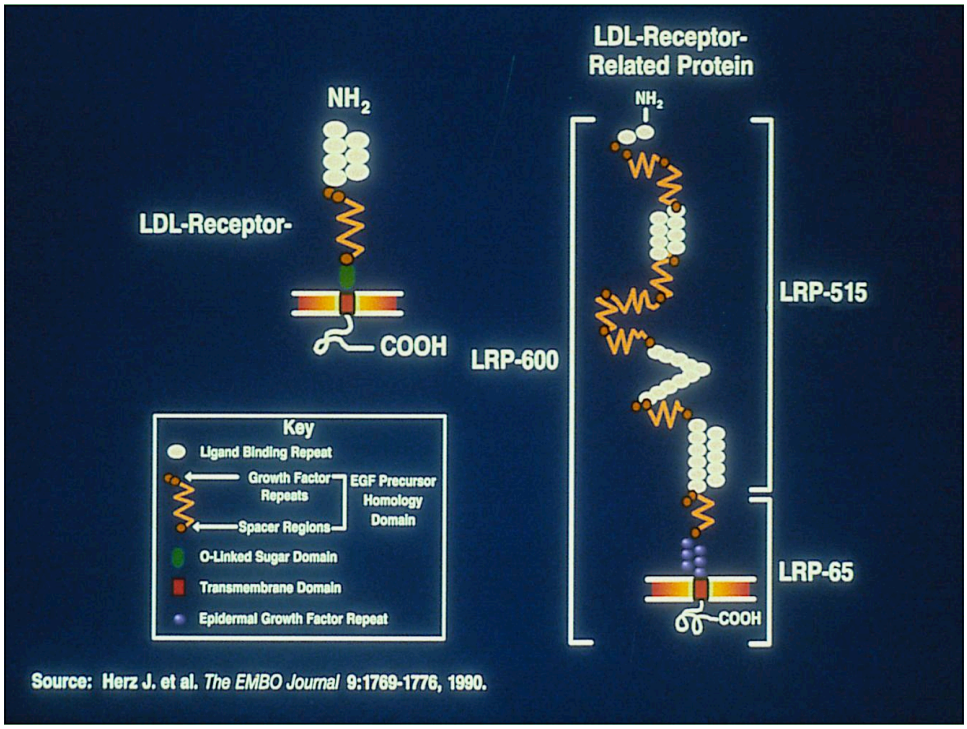


Clinical signs of severe hypertriglyceridemia

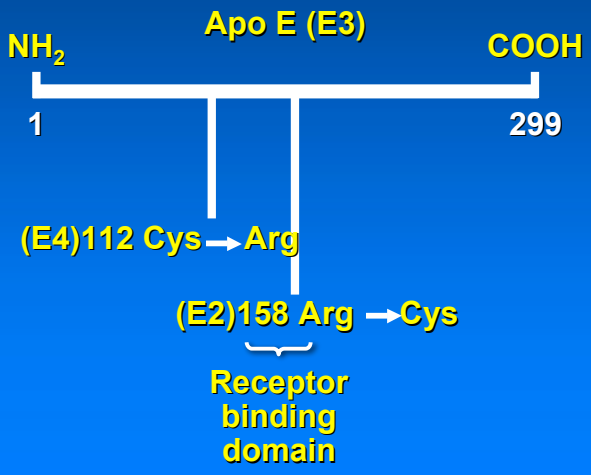
Eruptive xanthomas

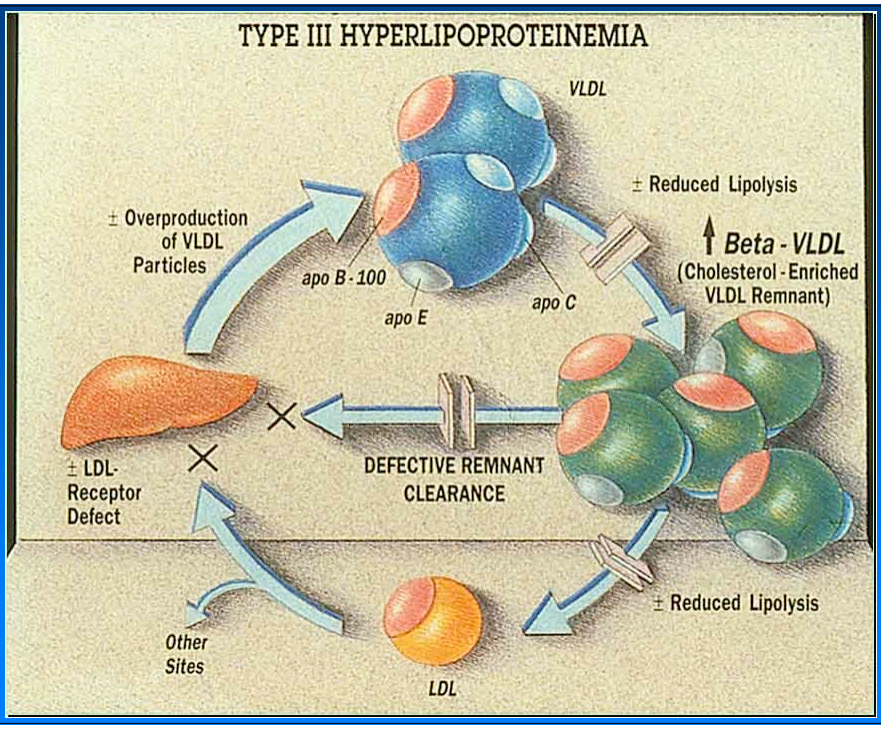
Lipemia Retinalis


CHYLOMICRON CATABOLISM
apo A-I
apo B-48
Triglyceride
Gut
apo C-II
apo A-IV
apo E
apo C-III
Fatty Acids
LIPOPROTEIN LIPASE
apo A-I, A-IV
apo C-II, C-III
Liver
Chylomicron Remnant
Cholesterol Ester
apo C


LDL-Receptor-Related Protein
NH2
LDL-Receptor-
COOH
LRP-600
LRP-515
LRP-65
COOH
Key
Ligand Binding Repeat
Growth Factor Repeats
EGF Precursor Homology Domain
Spacer Regions
O-Linked Sugar Domain
Transmembrane Domain
Epidermal Growth Factor Repeat
Source: Herz J. et al. The EMBO Journal 9:1769-1776, 1990.

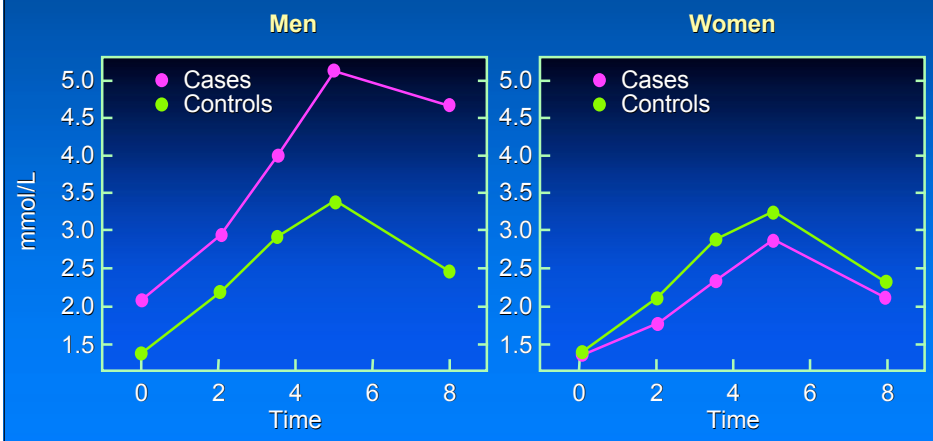
Structure Differences Between Apo E Alleles





Tuberous Xanthomas

Plasma TG Values Over Time



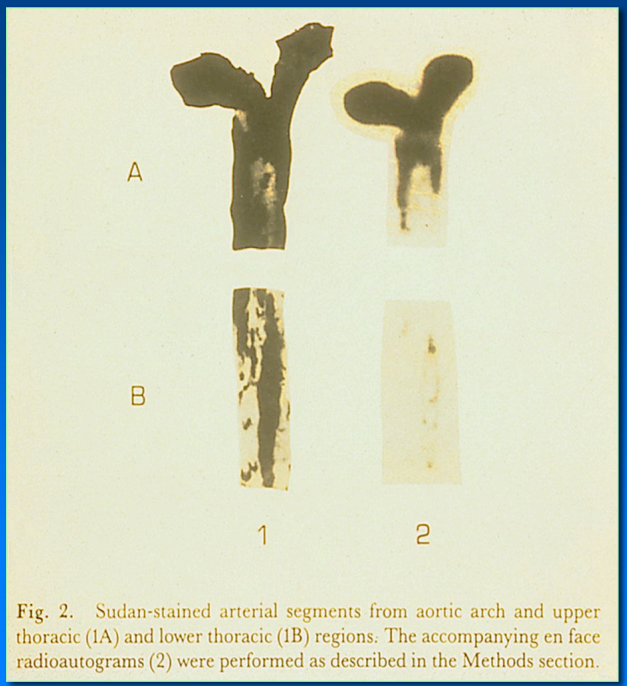
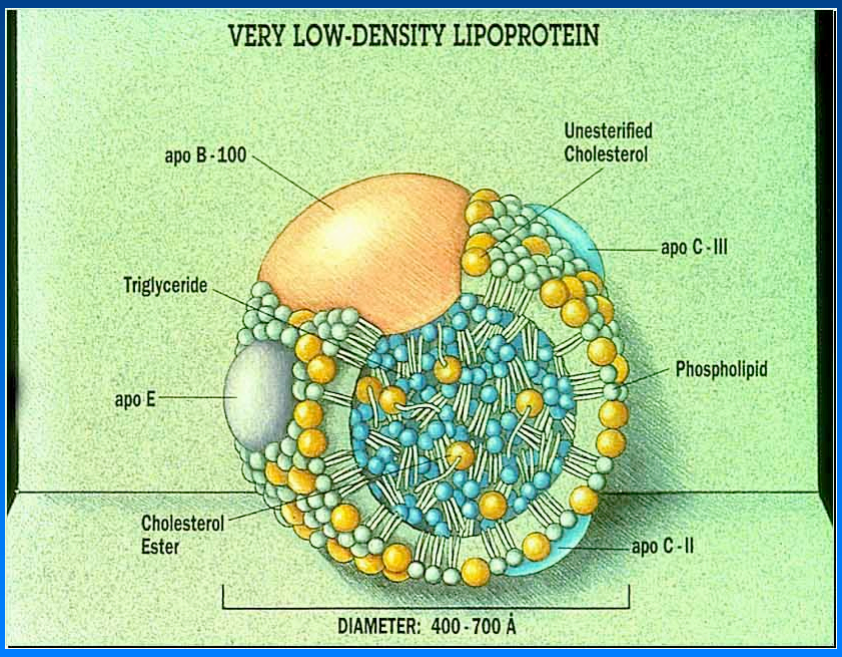
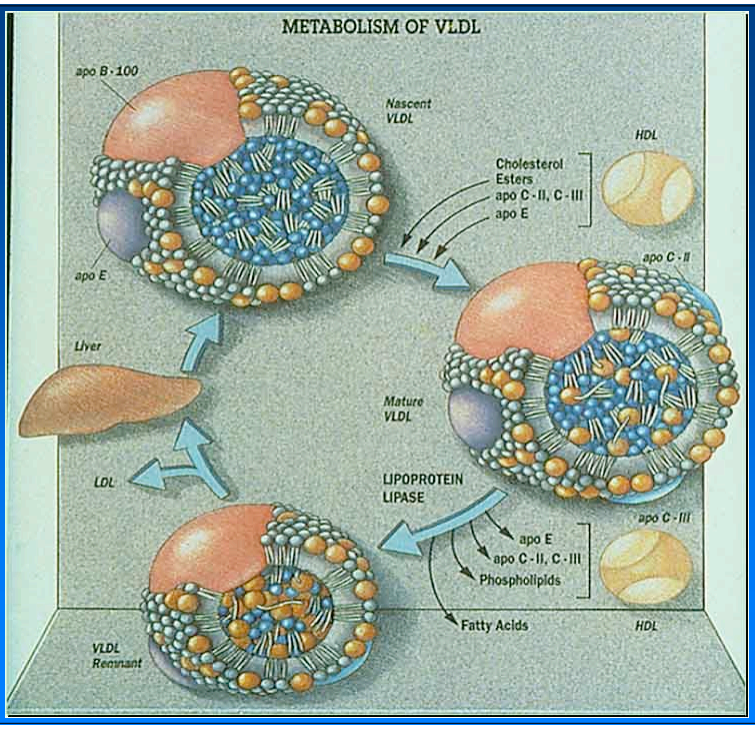
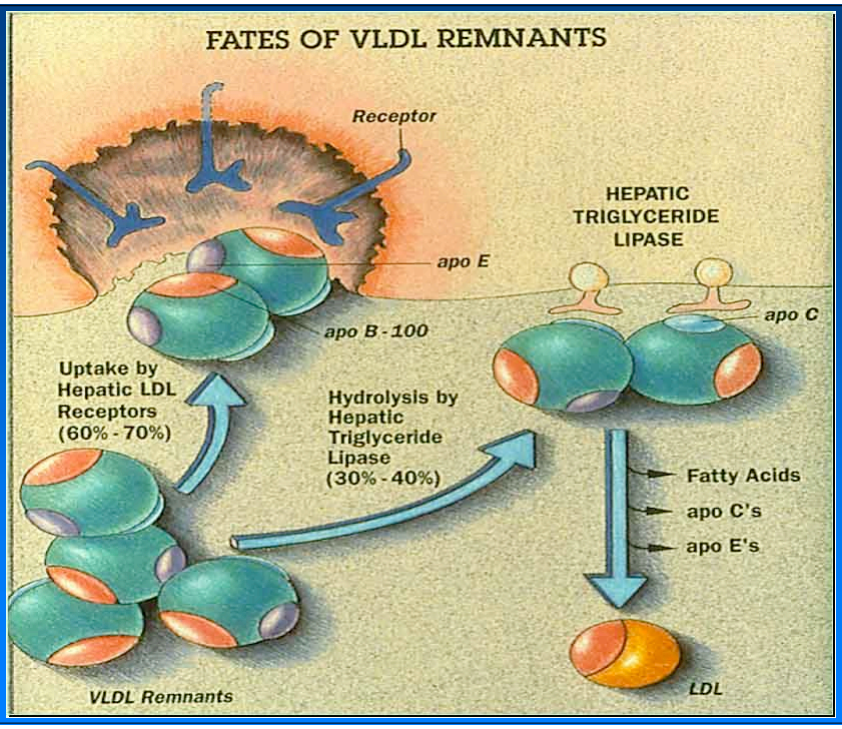


Fig. 2. Sudan-stained arterial segments from aortic arch and upper thoracic (1A) and lower thoracic (1B) regions. The accompanying en face radioautograms (2) were performed as described in the Methods section.


VERY LOW-DENSITY LIPOPROTEIN
apo B-100
Unesterified Cholesterol
apo C-III
Triglyceride
Phospholipid
apo E
Cholesterol Ester
apo C-II
DIAMETER: 400-700 Å

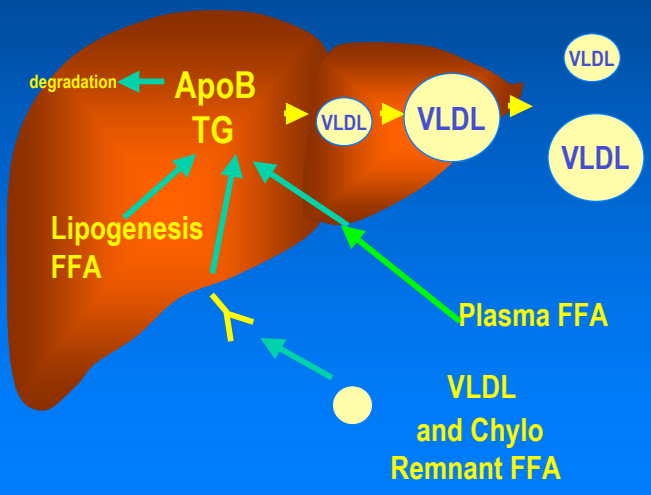

METABOLISM OF VLDL
apo B-100
Nascent VLDL
HDL
Cholesterol Esters
apo C-II, C-III
apo E
apo C-II
apo E
Liver
Mature VLDL
LDL
LIPOPROTEIN LIPASE
apo C-III
apo E
apo C-II, C-III
Phospholipids
Fatty Acids
HDL
VLDL Remnant



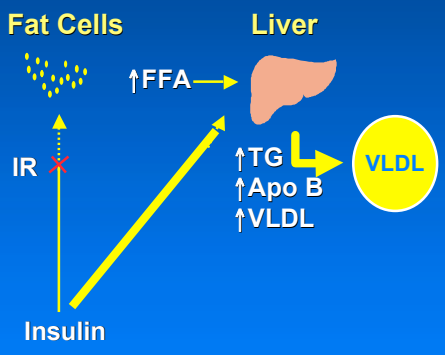
Common Causes of Hypertriglyceridemia

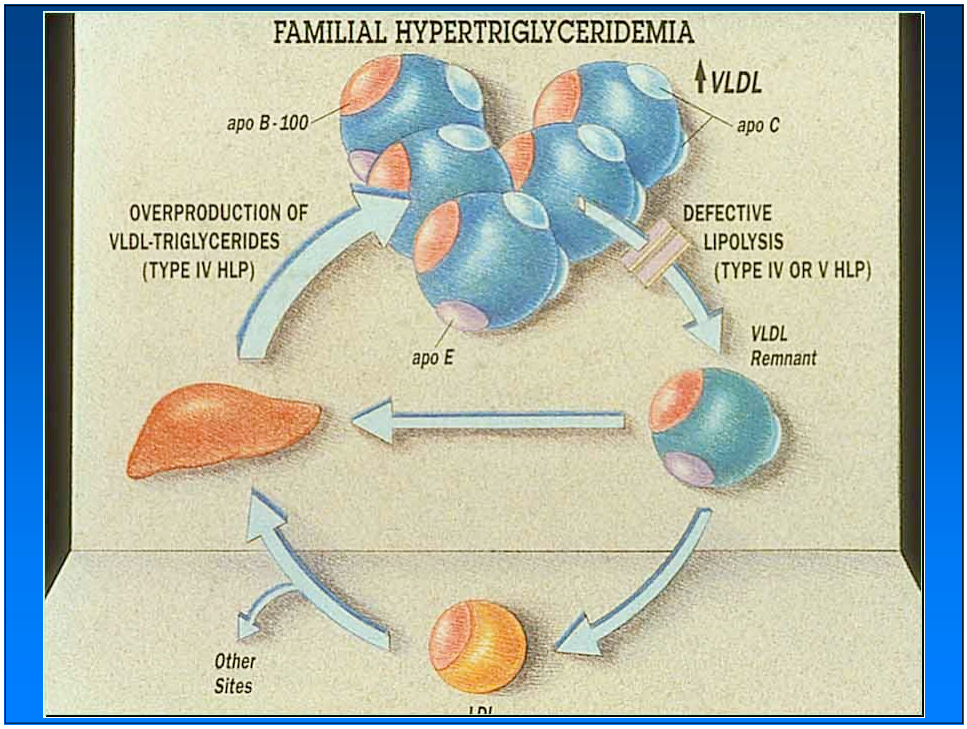
- Caloric excess/obesity
- Insulin resistance
- Diabetes mellitus
- High dietary simple carbohydrates
- Alcohol
- Estrogen therapy
- Lipoprotein lipase mutations

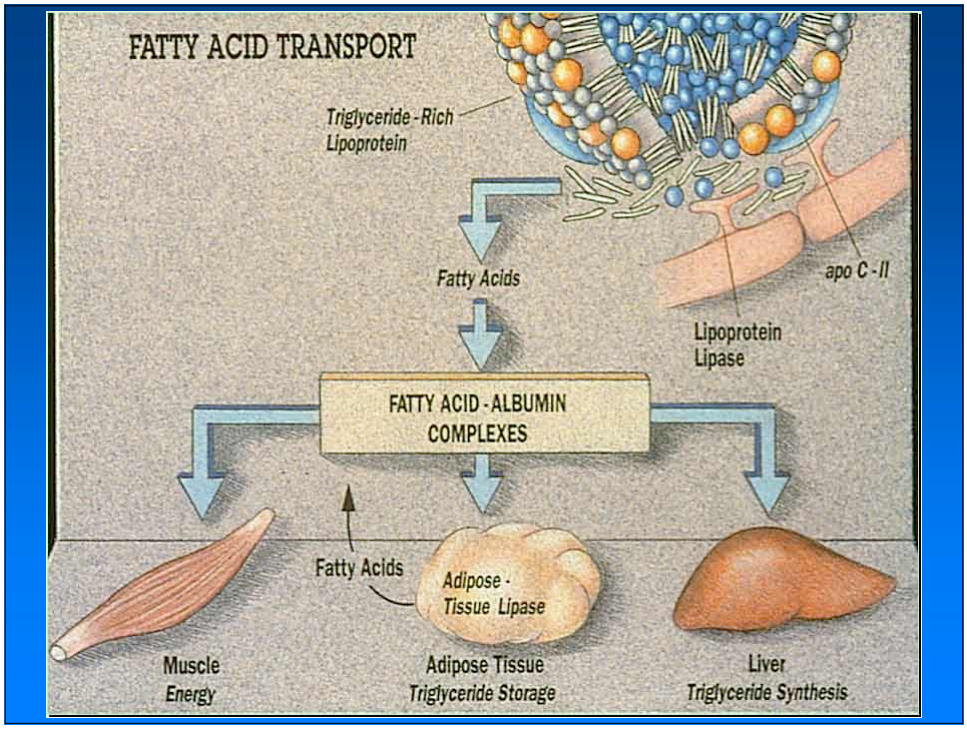
Substrate Driving Forces for the Assembly and Secretion of apoB-Lipoproteins

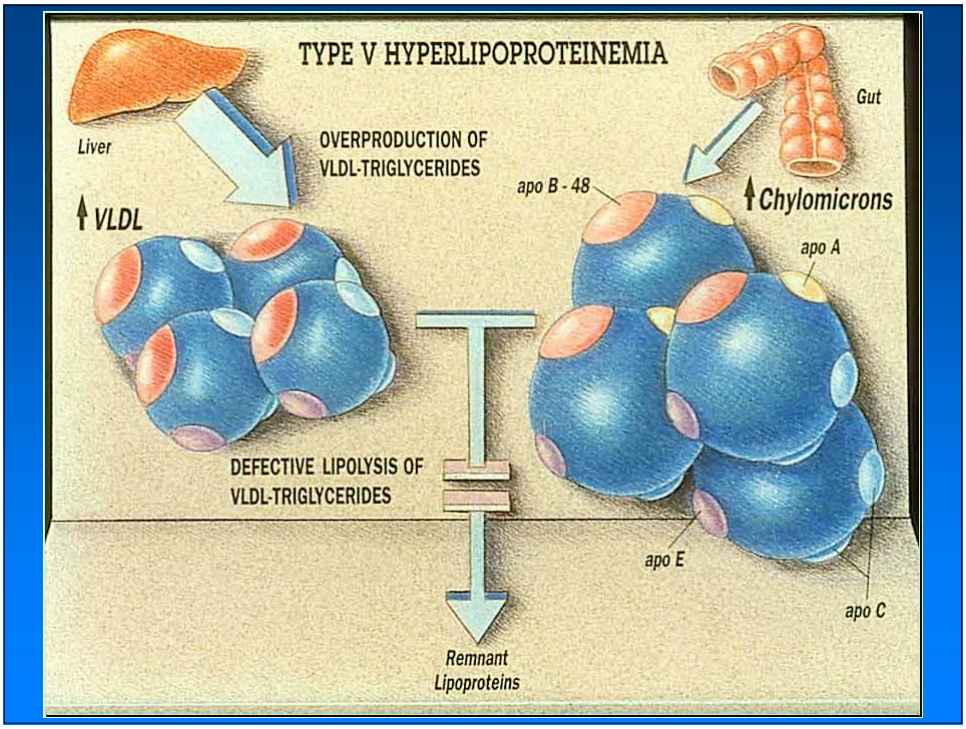


Mechanisms Relating Insulin Resistance and Dyslipidemia



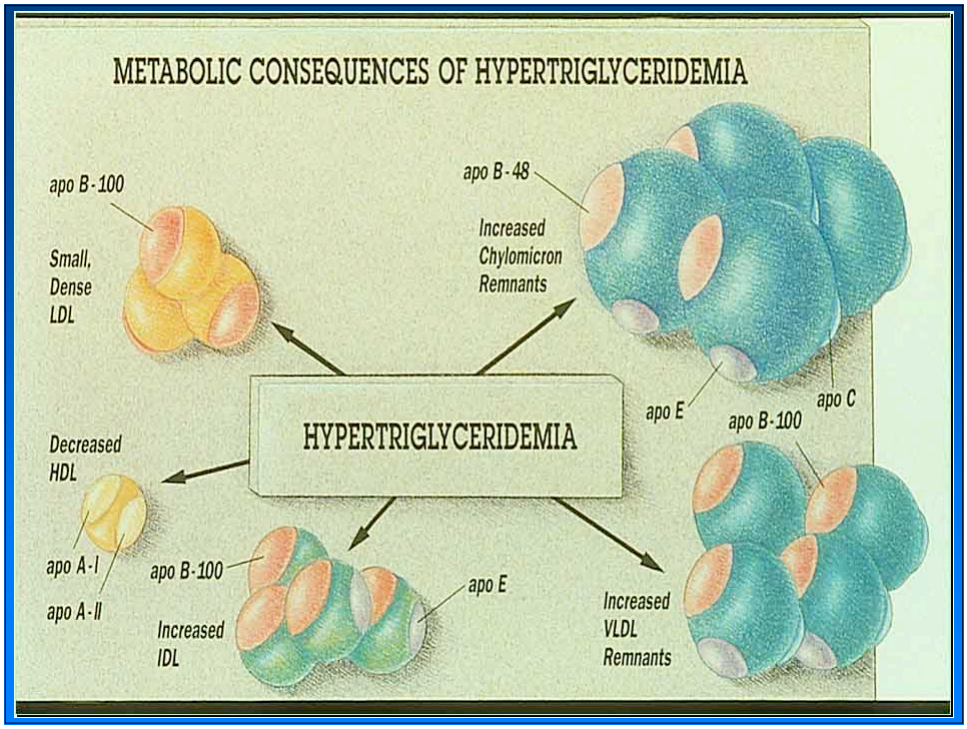

FAMILIAL HYPERTRIGLYCERIDEMIA
VLDL
apo B-100
apo C
OVERPRODUCTION OF
VLDL-TRIGLYCERIDES
(TYPE IV HLP)
DEFECTIVE
LIPOLYSIS
(TYPE IV OR V HLP)
apo E
VLDL
Remnant
Other
Sites

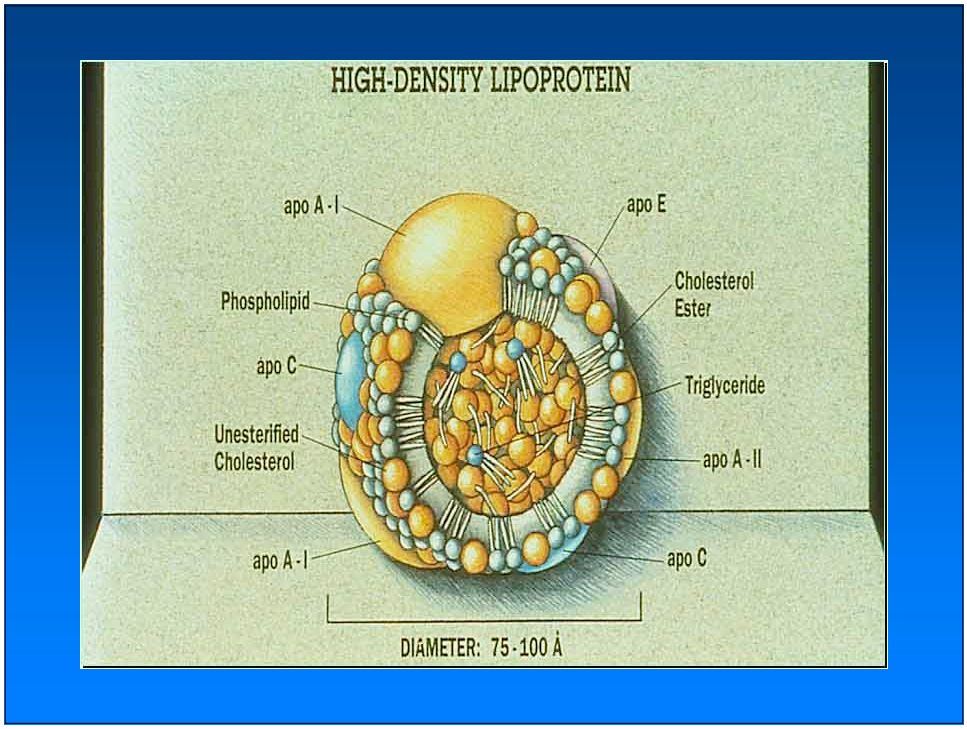

FATTY ACID TRANSPORT
Triglyceride-Rich
Lipoprotein
Fatty Acids
apo C-II
Lipoprotein
Lipase
FATTY ACID-ALBUMIN
COMPLEXES
Fatty Acids
Adipose-
Tissue Lipase
Muscle
Energy
Adipose Tissue
Triglyceride Storage
Liver
Triglyceride Synthesis



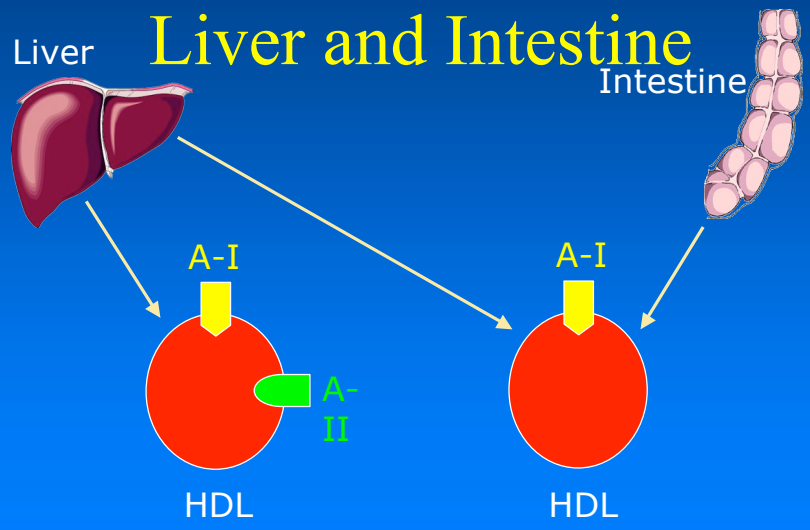
Hypertriglyceridemia: A risk factor for atherosclerosis

- VLDL can enter the artery wall
- Associated with increased factor VII, fibrinogen, and PAI-1
- Associated with other lipid abnormalities

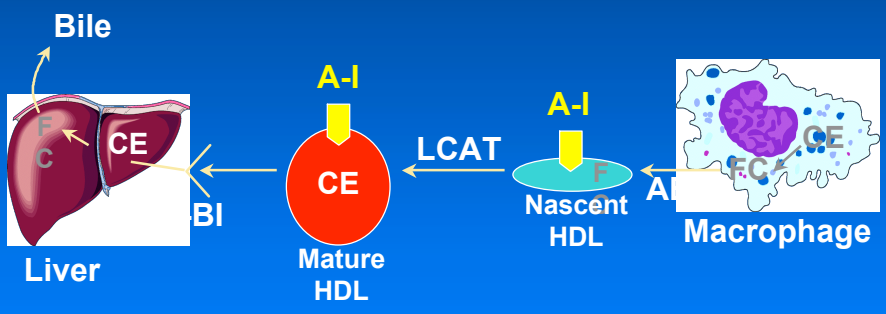

METABOLIC CONSEQUENCES OF HYPERTRIGLYCERIDEMIA
HYPERTRIGLYCERIDEMIA
apo B-100
Small, Dense LDL
apo B-48
Increased Chylomicron Remnants
apo E
apo C
apo B-100
Increased VLDL Remnants
Decreased HDL
apo A-I
apo A-II
apo B-100
Increased IDL
apo E


HIGH-DENSITY LIPOPROTEIN
apo A-I
apo E
Phospholipid
Cholesterol Ester
apo C
Triglyceride
Unesterified Cholesterol
apo A-II
apo A-I
apo C
DIAMETER: 75-100 Å

Production of HDL by Liver and Intestine

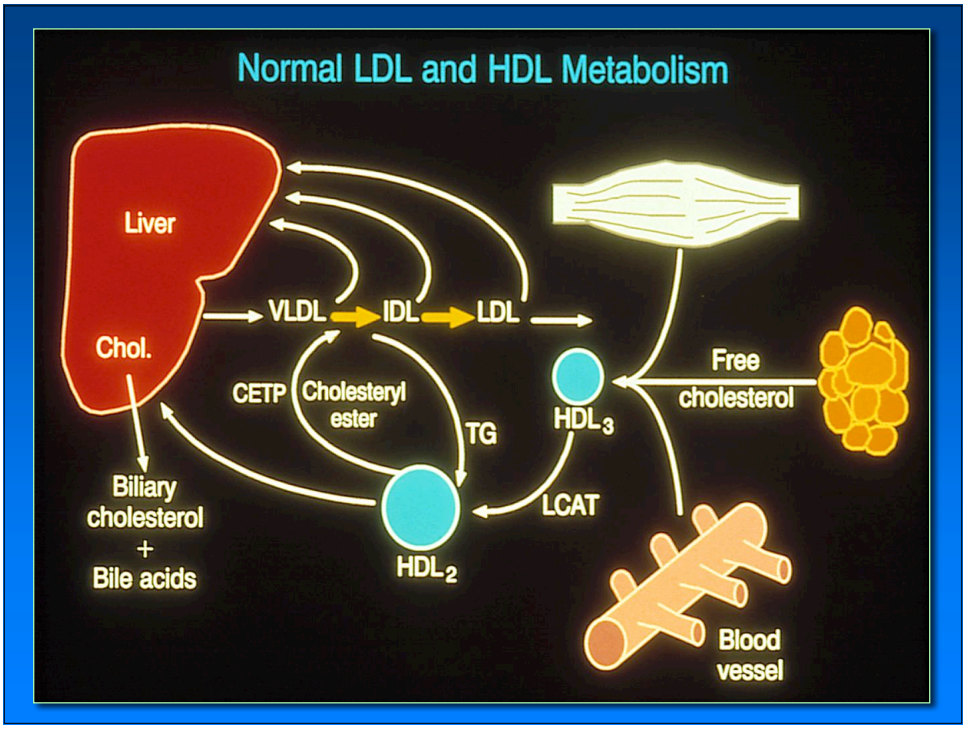


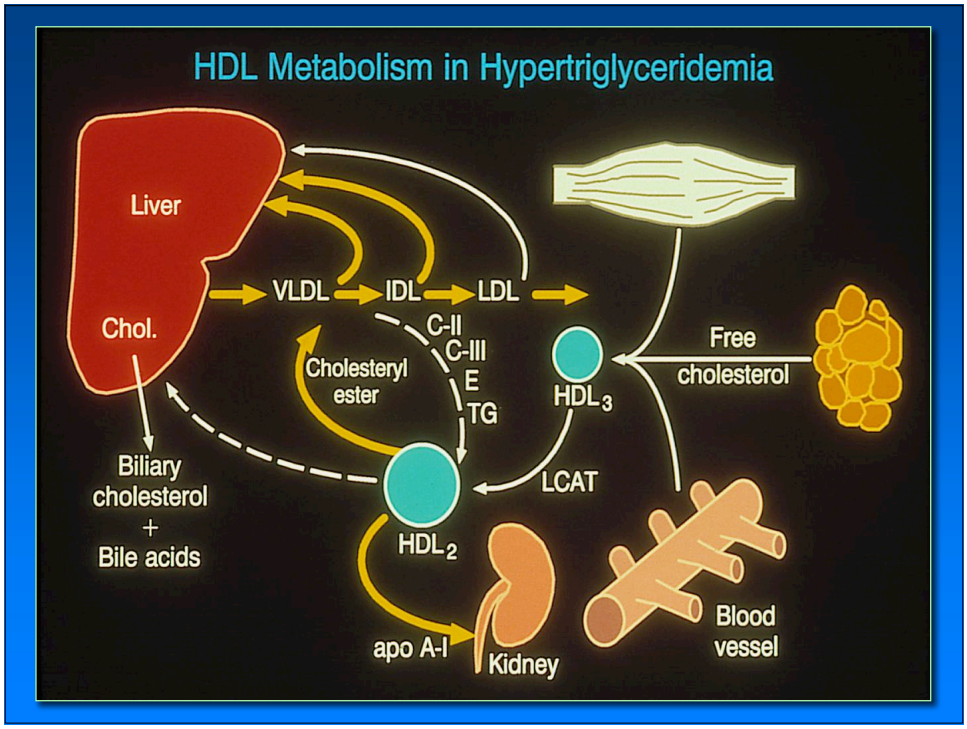
HDL Metabolism and Reverse Cholesterol Transport



Causes of low HDL cholesterol

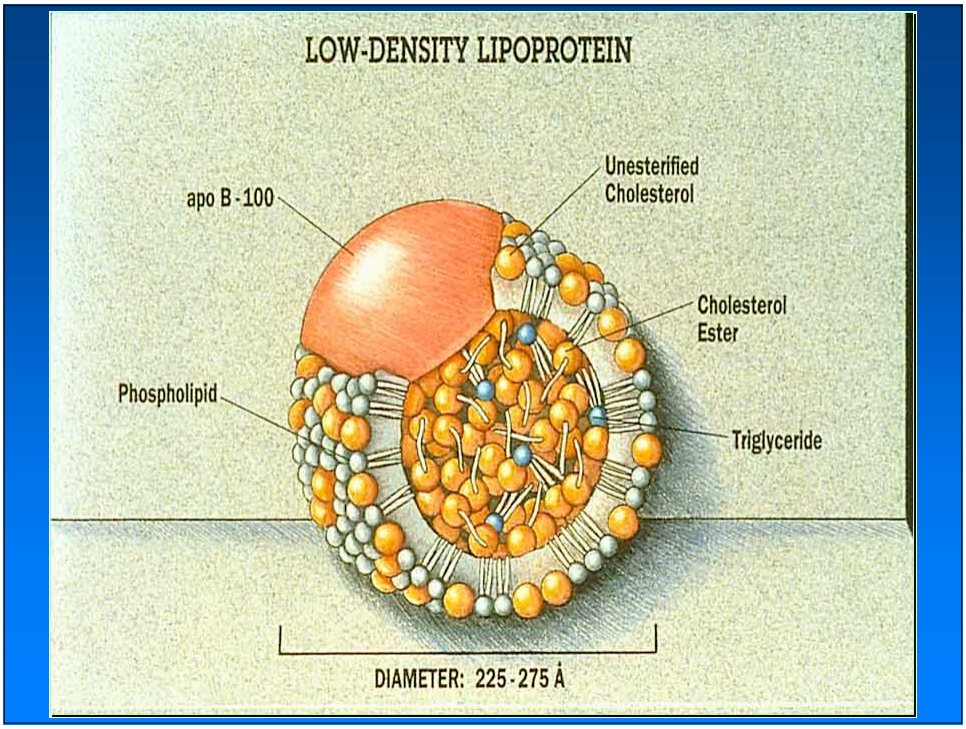
- Hypertriglyceridemia
- Obesity
- Insulin resistance
- Anabolic steroids

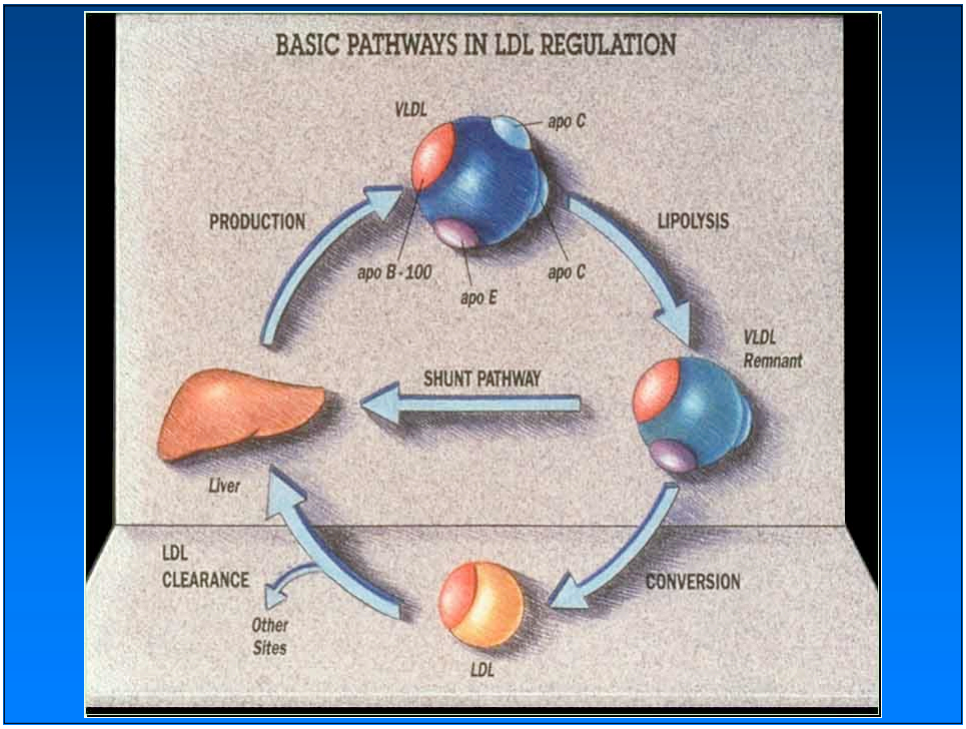


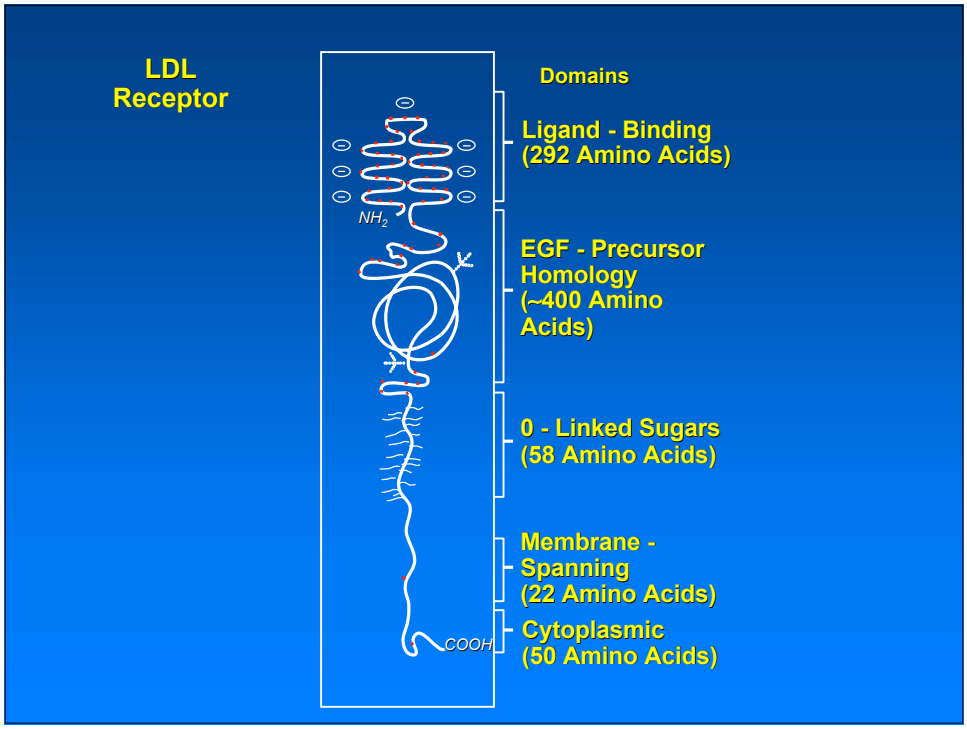


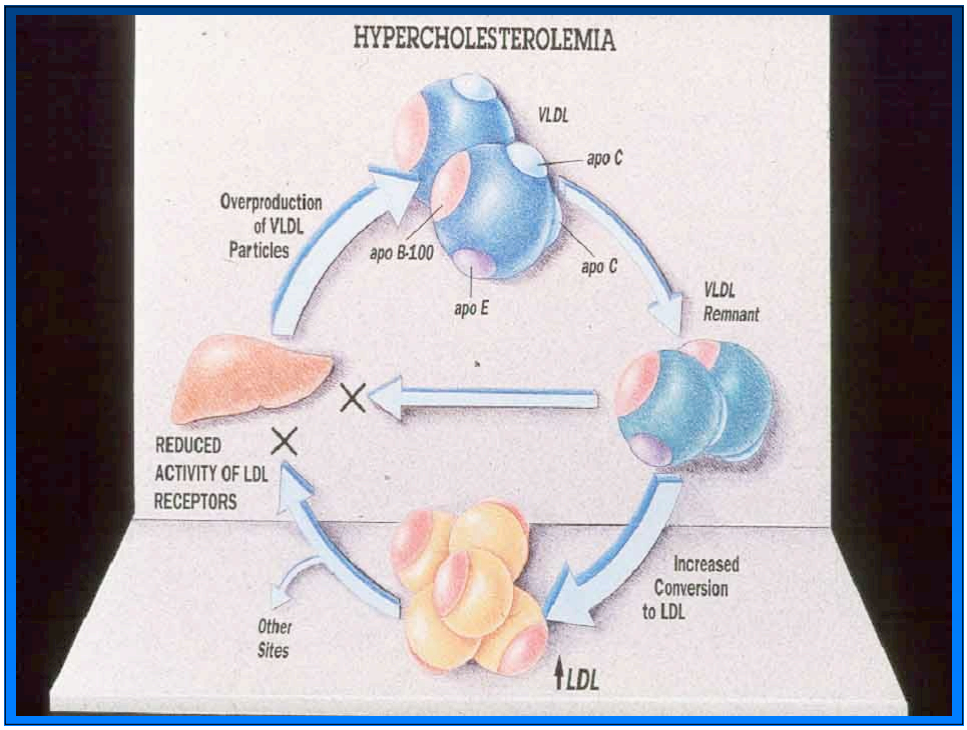
Mechanisms other than Reverse Cholesterol Transport by which HDL may be Anti-atherogenic

- Anti-oxidant effects
- Inhibition of endothelial adhesion molecule expression
- Prostacyclin stabilization
- Promotion of NO production

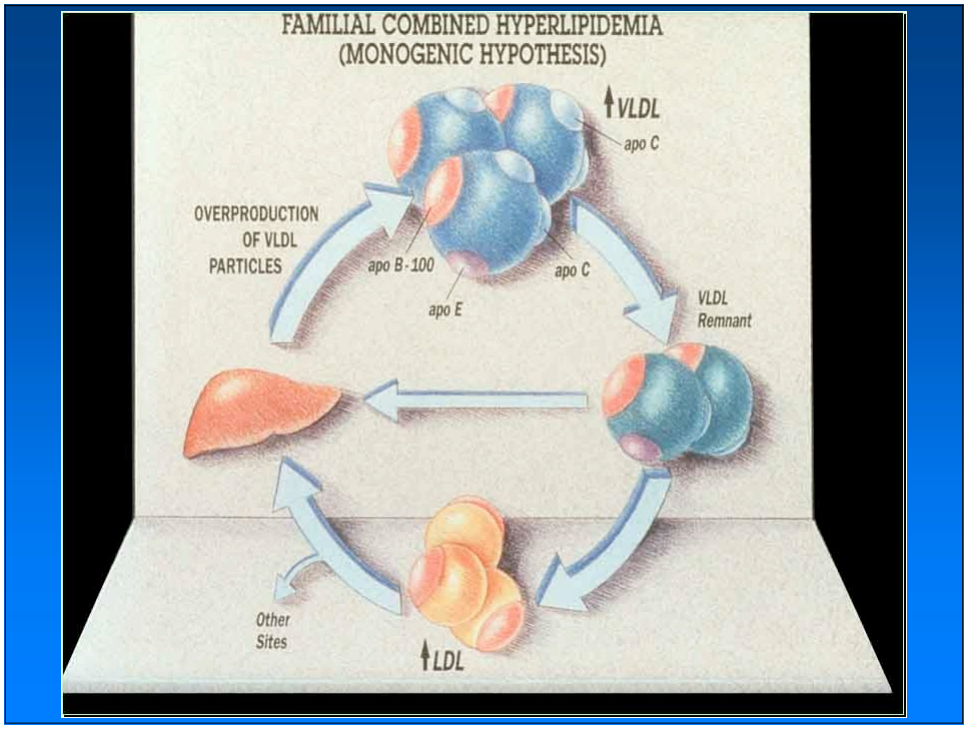

LOW-DENSITY LIPOPROTEIN
apo B-100
Unesterified Cholesterol
Cholesterol Ester
Phospholipid
Triglyceride
DIAMETER: 225-275 Å


BASIC PATHWAYS IN LDL REGULATION
VLDL
apo C
PRODUCTION
LIPOLYSIS
apo B-100
apo E
apo C
VLDL Remnant
SHUNT PATHWAY
Liver
LDL CLEARANCE
CONVERSION
Other Sites
LDL


LDL
Receptor
Domains
Ligand - Binding
(292 Amino Acids)
EGF - Precursor
Homology
(~400 Amino
Acids)
0 - Linked Sugars
(58 Amino Acids)
Membrane -
Spanning
(22 Amino Acids)
Cytoplasmic
(50 Amino Acids)
NH2
COOH


HYPERCHOLESTEROLEMIA
VLDL
apo C
Overproduction
of VLDL
Particles
apo B-100
apo C
apo E
VLDL
Remnant
REDUCED
ACTIVITY OF LDL
RECEPTORS
Increased
Conversion
to LDL
Other
Sites
LDL

Xanthelasma



Common Lipid Phenotypes

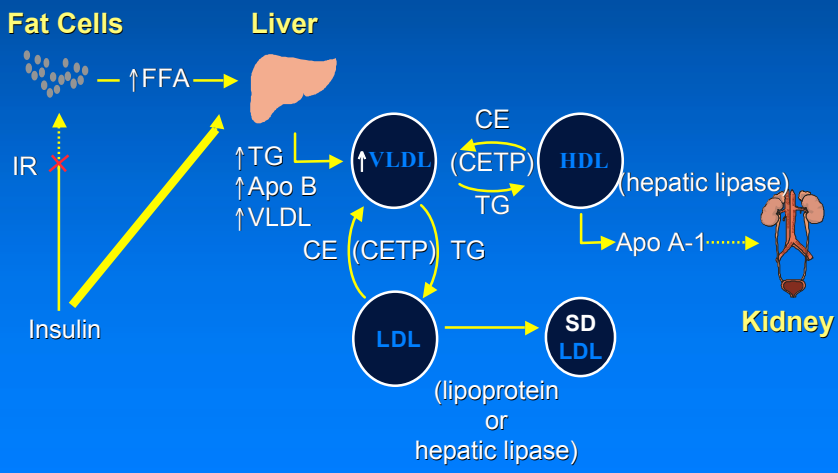
Hypercholesterolemia with normal triglycerides and HDL cholesterol levels:

- **High LDL cholesterol**

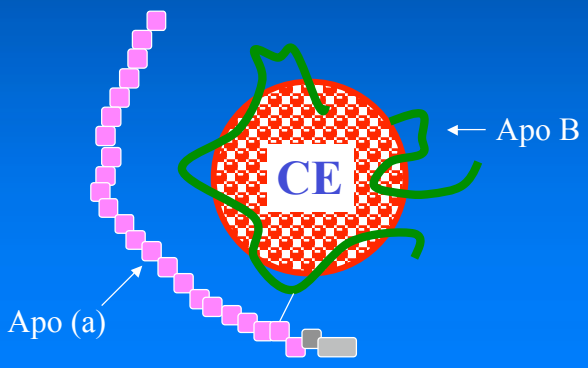
Low HDL cholesterol with high triglycerides and variable LDL cholesterol

- **Insulin resistance, Metabolic Syndrome**
- **Combined hyperlipidemia**

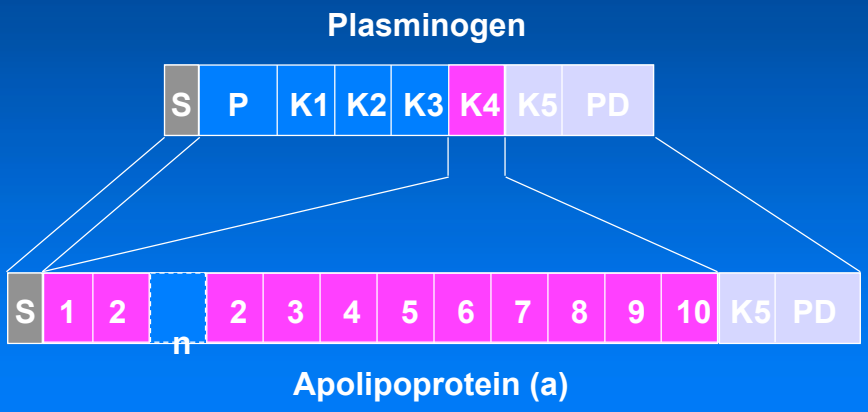
Mechanisms Relating Insulin Resistance and Dyslipidemia



Lipoprotein (a)



Apo (a) Gene Structure



Risk for CAD is mediated by small size (<22 K4) apo(a) isoform-containing Lp(a) particles, "s-i-Lp(a)" .