Atherosclerosis &lipoprotein metabolism

- Arteriosclerosis means hardening of arteries.
- In atherosclerosis lipids collect along the intimal surface producing a narrowing of the luminal diameter & reduction in flow.
- Atherosclerosis is the cause of half of the deaths in the west due mainly to CAD & stroke.

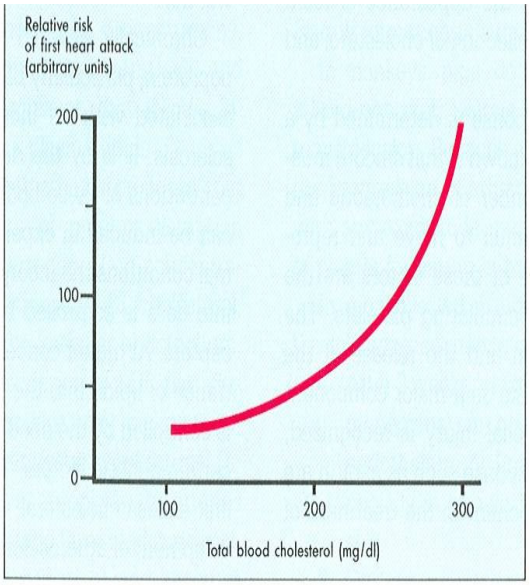


FIGURE 20-10 Summary of relationship between blood cholesterol concentrations and relative risk of initial heart attack.

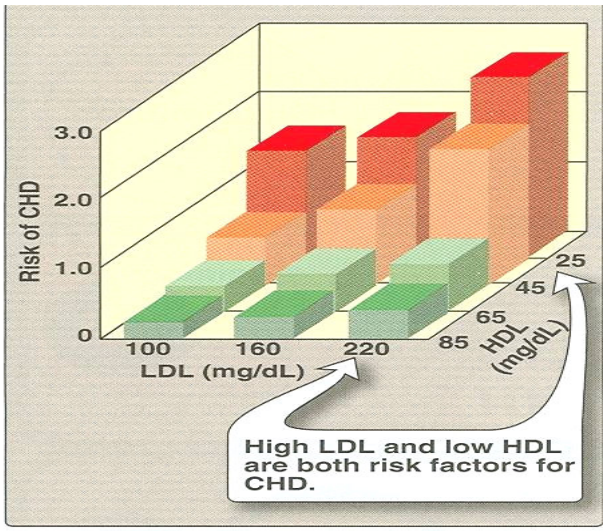


Figure 21.3
Effect of circulating LDL and HDL o the risk of coronary heart disease (CHD).

Classification of lipoproteins

Fraction	%Protein	cholesterol	TG	PL
HDL, α-lipoproteins	45	21	8	26
LDL, β-lipoproteins	21	51	10	18
VLDL,pre β-lipoproteins	1	21	54	9
Chylomicron	2	6	85	7

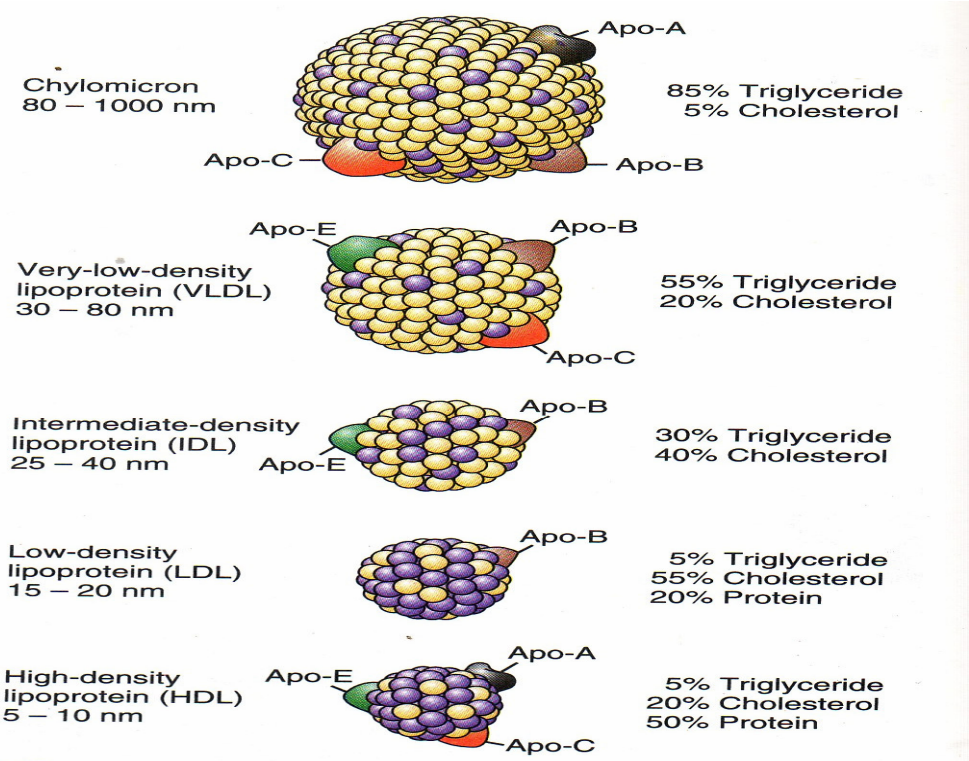


FIGURE 18—1. Serum lipoprotein fractions showing lipid composition and apoprotein components. Binding of lipoproteins to receptors is mediated through apoproteins.

Lipid Metabolism

- Lipids & cholesterol are transported in the plasma as lipoproteins.
- Chylomicrons transpot TG & cholesterol from the GIT to the tissues,
- Chylomicrons are split by lipoprotein lipases releasing FFA, which is taken up in muscles & adipose tissues,
- Chylomicron remenants are taken up in the liver ,
- Cholesterol is stored , oxidized or released into VLDL.
- VLDL transport cholesterol & newly synthesized TG to the tissues where TG are removed leaving LDL.
- Some of LDL is taken by tissues & some by liver , by endocytosis via specific LDL receptors.
- HDL adsorb C derived from cell break down in tissues & transfer it to VLDL & LDL.

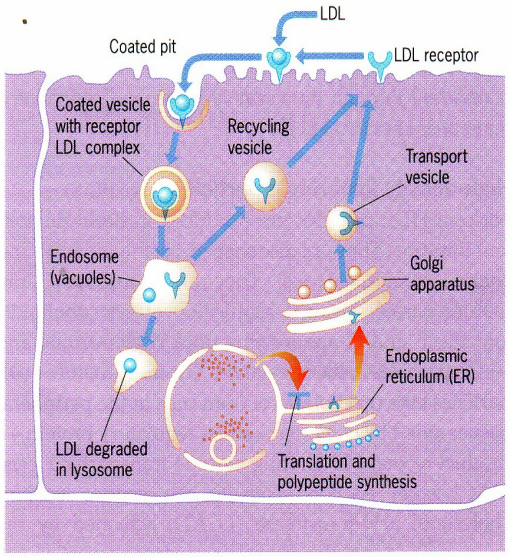
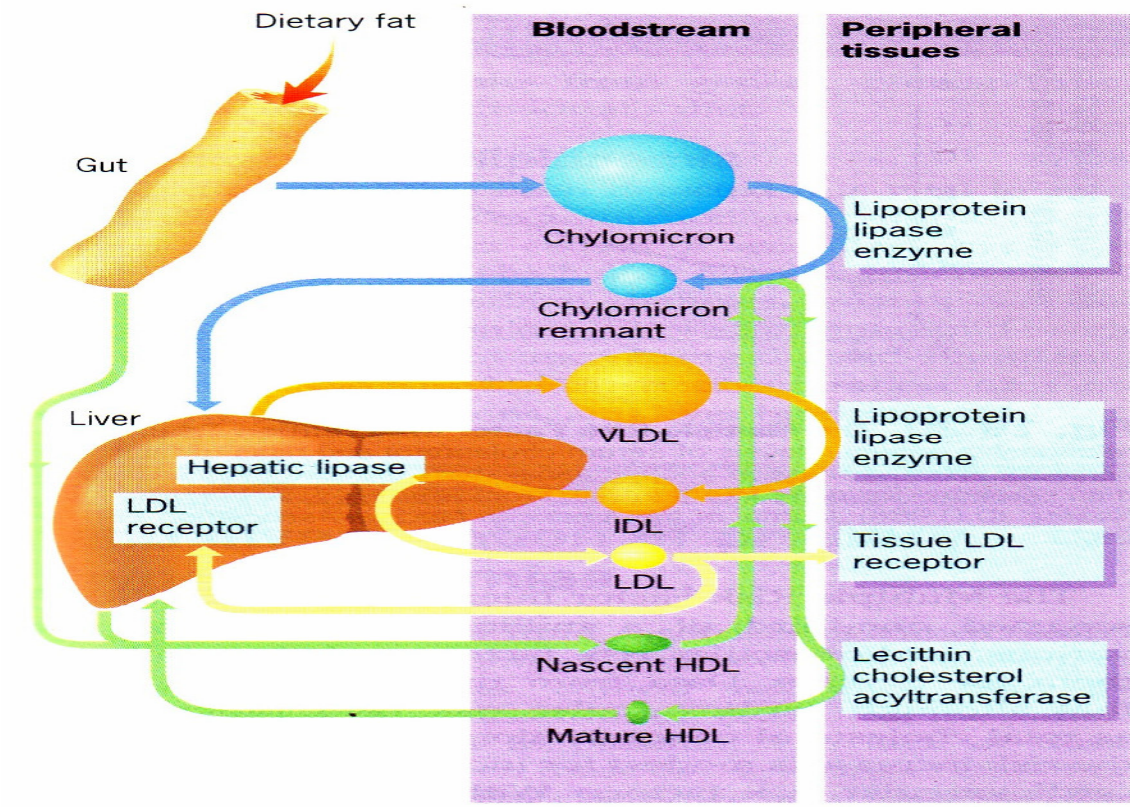


Fig. 19.19 Receptor-mediated endocytosis. LDL receptors are formed in the endoplasmic reticulum and transported via the Golgi apparatus to the surface of a hepatocyte. LDLs bind to these receptors, are internalized and taken up by the endosome. The receptor is recycled back to the surface, while the LDL is broken down by the lysosomes, freeing cholesterol needed for membrane synthesis.



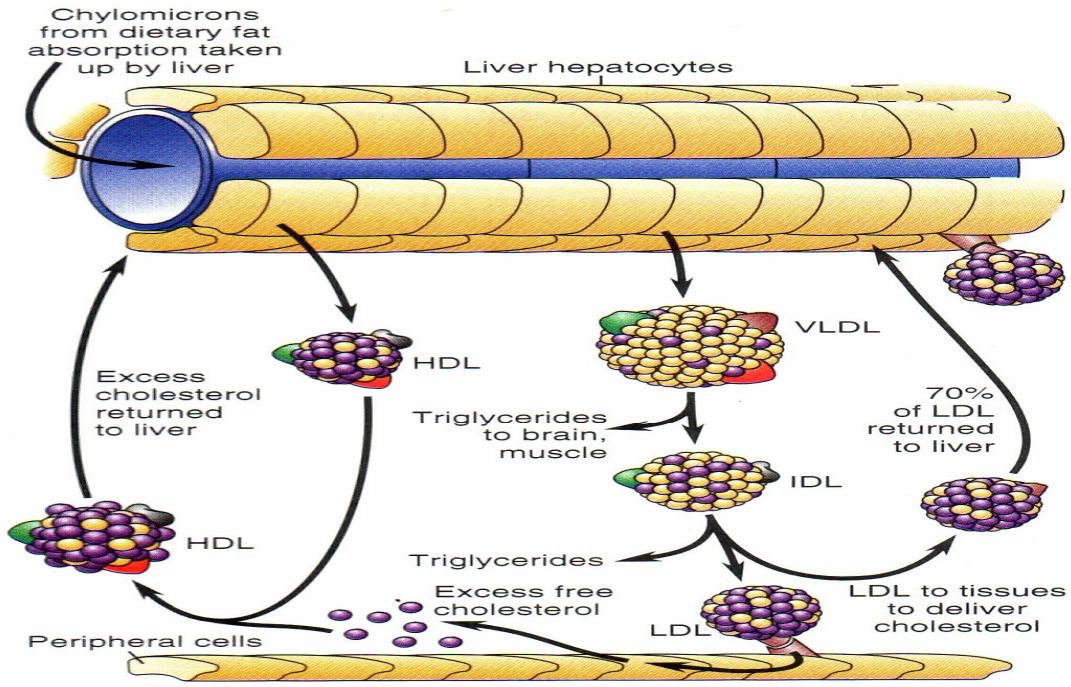


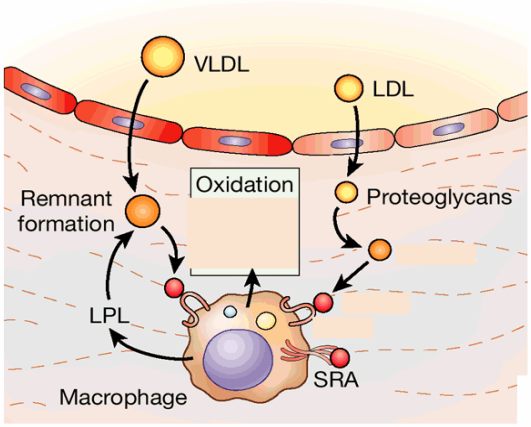
FIGURE 18–2. Schematic of lipoprotein metabolism in the body. Chylomicrons from dietary fat absorption are taken up by the liver and resynthesized into high-density lipoprotein (HDL) and very-low-density lipoprotein (VLDL). HDL circulates to the peripheral tissues and takes up excess cholesterol for transport back to the liver. Triglycerides are removed for tissue use from VLDL, which becomes intermediate-density lipoprotein (IDL). More triglyceride removal leads to the formation of low-density lipoprotein (LDL). LDL is taken up by peripheral tissues to obtain cholesterol. About 70% of the circulating LDL returns to the liver.

Function of lipoprotein

- **Chylomicron:-**transport of exogenous dietary TG.
- **VLDL:-**transport of endogenous dietary TG.
- **LDL:-**transport of cholesterol to tissues.
- **HDL:-** transport of cholesterol out of tissues.

Atherogenesis

- Lipoproteins are modified by oxidation by free radicals.
- Chemical modification of lipoproteins creates ligand for scavenger receptors.
- Lipoproteins are then endocytosed by these receptors.
- This causes formation of foam cells ,which are transformed macrophages and smooth muscle cells filled with cholesteryl esters.
- The atheroma grows with accumulation of foam cells , collagen ,fibrin and calcium.



Dyslipidaemia

- Dyslipidaemia may be primary or secondary.
- The primary forms are genetically determined , they are classified according to which lipoprotein is raised into 6 phenotypes.
- Secondary forms are consequence of other conditions.

Secondary hyperlipidemia

1-Hypertriglyceridaemia

- Diabetes mellitus, obesity ,alcoholism, estrogens,chronic renal & liver failure

2-Hypertriglyceridaemia with hypercholesterolaemia

- Diabetes mellitus, hypothyroidism, renal transplantation, nephrotic syndrome

3-Hypertriglyceridaemia with reduced HDL

- Non- selective β-blockers, Norgestrel, isoretinoin

Table 19.2 Frederickson/WHO classification of hyperlipoproteinaemia

Type	Lipoprotein elevated	Cholesterol	Triglycerides	Atherosclerosis risk	Drug treatment
I	Chylomicrons	+	+++	NE	None
IIa	LDL	++	NE	High	HMG-CoA reductase ± resins
IIb	LDL + VLDL	++	++	High	Fibrates, HMG-CoA reductase inhibitor, nicotinic acid
III	βVLDL	++	++	Moderate	Fibrates
IV	VLDL	+	++	Moderate	Fibrates
V	Chylomicrons + VLDL	+	++	NE	None

HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LDL, low density lipoprotein; VLDL, very low density lipoprotein; βVDL, a qualitatively abnormal form of VLDL identified by its pattern on electrophoresis; +, increased concentration; NE, not elevated.

Classification of Cholesterol levels

	Total Cholesterol mmol/l	LDL cholesterol mmol/l
Desirable	<5.2	<3.4
Borderline high	5.2 - 6.2	3.4 - 4.1
High	>6.2	>4.1

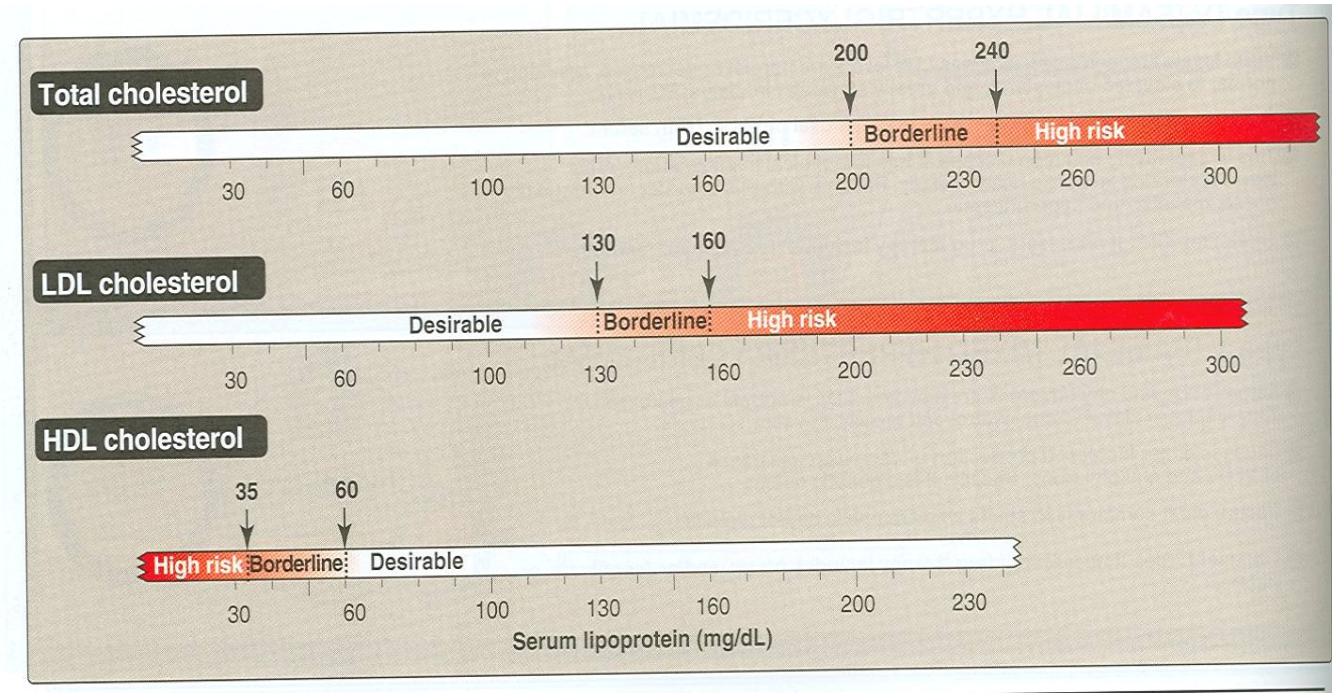


Figure 21.4
Goal lipoprotein levels achieved with dietary or drug therapy for the prevention of coronary heart disease. [Note: Lower goals for total and LDL cholesterol are recommended for patients with a history of heart disease.]

Dietary Management

- Cholesterol ,saturated fats and trans fats are the principal dietary factors that influence lipoprotein levels in plasma→↑ LDL.
- Acute ↑ in carbohydrates intake →↑ VLDL.
- Alcohol ↑ triglycerides by secreting VLDL from the liver.
- Some forms of dietary fiber reduce LDL modestly.
- Omega-3 fatty acids found in fish oils can induce profound lowering of triglycerides in some patients with endogenous or mixed lipemia.
- ↓Calories & loss of weight →↓LDL & VLDL.

Cigarette smoking

- Cigarette smoking is a major risk factor for coronary disease.
- It is associated with reduced levels of HDL,
- impairment of cholesterol retrieval,
- cytotoxic effects on the endothelium,
- increased oxidation of lipoproteins,
- and stimulation of thrombogenesis.

MECHANISMS OF DRUG THERAPY

1-SEQUESTER BILE ACIDS IN THE INTESTINE.

- ✓ **Exchange resins**

2-ALTER RELATIVE LEVELS OF DIFFERENT PLASMA LIPOPROTEINS

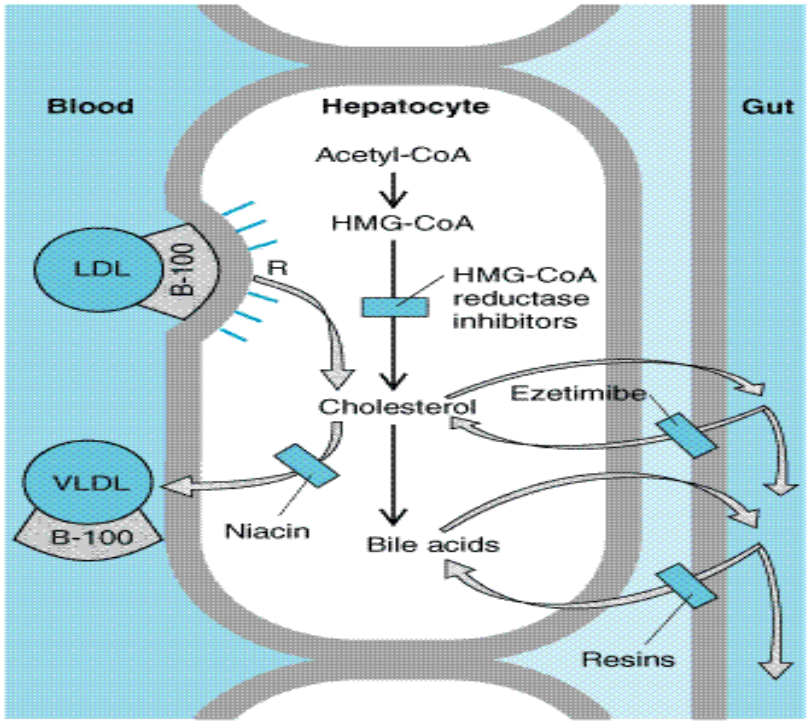
- ✓ **Fibrates, nicotinic acids.**

3-INHIBITS SYNTHESIS OF CHOLESTEROL

- ✓ **Inhibitors of hydroxymethylglutaryl coenzyme A reductase (HMG-COA reductase)**

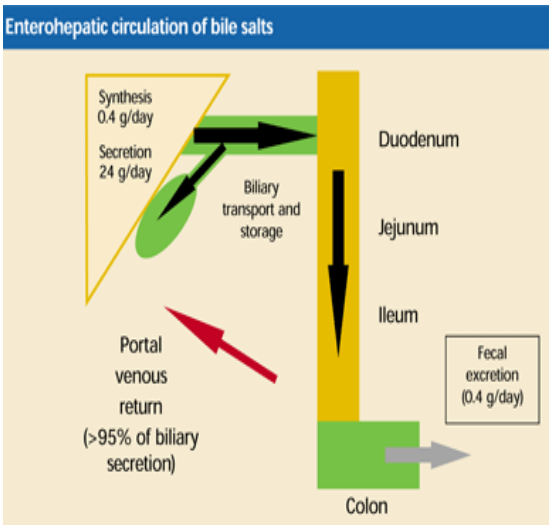
4-INHIBITS CHOLESTEROL ABSORPTION IN THE INTESTINE:-

- ✓ **Ezetimibe.**



Bile Acid binding resins:

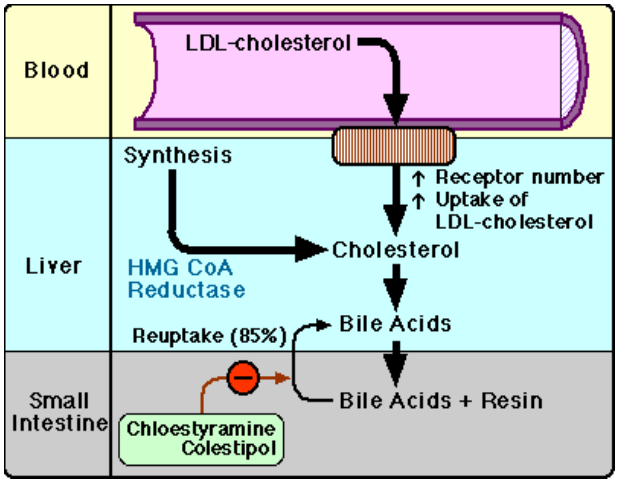
- Colestipol & cholestyramine large polymeric cation exchange resins, bind bile acids in the intestine preventing their absorption.
- ↓hypercholesterolaemia →↓LDL cholesterol, if used to ↓ LDL in patients with combined hyperlipidaemia →↑VLDL .



- Excretion of bile acid is increased up to tenfold when resins are given, resulting in enhanced conversion of cholesterol to bile acids in liver,
- Increased uptake of LDL and IDL from plasma results from upregulation of LDL receptors, particularly in liver.

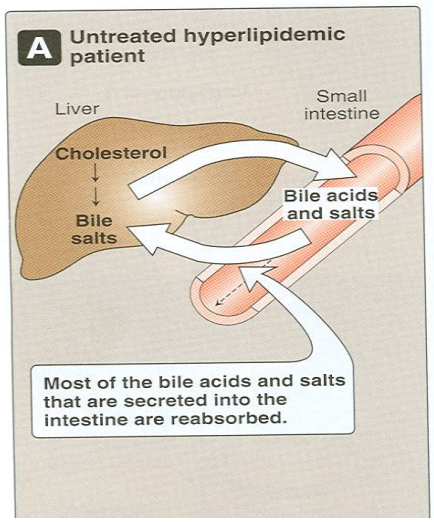
Therapeutic uses:-

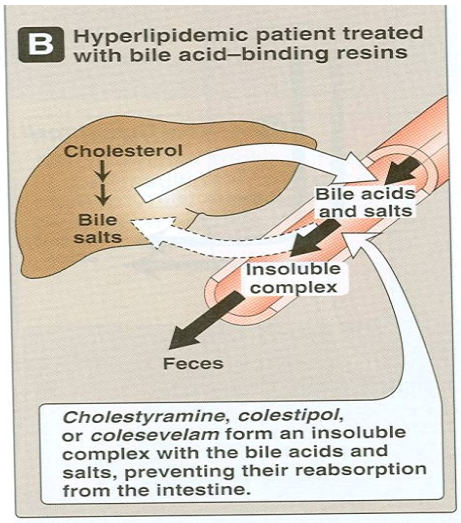
- The resins are used in treatment of patients with primary hypercholesterolemia
- Used to remove digitalis in case of overdose.
- They may be helpful in relieving pruritus in patients who have cholestasis and bile salt accumulation.
- Resins should be taken in two or three doses with meals, and they lack effect when taken between meals.



Toxicity:-

- constipation & bloating sensation, heart burn ,malabsorption of vit. A , D, E,K.
- dry flaking skin,
- ↓ absorption of thiazides, tetracyclines, folic acid
- Resins should be avoided in patients with diverticulitis.





Clinical uses of bile acid-binding resins (e.g. colestyramine)

- As an addition to a statin when response has been inadequate, e.g. in patients with heterozygous familial hypercholesterolaemia.
- For hypercholesterolaemia when a statin is contraindicated.
- Uses unrelated to atherosclerosis, including
  —pruritus in patients with partial biliary obstruction
  —bile acid diarrhoea (e.g. caused by diabetic neuropathy).

Clofibrate:

Mechanism of action: -

- it ↑clearance of TGs-rich lipoproteins ↑ activity of lipoprotein ,↓ secretion of VLDL inpatients with hyperglyceridaemia ,↓cholesterol biosynthesis ,↑HDL slightly.
- It is an **ester metabolized** by plasma seudocholinesterases, transported bound to albumin

Therapeutic uses:-

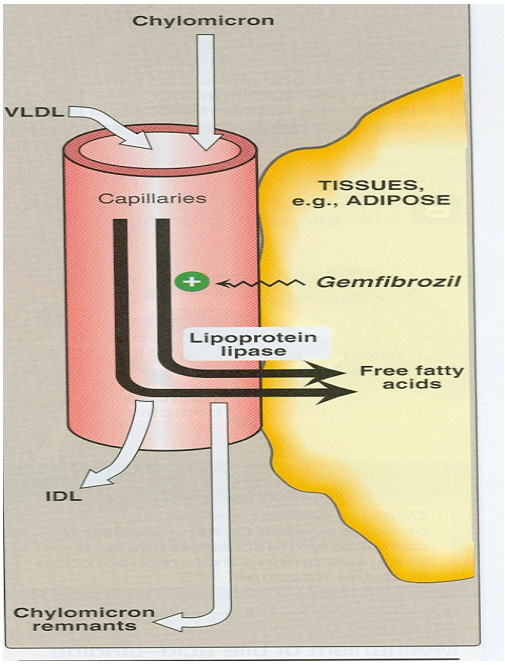
- Severe triglyceridaemia

ADR:-

- nausea, abdominal discomfort, myalgiaa →↑level of creatinine phosphokinase, malignancy ,
- ↑ Hypoglycaemic effect of hypoglycaemic agents.
- ↑activity of coumarine anticougulants
- ↓ Libido in man, breast tenderness, brittle hair, alopecia, lithiasis

Fibrates:

Gemfebrozil :



- **is a congener of clofibrate, supplied** as the free acid form ,undergoes **enterohepatic** recycling, lightly bound to plasma albumin, readily passes to the placenta,70% excreted unchanged in urine, t½=1.5hr.

Fenofibrate :

- is a methylethyl ester that is hydrolyzed completely in the intestine.
- Its plasma half-life is 20 hours. Sixty percent is excreted in the urine as the glucuronide, and about 25% in feces.
- **Mechanism of action**:- function primarily as ligands for the nuclear transcription receptor, peroxisome proliferator-activated receptor-alpha (PPAR-).
  - They increase lipolysis of lipoprotein triglyceride via LPL.
  - ↓lipolysis in adipose tissues,↓VLDL, modest ↓LDL.

Therapeutic uses:-

- severe triglyceridaemia.

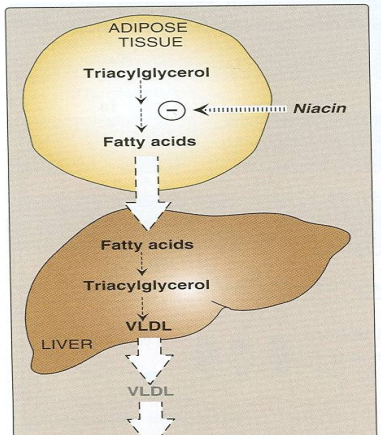
Toxic effects:-

- Rare adverse effects include rashes, gastrointestinal symptoms, myopathy, arrhythmias, hypokalemia, and high blood levels of aminotransferases or alkaline phosphatase.
- Both agents potentiate the action of coumarin.
- Risk of myopathy increases when fibrates are given with reductase inhibitors.
- There appears to be a modest increase in the risk of cholesterol gallstones, reflecting an increase in the cholesterol content of bile.
- fibrates should be used with caution in patients with biliary tract disease or in those at high risk such as women, obese patients.

Clinical uses of fibrates (e.g. gemfibrozil, fenofibrate)

- Mixed dyslipidaemia (i.e. raised serum triglyceride as well as cholesterol), provided this is not caused by excessive alcohol consumption. **Fenofibrate** is *uricosuric*, which may be useful where hyperuricaemia coexists with mixed dyslipidaemia.
- Patients with low HDL and high risk of atheromatous disease (often type 2 diabetic patients, see Ch. 25).
- Combined with other lipid-lowering drugs in patients with severe treatment-resistant dyslipidaemia. This may, however, increase the risk of rhabdomyolysis. (**Cerivastatin** was withdrawn because of this adverse event when it was coadminstered with **gemfibrozil**.)

Nicotinic Acid:



Mechanism of action:-

- Niacin inhibits VLDL secretion, in turn decreasing production of LDL ,Lp(a) &↑ HDL. , Converted in the body to nicotinamide , excreted in the urine as nicotinamide.

Therapeutic uses:-

- heterozygous familiar hypepercholesterolaemia [IIa] →↓ LDL
- & severe mixed lipaemia [IIb] →↓triglycerides.

ADR:-

- harmless cutaneous vasodilatation.
- Uncomfortable sensation of warmth after each dose [tachyphylaxis to these effects usually occurs] , can be ↓by aspirin.
- **Pruritus, rash rash ,dry skin,**
- **Impairment of** glucose tolerance in patients with latent diabetes,
- nausea, abdominal discomfort, hyperuricaemia.
- Reversible elevations in aminotransferases.

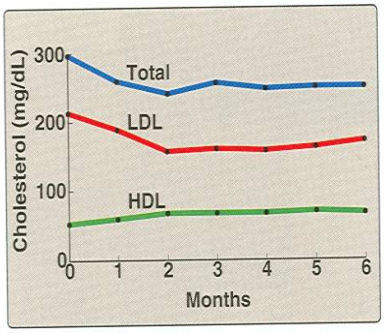
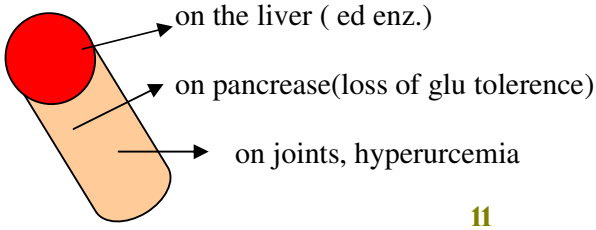


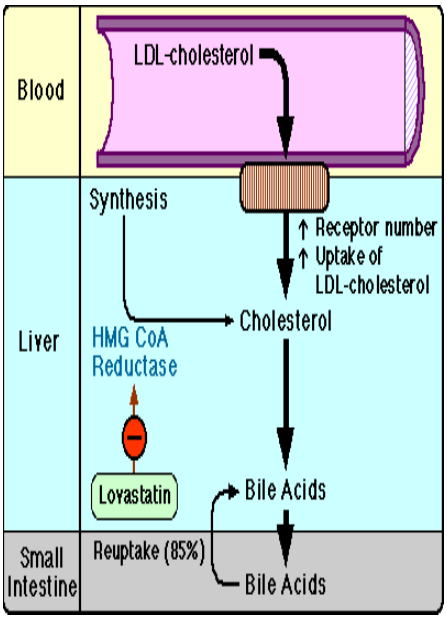
Figure 21.10
Plasma levels of cholesterol in hyperlipidemic patients during treatment with *niacin*.

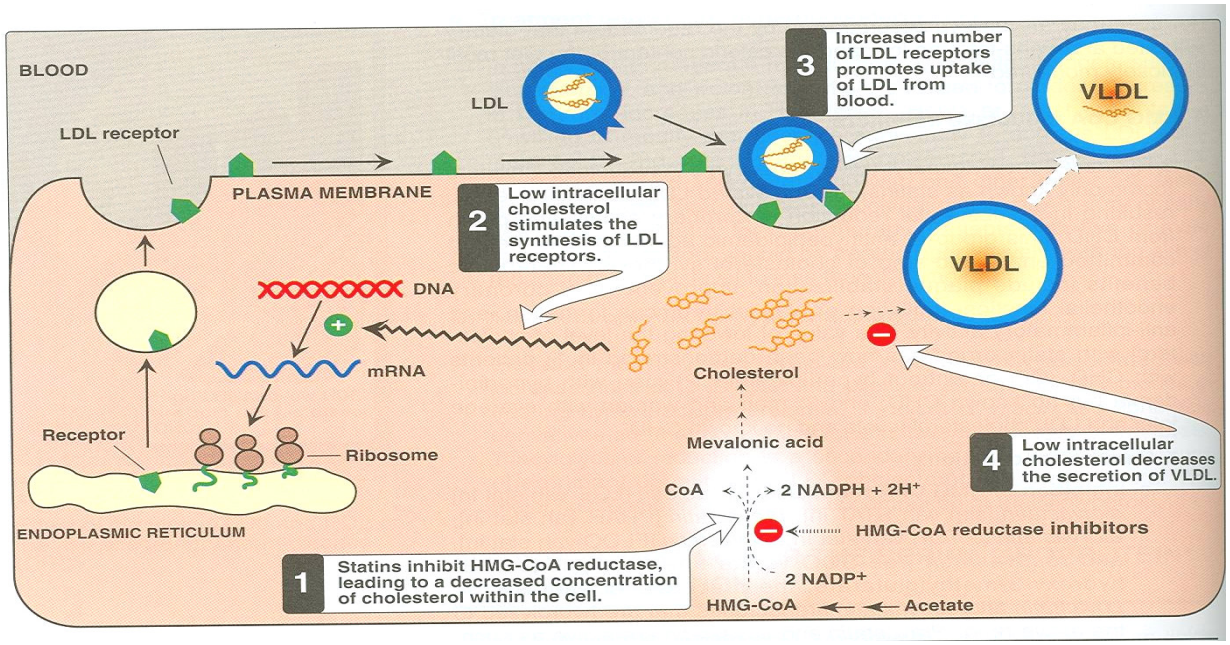
Nicotinic Acid adverse effects



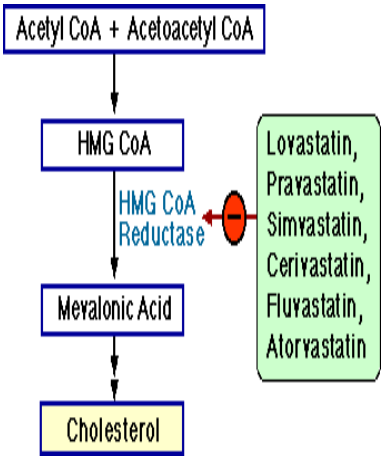
HMG-CoA reductase inhibitors:

- They are structural analogs of HMG-CoA.
  - ✓ e.g. **Lovastatin, atorvastatin, fluvastatin, pravastatin,simvastatin,** and **rosuvastatin.**
- They are most effective in reducing LDL.
- They decrease oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions.
- **HMG-CoA reductase** mediates the first step in steroid genesis →↓LDL.
  - They induce an increase in high-affinity LDL receptors.
  - This effect increases both the fractional catabolic rate of LDL and the liver's extraction of LDL precursors (VLDL remnants), thus reducing plasma LDL.





Pharmacokinetics:



- Lovastatin and simvastatin are inactive lactone prodrugs that are hydrolyzed in the GIT.
- Pravastatin has an open, active lactone ring.
- Atorvastatin, fluvastatin, and rosuvastatin are fluorine-containing congeners that are active as given.

- Absorption varies from 40% to 75% with the exception of fluvastatin, which is almost completely absorbed.
- Absorption generally (with the exception of pravastatin) is enhanced by taking the dose with food.
- All have high first-pass extraction by the liver.
- Most of the absorbed dose is excreted in the bile; about 5–20% is excreted in the urine.
- t½ range from 1 hour to 3 hours except for atorvastatin, which has a t½ of 14 hours, and rosuvastatin, 19 hours.
- The catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through cytochrome P450 3A4,
- Whereas that of fluvastatin and rosuvastatin is mediated by CYP2C9.
- Pravastatin is catabolized through other pathways, including sulfation.
  - Drugs that inhibit or compete for the 3A4 cytochrome cause reductase accumulation e.g.macrolide antibiotics, cyclosporine, ketoconazole.
  - phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase expression of CYP3A4 and can reduce the plasma concentrations of Inhibitors of CYP2C9 such as ketoconazole, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin.
- Plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated in patients ingesting more than 1 liter of grapefruit juice daily.

Therapeutic uses:

- **Useful** in reduction of LDL levels should not be given to pregnant or lactating woman,
- Because cholesterol biosynthesis occurs predominantly at night, reductase inhibitors—except atorvastatin and rosuvastatin—should be given in the evening if a single daily dose is used.

ADR:-

- ↑level of serum transaminase, may produce liver toxicity in patient with liver disease or history of alcohol abuse.
- Minor increases in creatine kinase activity in plasma
- Myopathy may occur when used in combination with clofibrate.
- Concomitant use of reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.
- ↑ lenticular opacity

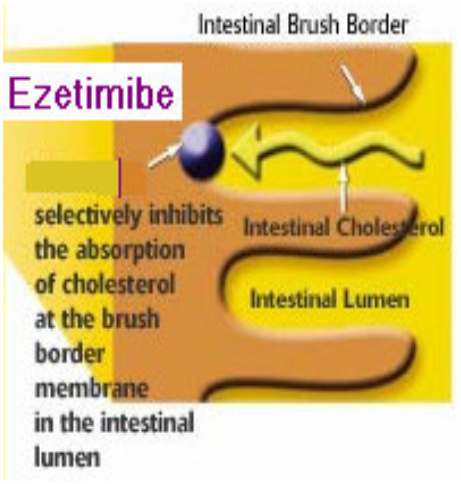
Clinical uses of HMG-CoA reductase inhibitors ('statins', e.g. simvastatin, pravastatin)

- Secondary prevention of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease (e.g. angina, transient ischaemic attacks, following acute myocardial infarction or stroke).
- Primary prevention of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration, especially if there are other risk factors for atherosclerosis. Tables (available for example in the British National Formulary) are used to target treatment to those at greatest risk.
- **Atorvastatin** lowers serum cholesterol in patients with homozygous familial hypercholesterolaemia.
- In severe drug-resistant dyslipidaemia (e.g. heterozygous familial hypercholesterolaemia), a bile acid-binding resin is added to treatment with a statin.

Characteristic	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Serum LDL cholesterol reduction produced (%)	50	24	34	34	50	41
Serum triacylglycerol reduction produced (%)	29	10	16	24	18	18
Serum HDL cholesterol increase produced (%)	6	8	9	12	8	12
Plasma half-life (hr)	14	1–2	2	1–2	19	1–2
Penetration of central nervous system	No	No	Yes	No	No	Yes
Renal excretion of absorbed dose (%)	2	<6	10	20	10	13

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIACYLGLYCEROLS
HMG-CoA reducatase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	Minimal
Cholesterol absorption inhibitor	↓	↑	↓

Ezetimibe:



- Ezetimibe inhibits intestinal absorption of phytosterols and cholesterol.
- Its primary clinical effect is reduction of LDL levels.
- Ezetimibe is readily absorbed and conjugated in the intestine to an active glucuronide, reaching peak blood levels in 12–14 hours.
- It undergoes enterohepatic circulation.
- Its half-life is 22 hours.
- Approximately 80% of the drug is excreted in feces.
- Plasma ezetimibe concentrations are substantially increased when it is administered with fibrates and reduced when it is given with cholestyramine.

Mechanism of Action:-

- Ezetimibe is a selective inhibitor of intestinal absorption of cholesterol and phytosterols.

Therapeutic Uses-:

- primary hypercholesterolemia, effective in patients with phytosterolemia.

ADR:-

- reversible impaired hepatic function

Effects of drugs on lipid categories

Drug	Chol.	TG	VLDL	LDL	HDL
Exchange resins	↓↓	↑	--	↓↓	↑
Fibrates	↓	↓↓↓	↓↓↓	↓	↑↑↑
HMG COA reduct. Inhibitors.	↓↓↓	↓	↓↓↓	↓↓↓	↑
Nicotinic acid analogues	↓	↓↓↓	↓	↓	↑

Treatment with Drug Combinations

- Combined drug therapy is useful :

(1) when VLDL levels are significantly increased during treatment of hypercholesterolemia with a resin;

(2) when LDL and VLDL levels are both elevated initially;

(3) when LDL or VLDL levels are not normalized with a single agent, or

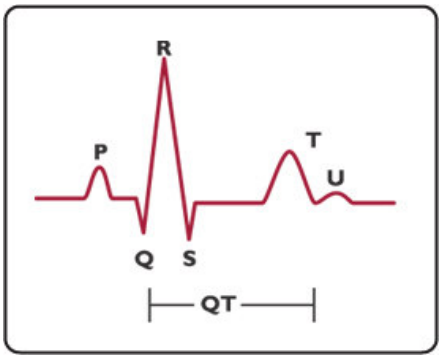
(4) when elevated levels of Lp(a) or HDL deficiency coexist with other hyperlipidemias.

Points to rememeber

- Most anti-hyperlipidemic drugs are excreted largely in feces with little conc. Excreted in urine.
- Some (like statins, Ezitimibe and nicotinic acid may have hepatotoxic effects (seen as elevated liver enzymes)
- Fibrates + statines cause massive muscle degeneration.
- Fibric Acid Derivatives & Bile Acid-Binding Resins
- useful in treating patients with familial combined hyperlipidemia who are intolerant of niacin. However, it may increase the risk of cholelithiasis.

Probucol:

- It may inhibits sterol biosynthesis.
- It is lipophylic, distributed into adipose tissues & persist for long time.
- ↓HDL & apo A-in plasma
- ↓Atherogenesis
- Has antioxidant property →↓ hydroperoxidation of lipoproteins & formation of foam cells in the arterial intima.
- Highly lipophilic, associated in blood with LDL, remains in body fats several months after discontinuation of treatment
- **ADR:-** GIT disturbances, arrhythmias, prolonged QT interval



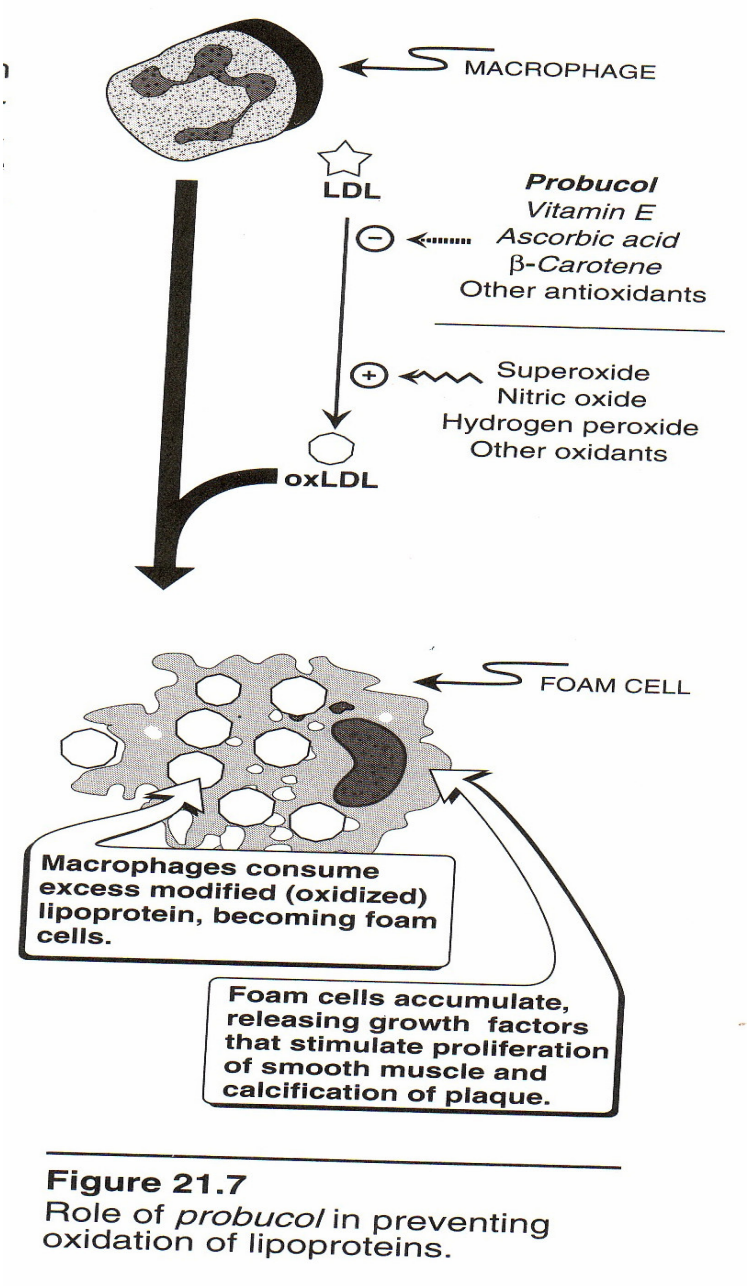


Figure 21.7
Role of *probucol* in preventing oxidation of lipoproteins.