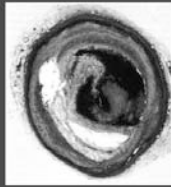


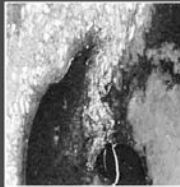
Pathophysiology of Lipid Disorders

Henry Ginsberg, M.D.
Division of Preventive Medicine
and Nutrition

Ruptured Atherosclerotic Plaque



Epicardial Coronary Artery Section
Magnification x 30



Epicardial Coronary Artery Section
Magnification x 120

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

CHD in the United States

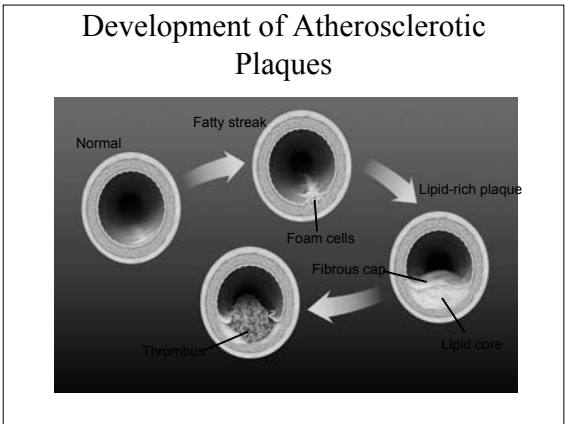
- CHD is the single largest killer of men and women
- 12 million have history of MI and/or angina
- Each year 1.1 million people have MI
 - 370,000 die of MI
 - 250,000 die within 1 hr
- By age 60, every 5th man and 17th woman develops CHD (1986 Framingham data)
- 1999 estimated direct and indirect costs 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

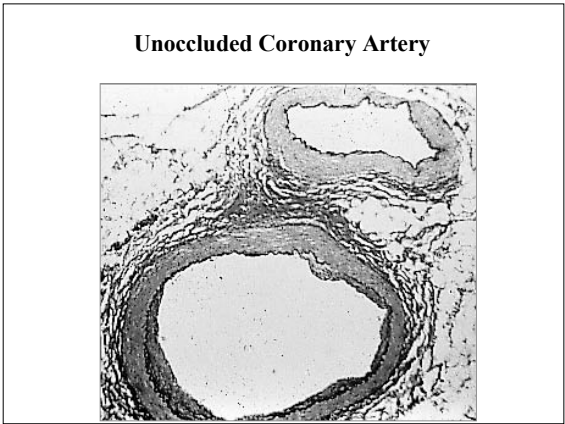
AHA. 1999 Heart and Stroke Statistical Update; 1998. National Center for Health Statistics. *National Health and Nutrition Examination Survey (III)*; 1994. (Data collected 1991-1994.)

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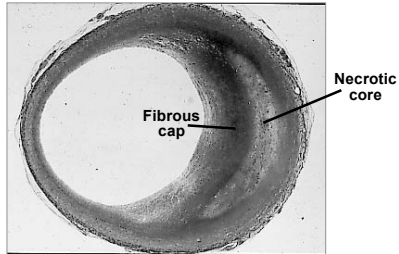
Number of Adults (Millions) Who Need Lifestyle and Drug Treatment

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

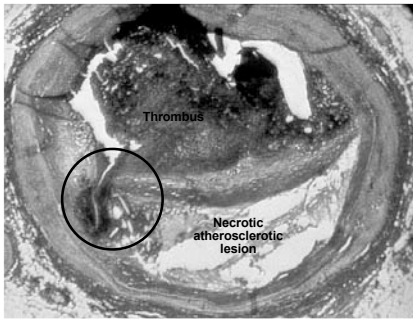




Fibrous Lesion with Necrotic Core

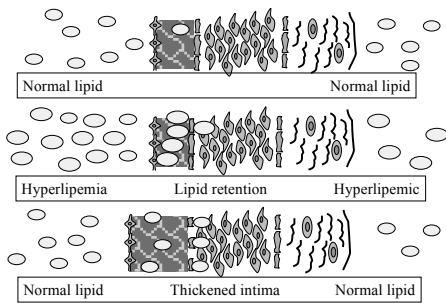


Occluded Coronary Artery

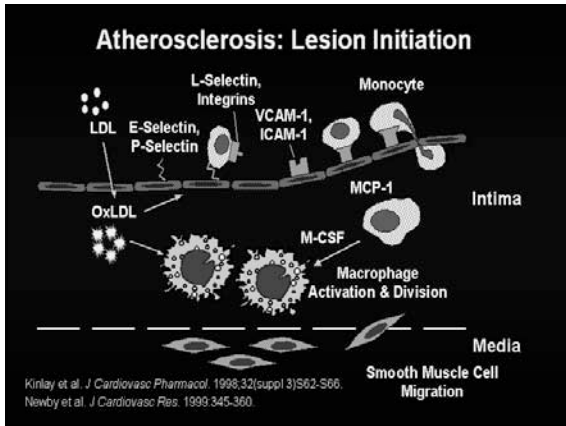


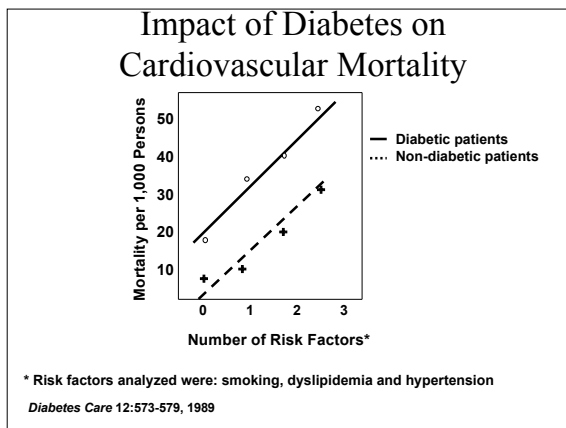
Filtration theory of atherogenesis

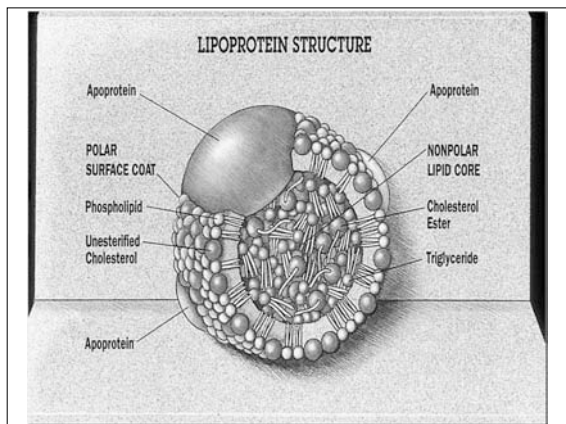
PLASMA -- VESSEL -- FILTRATE



Page, I. Connor Lecture, *Circ X*, 1954







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

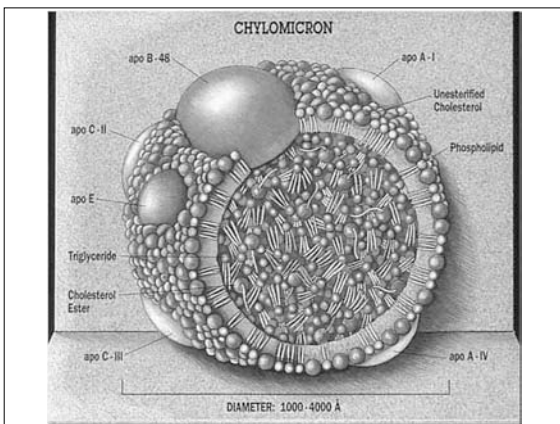
- | | |
|---|---|
| <ul style="list-style-type: none"> • Apo A-I, A-II, A-IV, AV <ul style="list-style-type: none"> – HDL, Chylomicron • Apo A-IV <ul style="list-style-type: none"> – Chylomicron • Apo B₄₈ <ul style="list-style-type: none"> – Chylomicron • Apo B₁₀₀ <ul style="list-style-type: none"> – VLDL, LDL | <ul style="list-style-type: none"> • Apo C-I, C-II, C-III <ul style="list-style-type: none"> – Chylomicron, VLDL • Apo E <ul style="list-style-type: none"> – Chylomicron, VLDL |
|---|---|

Apolipoproteins

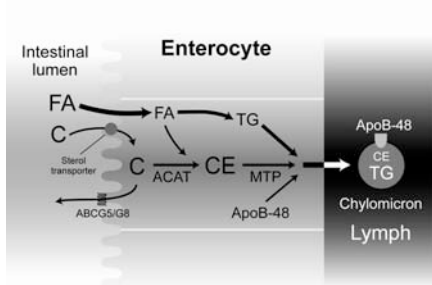
Apolipoprotein	MW (KDa)	Lipoproteins	Metabolic Function
Apo B100	540,000	VLDL, IDL, LDL	Essential structural protein Ligand for LDL receptor
Apo B48	250,000	chylomicrons	Essential structural protein
Apo C-I, C-II, C-III	8-12,000	VLDL, IDL, HDL, chylomicrons	C-I inhibits remnant uptake, C-II activate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

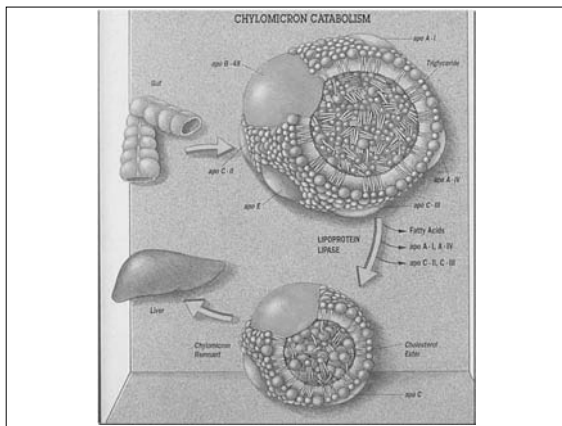
Apolipoproteins

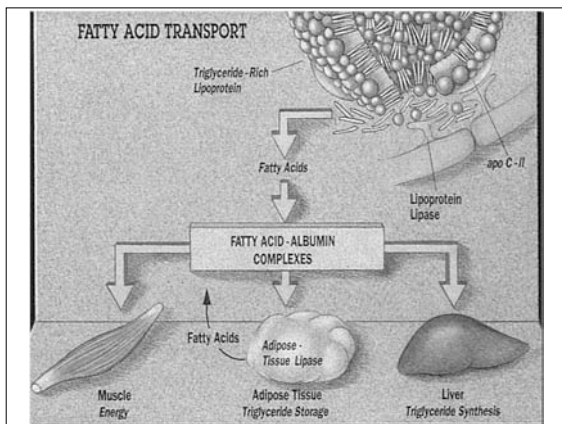
Apolipoprotein	MW (KDa)	Lipoproteins	Metabolic Function
Apo A-I	28	HDL, chylomicrons	Structural component of HDL, LCAT activator
Apo A-II	17	HDL, chylomicrons	Unknown
Apo A-V	40	HDL, chylomicrons	Unknown, but strong Association with hITG
Apo (a)	400-800	Lp(a)	Competitive inhibitor of plasminogen

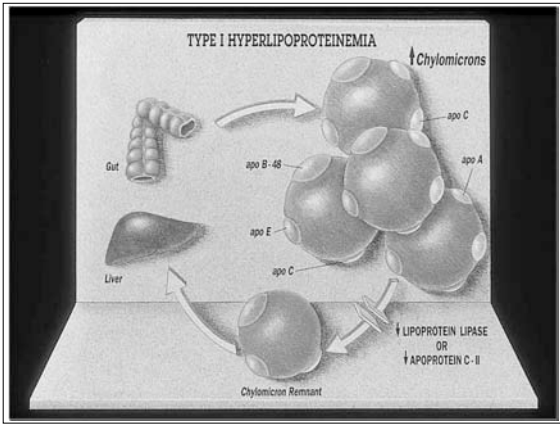


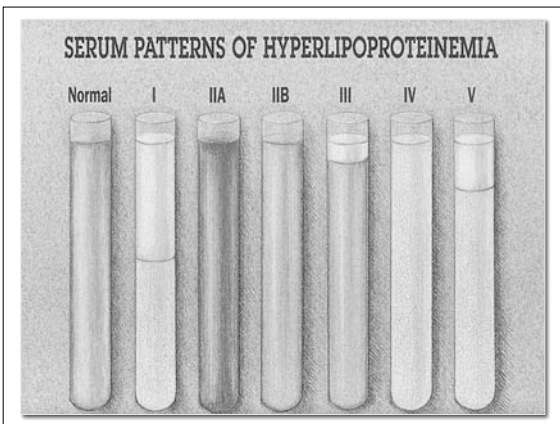
Transport of Intestinal Cholesterol













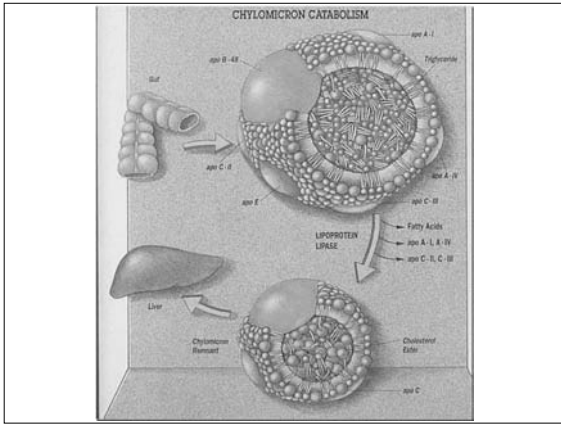
Clinical signs of severe hypertriglyceridemia

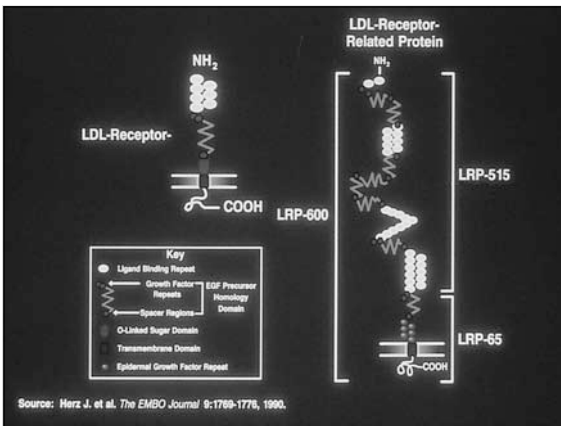


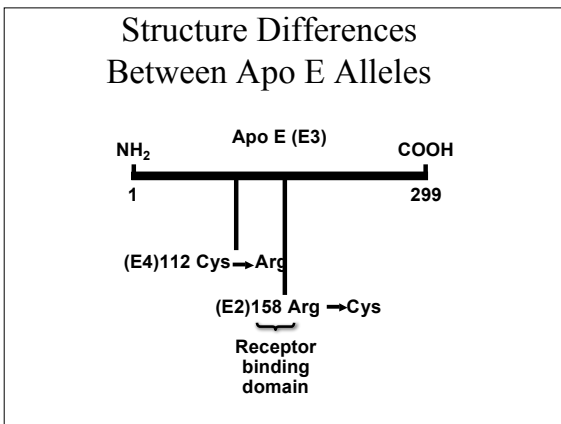
Eruptive xanthomas

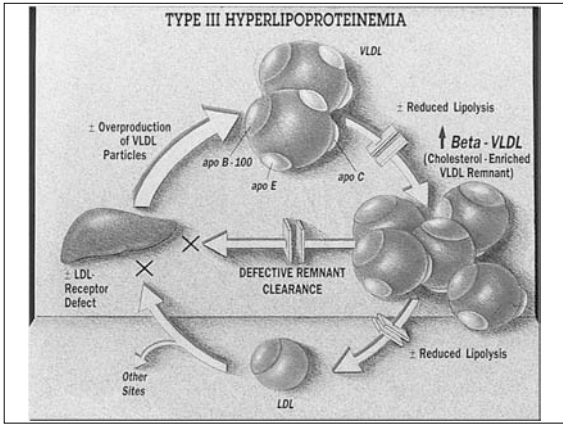


Lipemia Retinalis





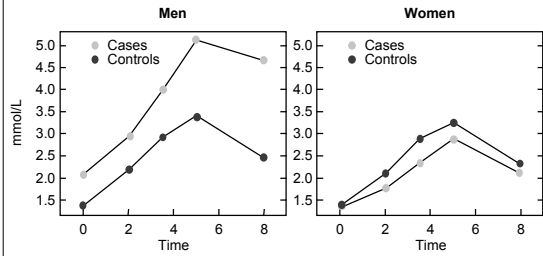








Plasma TG Values Over Time



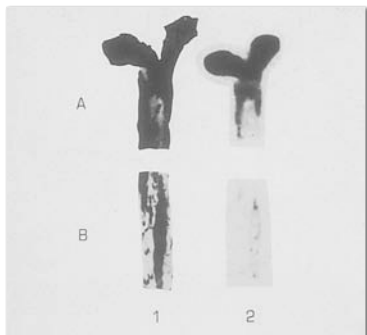
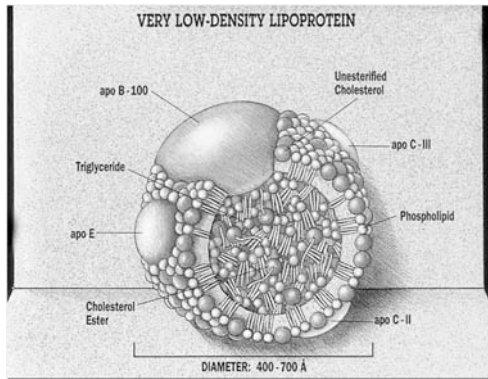
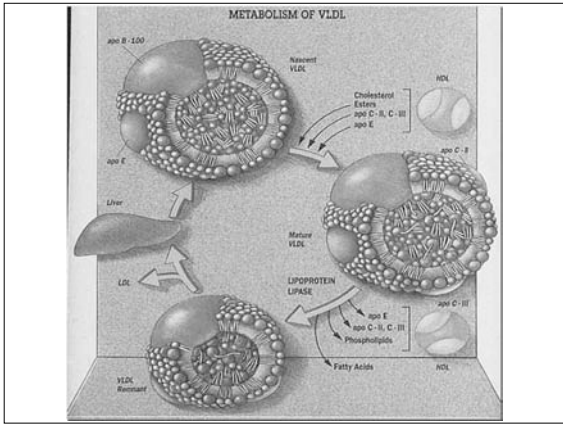
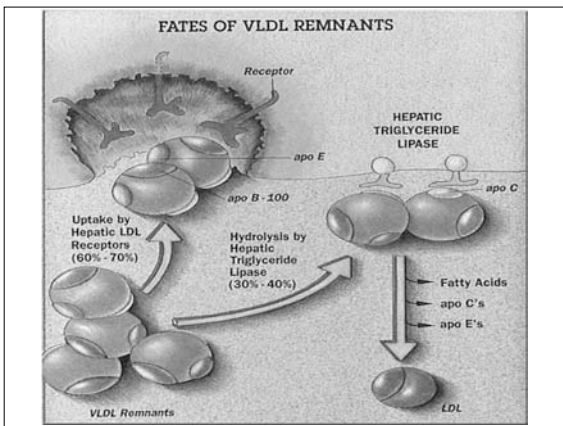


Fig. 2. Sudan-stained arterial segments from aortic arch and upper thoracic (A) and lower thoracic (B) regions. The accompanying en face radioautograms (2) were performed as described in the Methods section.



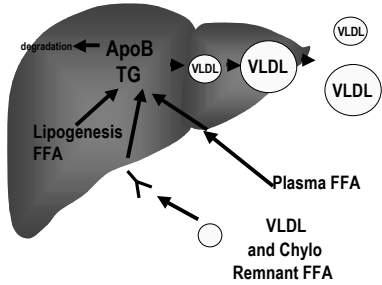




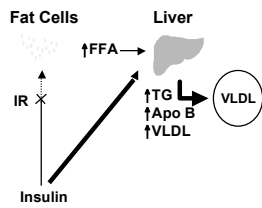
Common Causes of Hypertriglyceridemia

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

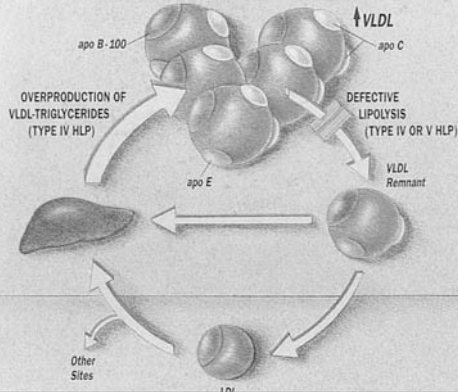
Substrate Driving Forces for the Assembly and Secretion of apoB-Lipoproteins

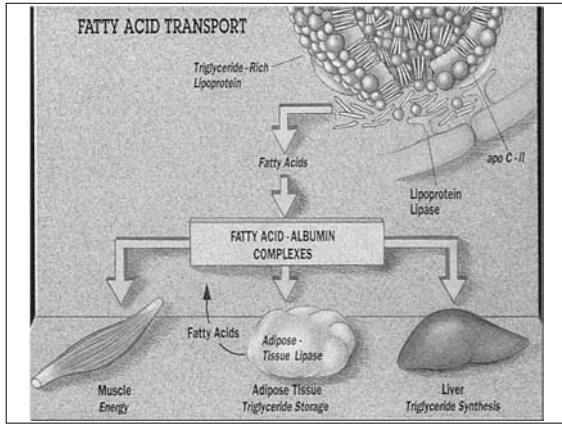


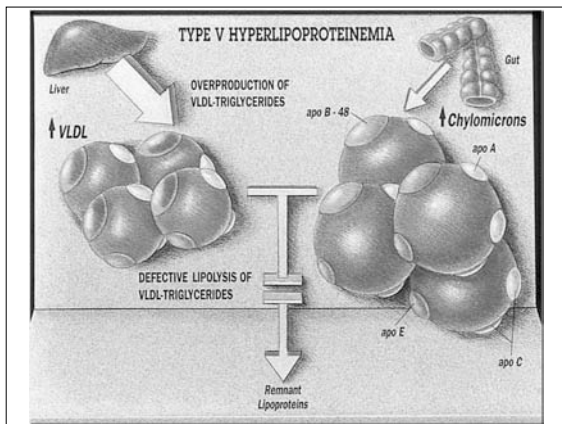
Mechanisms Relating Insulin Resistance and Dyslipidemia



FAMILIAL HYPERTRIGLYCERIDEMIA

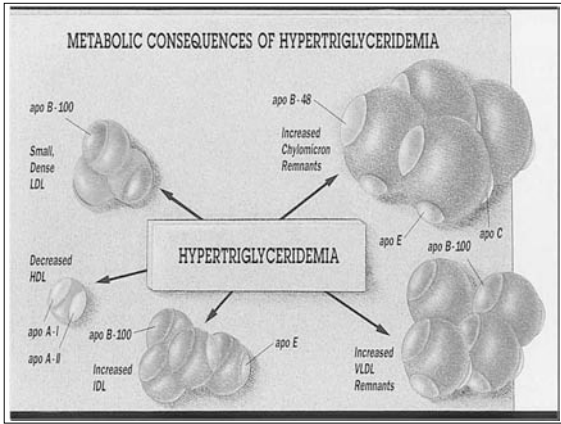


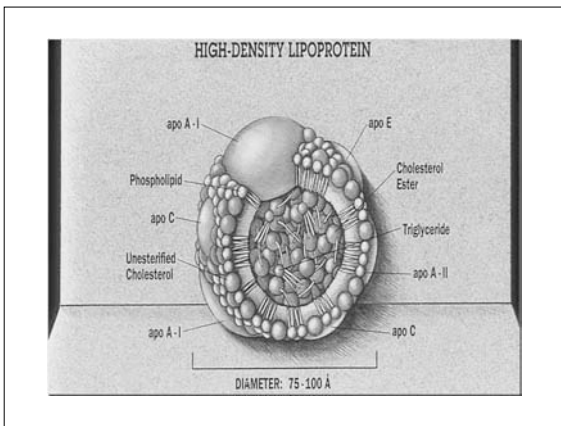


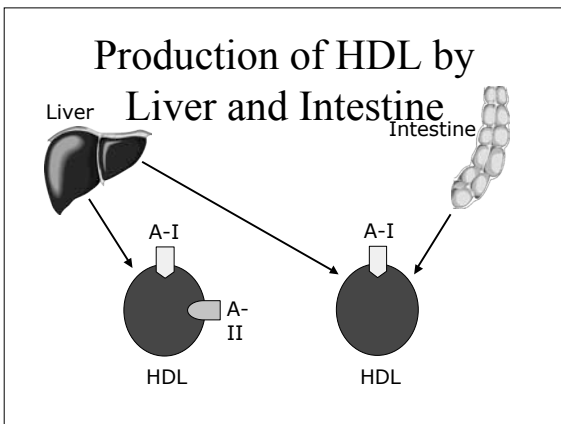


Hypertriglyceridemia: A risk factor for atherosclerosis

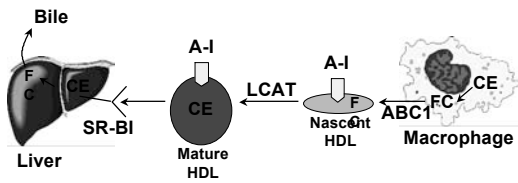
- VLDL can enter the artery wall
- Associated with increased factor VII, fibrinogen, and PAI-1
- Associated with other lipid abnormalities





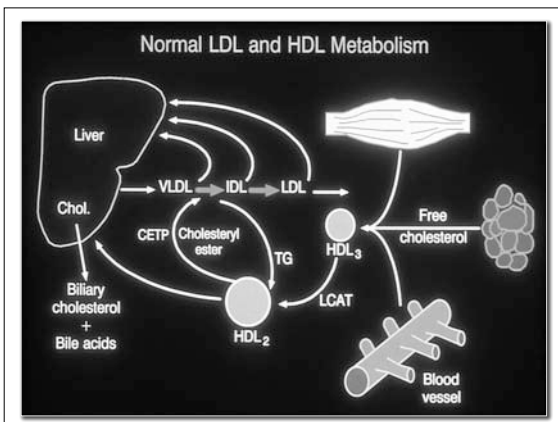


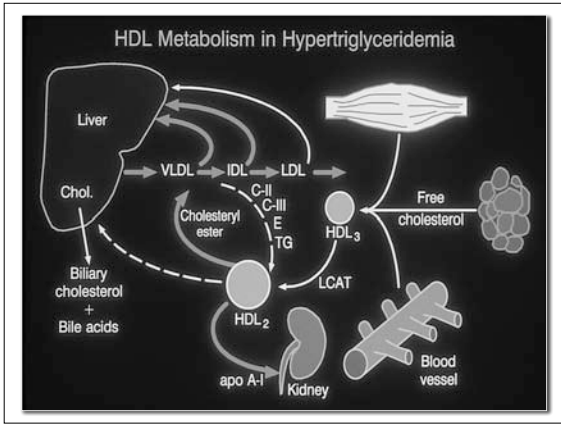
HDL Metabolism and Reverse Cholesterol Transport



Causes of low HDL cholesterol

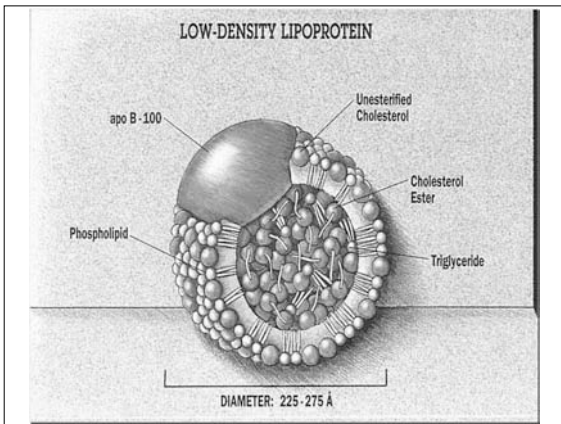
- Hypertriglyceridemia
- Obesity
- Insulin resistance
- Anabolic steroids

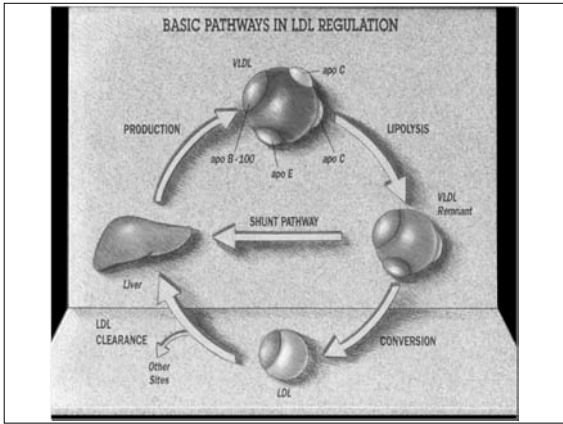


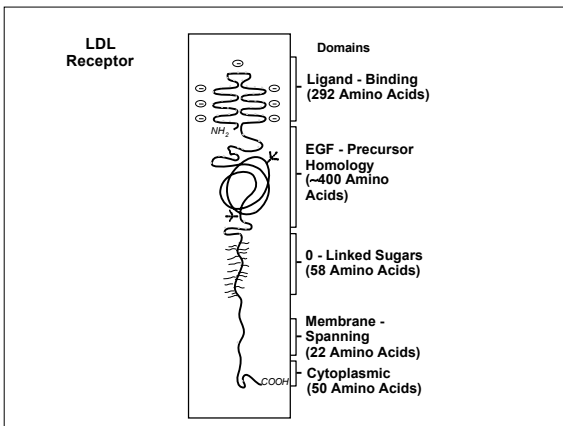


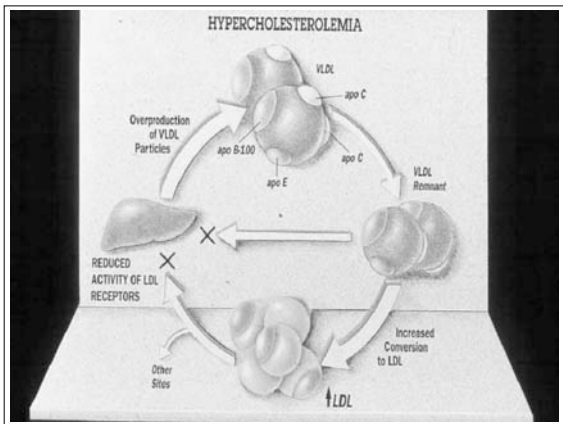
Mechanisms other than Reverse Cholesterol Transport by which HDL may be Anti-atherogenic

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



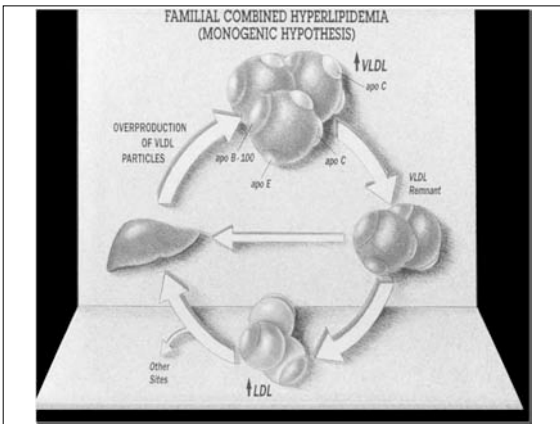










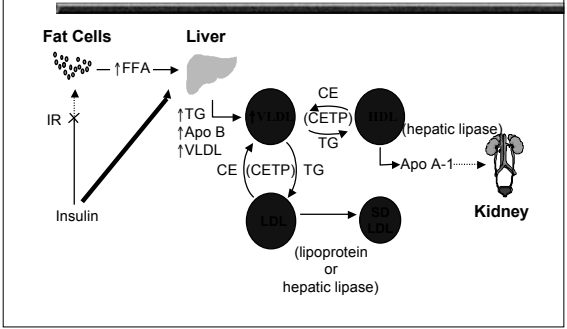


Common Lipid Phenotypes

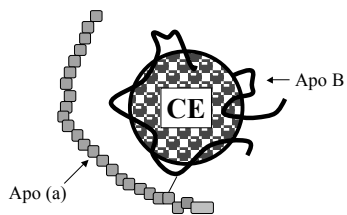
Hypercholesterolemia with normal triglycerides and HDL cholesterol levels:
High LDL cholesterol

Low HDL cholesterol with high triglycerides and variable LDL cholesterol
Insulin resistance, Metabolic Syndrome
Combined hyperlipidemia

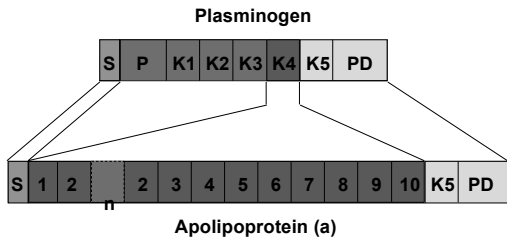
Mechanisms Relating Insulin Resistance and Dyslipidemia



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)” .

