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# THE EFFECT OF HYPOLIPIDEMIC DRUGS ON PLASMA LIPOPROTEINS

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In recent years advances in the study of normal and abnormal lipid metabolism have resulted in a broader understanding of the mechanisms and effects of hypolipidemic drugs (1). A clearer concept of how lipid is transported in the blood has helped clarify the etiology of the lipid disorders, which in turn has provided fresh insights into the reasons for the efficacy of lipid-lowering agents. Thus, the management of hyperlipidemia has become increasingly precise and the selection of therapy more rational.

It is now known that the major blood lipids—cholesterol, triglycerides, and phospholipids—are insoluble and do not circulate freely in aqueous solution. Rather, they are solubilized by proteins and are transported through the plasma as lipid-protein complexes or lipoproteins (2). The levels of these lipoproteins are subject to dynamic changes. The major lipoprotein families, separated according to electrophoretic mobility or density, are all interrelated within a complex metabolic system. The pathway of very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and low density lipoproteins (LDL) is of particular interest in the study of hyperlipoproteinemia and hypolipidemic drugs. VLDL, the main carrier of triglyceride, originates in the liver and small intestine from endogenous sources (Figure 1). It is catabolized rapidly into a transient intermediate form (IDL), which is further degraded into LDL (3) (Figure 2). Thus, LDL (which is 50% cholesterol by weight) appears to be in part, if not entirely, a remnant of VLDL and is presumably cleared by the liver (4). Transport of lipoproteins through the plasma then is not a passive affair; dynamic metabolic changes are occurring throughout their passage in the bloodstream.

It is now recognized that the lipid disorders are related to problems in lipoprotein metabolism (1). Specifically, excess lipid levels can occur because of either overproduction or faulty removal of one or more lipoproteins. Numerous mechanisms may

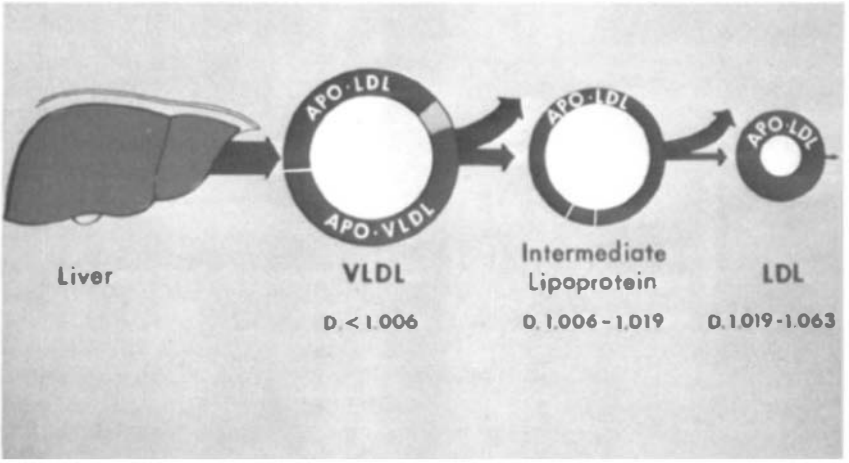


*Figure 1* Schematic representation of the metabolism of VLDL and chylomicrons. FFA = free fatty acids. From Levy et al (13). Reproduced by permission.

be responsible for the resulting hyperlipoproteinemia: increased influx of exogenous cholesterol or triglyceride entering from the intestine as chylomicrons; increased amounts of endogenous cholesterol or triglyceride released from the liver and small intestine as VLDL; defects in the clearing enzymes at sites of catabolism; abnormalities in plasma solubility or in the lipoproteins themselves (5). Other modifying factors include the state of carbohydrate or protein metabolism in general and the activity of hormones promoting lipogenesis or lipolysis in the muscle, liver, and adipose tissue.

The hyperlipoproteinemias are heterogeneous not only in etiology, but in clincial signs, prognosis, and responsiveness to therapy as well (1). *Hypercholesterolemia* and *hypertriglyceridemia* are nonspecific terms that do not identify either the site or the nature of the disorder. However, by translating these hyperlipidemias into hyperlipoproteinemia, it is possible to localize the area of lipid transport that is disordered. Patterns of hyperlipoproteinemia have been differentiated (6). A typing system represents a convenient code for the identification of lipoproteins that are present in excess (Table 1). None of the types is unique, however. To determine the disease mechanism in each case it is necessary first to rule out possibile secondary causes for the hyperlipoproteinemia such as alcoholism, myxedema, liver disease, diabetes mellitus, renal disease, stress, and dietary excess. In addition, each type when genetically determined may be associated with different modes of inheritance. Certain kinds of primary hyperlipoproteinemia have been linked with a greatly increased risk of premature atherosclerosis. Because of the multiplicity of possible origins for each hyperlipoproteinemia, there is no single diet or drug that is effective for all the types (7, 8). Some drugs may actually increase lipid levels in certain disorders. Looking at blood lipid abnormalities in terms of the lipoprotein or lipo-

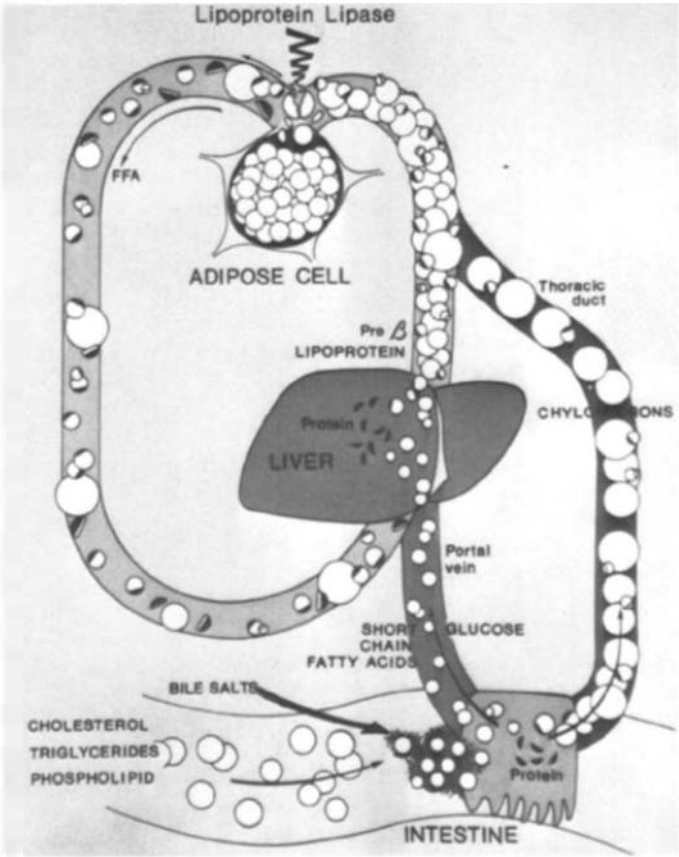


*Figure 2* Schema of normal lipoprotein metabolism. From Levy & Rifkind (7). Reproduced by permission.

proteins present in excess has helped eliminate much of the guesswork involved in selecting appropriate therapy. Management of hyperlipoproteinemia should always begin with a diet specific for the lipoprotein excess. Diet is the cornerstone of therapy that will reduce, and sometimes obviate, the need for potentially toxic drugs. If a drug is introduced, the diet should be continued since the combined effects of both forms of therapy are additive.

In the past, studies of drug efficacy focused primarily on how hypolipidemic drugs affected cholesterol biosynthesis and catabolism and bile acid formation (Figure 3). Moreover, no distinction was made between the various forms of hypercholesterolemia and hypertriglyceridemia. Thus, what would work for one patient would fail to work for another. The principal drawbacks of this approach included the failure to appreciate the heterogeneity of blood fat disorders as well as a failure to

**Table 1** Types of HLP

| Type | Abnormality |
|---|---|
| I | ↑ Chylomicrons |
| IIa | ↑ LDL |
| IIb | ↑ LDL and VLDL |
| III | ↑ IDL |
| IV | ↑ VLDL |
| V | ↑ VLDL and chylomicrons |



explain the mode of action and the reason for the effectiveness of the drugs. For instance, nicotinic acid was recognized as a highly effective hypolipidemic agent but which had no clearly demonstrable influence on either cholesterol synthesis or catabolism. The efficacy of cholestyramine was originally attributed to its capacity to bind bile acids in the gastrointestinal tract and prevent their reabsorption, thereby increasing their turnover and the breakdown of cholesterol. This concept was challenged by further studies on cholestyramine which demonstrated that de novo cholesterol biosynthesis in the liver was increasing concomitantly with the catabolism of cholesterol, so that the total cholesterol balance in the liver remained unchanged. Why then should plasma cholesterol levels fall so dramatically? In seeking a reply to this question, the focus of drug studies began to shift away from lipid and fatty acid biosynthesis toward lipoprotein metabolism. At the root of this change in direction was the simple fact that the plasma lipid levels are dependent upon the amounts of circulating lipoproteins. Thus, the amount of lipoproteins entering the plasma and the amount being cleared determine how much lipid is found at any time in the plasma. The utility of hypolipidemic drugs in each disorder should then be sought in their effect—whether primary or secondary—upon *lipoprotein*, rather than lipid, concentrations (9). On the basis of this concept, the hypolipidemic drugs currently available can be classified into two basic categories: (*a*) those that effect lipoprotein production, and (*b*) those that affect lipoprotein removal (Figure 4).

## DRUGS THAT AFFECT LIPOPROTEIN PRODUCTION

### *Nicotinic Acid*

Nicotinic acid has been a consistently effective lipid-lowering agent when given in doses exceeding its requirement as a vitamin. Its mode of action had long been a puzzle because no direct effect by the drug could be demonstrated on cholesterol biosynthesis, catabolism, or bile acid formation (10). Recent studies have shown that nicotinic acid acts primarily by depressing VLDL synthesis and subsequently that of its plasma products, IDL and LDL. Plasma triglyceride levels generally fall within 4 to 6 hr as a direct result of the decreased VLDL production. Plasma cholesterol levels are lowered because of the decreased rate of LDL snythesis. This latter effect, however, occurs only after several days, undoubtedly because of the longer half-life of LDL (11).

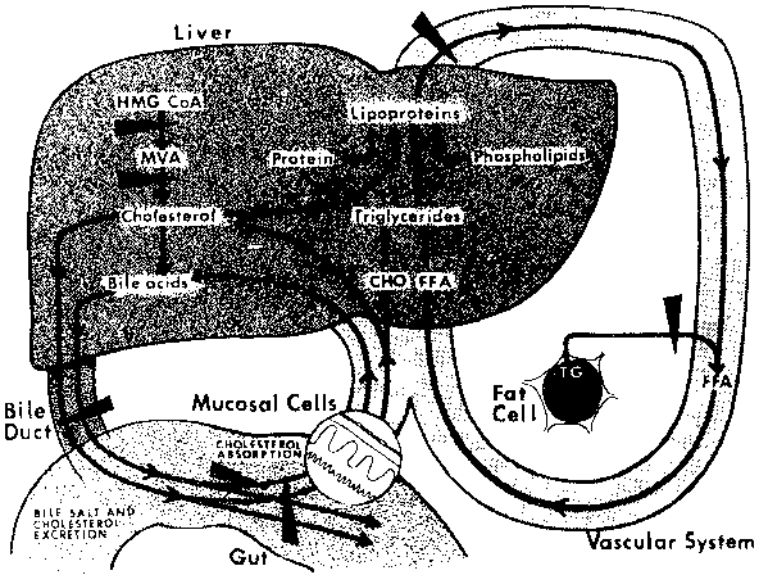


*Figure 3* Schematic representation of the systems involved in endogenous lipid transport. *Arrows* indicate previously proposed sites of action of hypolipidemic drugs. From Levy & Langer (8a). Reproduced by permission.

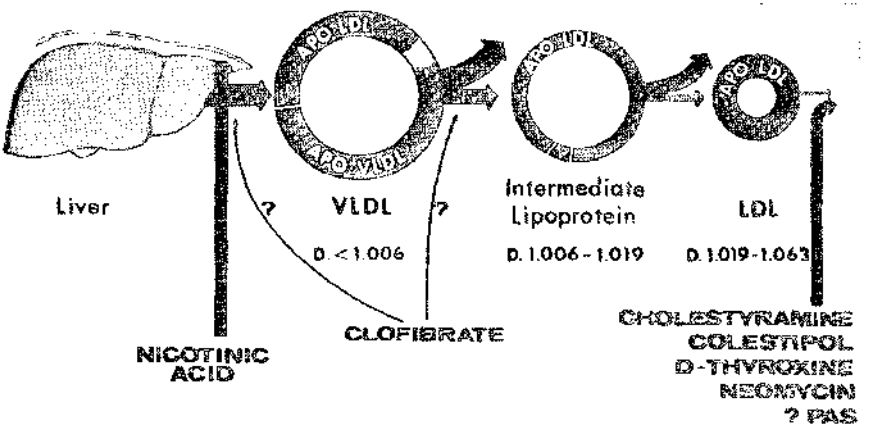


*Figure 4* Possible site of action of hypolipidemic drugs. From Levy & Rifkind (7). Reproduced by permission.

Reports on the use of nicotinic acid in hypercholesterolemic subjects have demonstrated a reduction in cholesterol ranging from 15–30% (10). The effect of nicotinic acid on plasma triglyceride has been variable, but decreases of over 60% have been noted (12). In studies conducted at the National Institutes of Health Clinical Center, nicotinic acid was found to be effective in treating homozygous type II patients in combination with diet and cholestyramine therapy (13). Nicotinic acid given in divided doses of 55 and 87 mg/kg body weight per day reduced total plasma cholesterol from 19 to 49% in five out of six patients. In severe heterozygotes who had responded inadequately to a diet and cholestyramine regimen, cholesterol levels were normalized with the use of larger doses of nicotinic acid (4 to 6 g/day).

INDICATIONS Primary indications for nicotinic acid include any hyperlipidemic states characterized by increases in VLDL or its products, IDL and LDL.

DOSE Nicotinic acid is available in tablets of 100 and 500 mg. The 100 mg tablet is generally absorbed better. The initial dose is 100 mg orally three times a day, incremented by 300 mg/day every four to seven days until a maintenance dose of 3 to 9 g/day is attained. The drug should be taken at mealtimes to reduce gastric irritation.

SIDE EFFECTS The most common and annoying effect of nicotinic acid therapy is intense cutaneous flushing and pruritus which generally develop within one to two hours of a dose. This symptom disappears in 85% of patients within one to two weeks. Other transitory side effects may include nausea, vomiting, and diarrhea.

More troublesome side effects that can occur are hepatotoxicity, abnormal glucose tolerance, glycosuria, and hyperuricemia. These normally regress after the drug is discontinued. Prolonged therapy may also cause hyperpigmentation, dry skin, and acanthosis nigricans.

OTHER EFFECTS Recent evidence from the Coronary Drug Project (CDP), a secondary coronary prevention trial in subjects with a previous history of myocardial infarctions, shows that nicotinic acid did not affect overall mortality from coronary heart disease in these subjects, in spite of a significant decrease in recurrent infarctions (14). Moreover, the drug was associated with an excess incidence of arrhythmias, as well as skin and gastrointestinal findings.

DRUG INTERACTIONS Nicotinic acid may increase the vasodilating and postural hypotensive effect of ganglioplegic antihypertensive agents.

### *Clofibrate*

Clofibrate is a branched fatty acid ester (ethyl-parachlorophenoxyisobutyrate) that can affect a wide range of metabolic activites of lipids and lipoproteins. These include reduced cholesterol synthesis, decreased hepatic lipoprotein secretion, decreased free fatty acid and triglyceride synthesis, increased triglyceride catabolism, decreased hepatic cholesterogenesis from glucose but not pyruvate, inhibition of microsomal reduction of hydroxymethylglutamyl COA to mevalonate, increased

excretion of fecal neutral and acid sterols, and increased cholesterol efflux from tissues (15–26).

The principal hypolipidemic action of clofibrate is the reduction of VLDL concentrations, both by inhibiting the synthesis and by increasing the clearance of this lipoprotein. Recent reports, however, suggest that the latter effect may be dominant. VLDL and IDL levels usually fall predictably but the effect on LDL is variable. The rise in cholesterol levels which has been reported (27) would seem to emphasize the effect of clofibrate on VLDL catabolism rather than production. In hypertriglyceridemic states, clofibrate has been shown to decrease triglyceride levels by 10–40% (13), but its ability to reduce cholesterol varies from 5–20% (28). In a recent report, clofibrate lowered triglycerides and depressed cholesterol levels below baseline in subjects with type IV hyperlipoproteinemia. It reduced VLDL but raised LDL levels (29).

Clofibrate can also produce changes in blood coagulation and fibrinolysis (30, 31), which may have clinical implications independent of its lipid-lowering abilities.

INDICATIONS Because of its beneficial effect on VLDL and IDL levels, clofibrate has been most useful in the treatment of type III and some subjects with types IV and V hyperlipoproteinemia. Because of its unpredictable influence on cholesterol, its usefulness in type II has been limited.

DOSE Clofibrate is prepared in tablets of 500 mg and is administered in two or four divided doses. The total daily dose is 2 g/day.

SIDE EFFECTS Clofibrate has been associated with relatively few overt side effects. It can occasionally cause nausea, diarrhea, and weight gain but these usually disappear quickly. Rare side effects include skin rash, myositis, weakness, giddiness, and alopecia. Liver function tests may be slightly elevated.

OTHER EFFECTS The most important effects associated with clofibrate use reported to date were found by the Coronary Drug Project group. The drug was linked with a twofold increase in cholelithiasis and a significant increase in arrhythmias, new angina, increased heart size, heart failure, and thromboembolism in patients with existing cardiovascular disease. No beneficial effect on cardiac or overall mortality was observed (14).

DRUG INTERACTIONS Clofibrate can enhance the hypoprothrombinemic effects of warfarin sodium, necessitating an adjustment in warfarin dosage.

## DRUGS THAT AFFECT LIPOPROTEIN CATABOLISM

### *Cholestyramine*

Cholestyramine is the quaternary ammonium chloride salt of a high molecular-weight copolymer composed of a styrene 2% divinyl benzene skeleton. It is hydrophilic but insoluble in water and remains completely unchanged in the gastrointestinal tract. The drug is an anion exchange resin that binds bile acids in the small intestine, thus interfering with their enterohepatic circulation. The result-

ing increases in bile acid production and cholesterol catabolism, however, are compensated for by an increase in de novo cholesterol synthesis (32). Thus, the cholesterol-lowering effect of cholestyramine cannot be explained by its action on cholesterol metabolism, since the total cholesterol balance remains unchanged.

Recent studies have demonstrated that the primary effect of cholestyramine is on the low density lipoprotein. Turnover experiments using $^{125}$I-labeled LDL have shown that the drug increases the fractional catabolic rate of the apoprotein moiety (33). No changes were observed in the rate of synthesis of the lipoprotein, nor in its intravascular distribution.

Cholestyramine has been consistently reported to reduce total plasma cholesterol levels by 20–25% in subjects with type II hyperlipoproteinemia (13, 34–36). In a double-blind trial conducted at NIH comparing the effects of cholestyramine versus placebo in patients with primary type II, the drug lowered plasma cholesterol by 20.6% and LDL cholesterol by 27.3% (37). A more recent report further confirms earlier findings that the total cholesterol reduction obtained with cholestyramine therapy is due to a decrease in LDL concentrations (38).

In subjects with hypercholesterolemia due to increased VLDL or IDL, cholestyramine may actually increase cholesterol levels (12, 36, 37). Its effect on triglyceride levels is variable; transient, usually insignificant, to marked triglyceride increases have been observed (34–38).

INDICATIONS Cholestyramine is the drug of choice for treatment of primary type II hyperlipoproteinemia, particularly IIa where LDL alone is elevated. It is contraindicated in states characterized by VLDL or IDL excesses (types III, IV, V) because it may increase the production of these lipoproteins.

DOSE The initial dose of cholestyramine is 16 g/day given in two to four divided doses. This is generally incremented by 4–8 g every 2–3 weeks until a maximum of 32 g/day is achieved.

SIDE EFFECTS Gastrointestinal side effects are the most common, particularly constipation in older patients, and often make this agent difficult to use. Other symptoms include nausea, vomiting, cramps, and abdominal distention. Rare side effects which have been reported include steatorrhea, alkaline phosphatase elevations, and gastrointestinal obstruction.

DRUG INTERACTIONS Cholestyramine may interfere with the absorption of fat-soluble vitamins and acidic compounds. It is recommended that drugs such as phenylbutazone, digitalis, iron, warfarin, thiazides, tetracycline, and thyroid preparations be taken at least one hour prior to cholestyramine.

### *D-Thyroxine*

Dextrothyroxine sodium is the sodium salt of the dextrorotatory isomer of thyroxine. Thyroid active agents increase both the production and clearance of hepatic cholesterol. D-Thyroxine lowers plasma cholesterol by reducing LDL concentrations (39). Reductions of 15–25% in total cholesterol are generally reported. It is suspected that the drug acts primarily by accelerating LDL catabolism.

INDICATIONS D-Thyroxine is indicated for disorders caused by LDL elevations (type II). Its effects on VLDL and IDL have not been fully evaluated.

DOSE The initial dose is 2 mg daily with increases of 1 to 2 mg per month. The adult maintenance dose is generally 4 to 8 mg per day.

SIDE EFFECTS The most serious effect of D-thyroxine is its cardiotoxicity, which limits its utility as a hypolipidemic agent. Originally selected for trial by the Coronary Drug Project, the drug was abandoned because of excessive morbidity and mortality in the D-thyroxine treatment group (40).

Other symptoms associated with the drug include neutropenia, glucose intolerance, glycosuria, and abnormal liver function.

DRUG INTERACTIONS D-Thyroxine increases the hypoprothrombinemic effect of warfarin sodium, requiring up to 30% reduction in warfarin dosage.

## OTHER HYPOLIPIDEMIC DRUGS

### *β-Sitosterol*

β-Sitosterol is a plant sterol with a structure similar to that of cholesterol, except for the substitution of an ethyl group at the C-24 of its side chain. Like most plant sterols it is unabsorbed in man. Although the mechanism of its hypolipidemic effect is unknown, it is suspected that the drug inhibits cholesterol absorption competitively. Its special effect on lipoprotein metabolism has not been studied, but its primary efficacy is in states characterized by LDL excess. The drug probably affects LDL clearance.

It is available as a liquid with a recommended dose of 30 cc one half hour before meals and at bedtime. A mild laxative effect may occur; diarrhea and nausea have also been noted.

### *Colestipol*

Colestipol is a bile acid sequestrant with an action similar to that of cholestyramine. It has not yet been approved by the FDA for use in lipid lowering. It is an insoluble, high molecular weight granular copolymer of tetraethylenepentamine and epichlorhydrate. Like cholestyramine, it has a high binding capacity for bile acids. Both drugs have a similar effect on plasma cholesterol levels. Colestipol has had no demonstrably significant effect on plasma triglycerides (41, 42). Its effects on lipoprotein metabolism are unclear.

The drug is prepared as water-insoluble beads. The usual dose is 4 to 5 g three or four times per day.

## PAS-C

Para-aminosalicylic acid recrystallized in vitamin C (PAS-C) is a highly purified new agent that is still being investigated. PAS was first found to have a hypocholesterolemic effect in patients being treated for pulmonary tuberculosis (43). Recently,

the new preparation with ascorbic acid was reported to be successful in lowering serum cholesterol and triglycerides in patients with type IIa and IIb hyperlipoproteinemia (44). Although its effect on lipoprotein metabolism has not been studied, PAS-C has been found to reduce LDL levels.

The maintenance dose generally used is 8–9 g/day for adults, 5–6 g/day for children. Some gastrointestinal effects were reported but the drug is generally well tolerated and remains effective for prolonged periods. Excessive alcohol intake can offset the hypolipidemic effect of the drug.



### *Neomycin*

Neomycin is an antibiotic produced from *Streptomyces gradiar* which has a hypolipidemic effect only when administered orally (45). This effect is not dependent on its antibiotic action in intestinal flora, but seems to be secondary to the formation of insoluble complexes with bile acids in the intestine (46). It is suspected that the mechanism of neomycin is similar to that of cholestyramine by increasing bile acid excretion and LDL clearance. Cholesterol reduction of 15–25% has been reported with little or no change in triglyceride levels (47, 48).

Neomycin has been administered in divided doses of 0.5–2.0 g/day. Ninety-seven percent of an oral dose remains unabsorbed. Mild diarrhea may occur and there have been some reports of serious oto- and nephrotoxicity, although these are rare. Further studies into its potential long-term toxicity are needed before the drug can be recommended for general use.

### *Combined Chemotherapy*

The combination of hypolipidemic agents has proven clinically efficacious in certain cases, particularly in controlling the more severe forms of hyperlipoproteinemia. For instance, cholestyramine combined with nicotinic acid—two drugs that act by alternate mechanisms—has been useful in treating patients with homozygous type II in whom diet and cholestyramine alone had proved inadequate (13). Other combinations that have been used successfully include cholestyramine and clofibrate, nicotinic acid and clofibrate, as well as others, but these are still under investigation.

## CONCLUSION

Much has been learned about lipid-transport physiology and lipid disorders in recent years. This in turn has shed light on the effects and mechanisms of hypolipidemic agents, so that therapy of hyperlipoproteinemia has become increasingly more precise. A dietary prescription should always be tried first but if lipid lowering is inadequate, drug therapy may be added. Drugs should be used with caution, however, because all are associated with side effects. Further studies are needed to determine the molecular defects underlying the lipid disorders so that the mode of action of the drugs may be clarified further.

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