The most frequent indication for treatment of hyperlipidemia is for prevention of arteriosclerosis, a suspected but unproved benefit. The cornerstone of treatment of primary hyperlipidemia is diet; drugs may be added to, but do not replace, diet. When a drug is used with any patient, its potential benefits and hazards must be carefully weighed for the given subject. The subjects should be carefully followed and observed for side effects. Plasma lipids should be monitored during the course of treatment. Five drugs have been approved by the U.S. Food and Drug Administration for the treatment of hyperlipidemia: cholestyramine, clofibrate, nicotinic acid, sodium dextrothyroxine and beta-sitosterol. The use, the actions and the side effects of each and of several nonapproved agents are discussed.

Interest in the treatment of hyperlipidemia has increased because of its importance as a risk factor for early coronary artery disease, the development of dietary and drug regimens that can usually normalize plasma lipid levels and the popularization of a simple system for classifying lipoprotein phenotypes. Classification is based largely on the distribution of the plasma lipoproteins. Hyperlipidemia may be either primary or secondary in etiology. The most frequent indication for treatment of hyperlipidemia is for the prevention of arteriosclerosis, a suspected but unproved benefit. Prevention of abdominal pain and pancreatitis, and reduction of xanthomas associated with hypertriglyceridemia are less frequent indications. The cornerstone of treatment of primary hyperlipidemia is diet; drugs may be added, but they do not replace the diet. When a drug is used in any patient, its potential benefits and hazards must be carefully weighed for the given subject. The subjects should be carefully followed and observed for side effects. Plasma lipid levels should be monitored during the course of treatment. Five drugs have been approved by the U.S. Food and Drug Administration for the treatment of hyperlipidemia. Cholestyramine is an ion-exchange resin which lowers cholesterol and low density lipoprotein levels (LDL). It is the drug of choice for treatment of type II hyperlipidemia. Clofibrate lowers triglycerides and the very low density lipoprotein levels (VLDL), but it has only a very small effect on LDL. It is the drug of choice for type III hyperlipidemia and is the first drug that should be tried in type IV hyperlipidemia. Nicotinic acid reduces cholesterol, triglyceride, LDL and VLDL levels. It is very effective in types IIA, IIB, III, IV and V hyperlipidemia. Sodium
TABLE I Characteristics of Families of Plasma Lipoproteins

<table>
<thead>
<tr>
<th>Density (g/cc)*</th>
<th>Electrophoretic Protein</th>
<th>Per Cent of the Total Lipid (by weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td></td>
<td>Per Cent Protein (by weight)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholesterol</td>
</tr>
<tr>
<td>VLDL</td>
<td>0.95-1.006</td>
<td>Pre-beta†</td>
</tr>
<tr>
<td>LDL</td>
<td>1.006-1.633</td>
<td>Beta†</td>
</tr>
<tr>
<td>HDL</td>
<td>1.063-1.210</td>
<td>Alphat</td>
</tr>
</tbody>
</table>

* Used to separate and classify lipoproteins in the preparative or analytical ultracentrifuges.
† On paper or agarose gel.
‡ As compared to the globulins.

Dextrothyroxine reduces LDL and cholesterol levels in type II hyperlipidemia. It is contraindicated in patients with known coronary artery disease or cardiac arrhythmia. Beta-sitosterol is a plant sterol with a structure similar to cholesterol; it causes approximately a 10 per cent reduction in cholesterol and LDL levels; it is useful only in type II hyperlipidemia.

The most frequently used non-(FDA) approved drugs for treating hyperlipidemia are the progesterone analogs and anabolic steroids which lower the hypertriglyceridemia in type V hyperlipidemia. Neomycin sulfate and para-aminosalicylic acid have also been used in a limited number of patients with type II hyperlipidemia. Estrogens have no place in the treatment of primary hyperlipidemia at the present time. A number of new drugs are currently under investigation.

INTRODUCTION

Over the past 10 years interest in the clinical diagnosis and management of hyperlipidemia or hyperlipoproteinemia has burgeoned. There are several reasons for the popularity of this subject. One is the importance of hyperlipidemia as a risk factor for the development of premature arteriosclerosis. Hypercholesterolemia is recognized as one of the three major risk factors for the development of coronary artery disease. The younger the patient at the time of detection, the greater the significance attached to an elevated serum cholesterol level as a predictor of early coronary artery disease [1-7]. Numerous studies have also suggested a relationship between endogenous hypertriglyceridemia or type IV hyperlipidemia and arteriosclerosis. However, hypertriglyceridemia is not as firmly established as cholesterol as a risk factor. This is partly due to the difficulty in population studies in correcting for the degree of hypercholesterolemia that accompanies endogenous hypertriglyceridemia [6,8-11].

A second reason for the interest in hyperlipidemia is the recognition that elevated blood lipid levels can usually be controlled by a combination of diet and medication, even when there is an underlying genetic predisposition [12-14]. A third reason, and perhaps the most significant one, is that a popularized system of classification of hyperlipidemia has been introduced, based on the distribution of families of the plasma lipoproteins [14,15].

The Plasma Lipoproteins as a Basis for Defining Hyperlipidemia or Hyperlipoproteinemia. Except for the unesterified fatty acids, virtually all the plasma lipids, including cholesterol, cholesteryl esters, triglycerides and phospholipids, are transported in association with proteins in macromolecular complexes called the plasma lipoproteins. The plasma lipoproteins are usually classified on the basis of their rates of flotation in salt solutions in the ultracentrifuge and thin electrophoretic mobilities. The four major families are the chylomicrons, the very low density (VLDL or pre-beta), the low density (LDL or beta), and the high density (HDL or alpha) lipoproteins. The properties of these four families are summarized in Table I. The most widely accepted classification of hyperlipidemia is based largely on the distribution of the chylomicrons, VLDL and LDL [14-17]. This system, or a modification thereof, has been adopted by the World Health Organization [15] and by the Lipid Research Clinics of the National Heart and Lung Institute [18]. The relationship of the plasma lipoproteins to the definitions of hyperlipidemia and hyperlipoproteinemia is summarized in Table II. Six different phenotypes, designated by roman numerals I, IIa, IIb, III, IV and V define the spectrum of hyperlipidemias. Each of these phenotypes may be defined as primary etiology, either sporadic or familial, or may be secondary to an underlying disease such as hypothyroidism, uncontrolled diabetes, nephrosis, renal failure, obstructive liver disease, acute and chronic pancreatitis, alcoholism, dysesthesiemia and glycogen storage disease. Various clinical signs and symptoms are associated with these phenotypes [12-17].
**TABLE II**  Laboratory and Biochemical Characteristics of the Hyperlipoproteinemias*

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Definition</th>
<th>Plasma Cholesterol</th>
<th>Plasma Triglycerides</th>
<th>Electrophoresis Pattern</th>
<th>Plasma Appearance, 12 hours at 4°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chylomicrons present; Absence of adipose tissue lipoprotein lipase</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>Chylomicrons present</td>
<td>Creamy layer with clear infranatant</td>
</tr>
<tr>
<td>IIa</td>
<td>LDL increased</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased beta lipoproteins</td>
<td>Clear</td>
</tr>
<tr>
<td>IIb</td>
<td>Increased LDL and VLDL</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased beta and pre-beta lipoproteins, band present, extending into pre-beta region</td>
<td>Uniform turbidity</td>
</tr>
<tr>
<td>III</td>
<td>Floating beta-lipoprotein present†</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased pre-beta lipoproteins</td>
<td>Uniform turbidity</td>
</tr>
<tr>
<td>IV</td>
<td>Increased VLDL</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>Chylomicrons present, pre-beta lipoproteins</td>
<td>Creamy layer with turbid infranatant</td>
</tr>
<tr>
<td>V</td>
<td>Chylomicrons present; Increased LDL, adipose tissue lipoprotein lipase</td>
<td>Normal or increased</td>
<td>Increased</td>
<td>Chylomicrons present</td>
<td>Creamy layer with clear infranatant</td>
</tr>
</tbody>
</table>

*These findings applied to the untreated hyperlipoproteinemia.
†Floating beta-lipoprotein is an abnormal lipoprotein, with beta electrophoretic mobility, present in the plasma fraction of density <1.006 g/cc.

**Evaluation of Hyperlipidemia.** The work-up of a patient with hyperlipidemia may be approached in the following way: (1) Obtain a complete history and physical examination with attention directed toward a personal and/or family history of premature vascular disease, abdominal pain, xanthomas and xantheimata, diabetes mellitus, hypothyroidism and hepatic or renal disease. (2) Define the phenotype by measuring cholesterol and triglyceride levels in a fasting plasma sample, by observing the plasma after 12 to 16 hours storage in the refrigerator and by estimating the concentration of LDL-cholesterol when the total cholesterol is 260 to 300 mg/100 ml or when both cholesterol and triglyceride levels are increased. Special tests, such as postheparin lipolytic activity and ultracentrifugal analysis for an abnormal, floating LDL, are required for establishing the diagnoses of the rarer forms of hyperlipidemias, types I and III, respectively. (3) Exclude secondary causes of hyperlipidemia. (4) Carry out family screening to determine if relatives are affected. Fredrickson and Levy [16] and Goldstein et al. [19] have shown that more than one phenotype may be present in a given kindred with familial hyperlipidemia. Since familial type II hyperlipidemia or familial hypercholesterolemia may be manifested in childhood, screening of the first degree relatives is of particular importance in this disorder even among small children or in the newborn.

Correct diagnosis of the phenotype is important in determining the treatment for different subjects. A consideration that should be emphasized is that measurement of the plasma lipids or lipoproteins to determine phenotype must be carried out under carefully defined conditions. The subjects should be fasting, on a regular diet, with stable weight, not acutely ill and not taking medications known to lower levels of plasma lipids. For example, during the stress of an acute myocardial infarction, LDL tend to decrease while VLDL increase; similar changes may occur in other acute illnesses. Hyperlipidemic agents such as thyroid hormone, estrogens and progesterones are very commonly used and may alter plasma lipid and lipoprotein concentrations. Although insulin causes lowering of plasma lipid levels, it is obviously not desirable to stop giving this medication to an insulin-dependent diabetic subject. When feasible, administration of the hypolipidemic agent should be discontinued for two to three weeks prior to a blood analysis. One such agent, clofibrate, is known to have a rebound effect so that hyperlipidemia may be exacerbated if measured too soon after administration of the medication is discontinued [20].

**Indications for Treatment of Hyperlipidemia.** One well recognized indication for the treatment of hyperlipidemia is based on the fact that reduction of the chylomicronemia and hypertriglyceridemia accompanying types I and V hyperlipidemia may reduce the dangerous episodes associated with recurrent abdominal pain and pancreatitis to a minimum. The bouts of abdominal pain are common manifestations in patients with severe chylomicronemia [16,21]. The most frequently given reason for treating hyperlipidemia is the expectation of decreasing the risk of arteriosclerotic cardiovascular events. Numerous studies have dealt with this problem [22–28], often with conflicting results. The Coronary Drug Project just completed [28] did not show a decreased mortality in men with postmyocardial infarction who were treated with clofibrate, nicotinic acid, D-thyroxine or estrogen. The participants were not preselected for...
hyperlipidemia and only about one-half had serum cholesterol values greater than 250 mg/100 ml. This study cannot be extrapolated to men who have not had myocardial infarctions or necessarily to groups of subjects preselected for hyperlipidemia. A national primary prevention trial has been mounted by the National Heart and Lung Institute through the Lipid Research Clinics program to test whether lowering of LDL-cholesterol levels with diet and cholestyramine will lower the risk of myocardial infarction and cardiovascular death. Since it is not known whether the clinical manifestations of arteriosclerosis can be prevented by lowering plasma lipid levels, the potential risks and benefits of treatment must be carefully assessed for each patient. Factors such as family history, age, severity of hyperlipidemia, presence of associated disease including clinical manifestations of arteriosclerosis, must all be taken into account in determining when to treat primary hyperlipidemia and, particularly, when to use drugs. Occasionally, the cosmetic disturbance associated with lipid deposits on the skin may be an indication for treating hyperlipidemia. Eruptive xanthomas, typical of severe hypertriglyceridemia, rapidly clear with correction of the hypertriglyceridemia. Tuberous xanthomas, characteristic of type III hyperlipidemia, are reduced in size with treatment over a period of months to two to three years. The disappearance of tuberous xanthomas in a patient with type III hyperlipidemia whose plasma lipid levels were normalized over a period of three years is illustrated in Figure 1. Unfortunately, the tendonous xanthomas and xanthelasma associated with type II hyperlipidemia respond very slowly, if at all, to treatment.

**DRUG TREATMENT OF HYPERLIPIDEMIA**

Treatment of any primary hyperlipidemia begins with diet. The addition of a drug may be considered if the patient, for objective or subjective reasons, is unable to follow the diet, if dietary treatment fails to produce a satisfactory reduction in the elevated blood lipid levels, or if the patient has severe hyperlipidemia and is at high risk of complications developing. People who are homozygotes for familial type II hyperlipidemia or who have severe type I or type V hyperlipidemia would fall into this last category.

Our aim in this communication is to review the present knowledge concerning the use of drugs for treating hyperlipidemia. The indications, contraindications, side effects and efficacy of drugs in the treatment of different types of primary hyperlipidemia will be discussed.

**Drugs Approved by the U.S. Food and Drug Administration for Treatment of Hyperlipidemia**

**Cholestyramine.** Cholestyramine is a high molecular weight, quaternary ammonium salt attached to a styrene-divinyl-benzene polymer lattice. The resin is completely insoluble in water and is not absorbed to an appreciable extent from the gastrointestinal tract. In the small bowel, the cholestyramine resin exchanges chloride ion for bile acids, which are diverted from the enterohepatic circulation [29-34]. In the dosage of 16 to 24 g/day, this drug does not cause significant fat malabsorption [29-34]. It is a very potent agent for lowering plasma cholesterol and LDL-cholesterol levels.

**Mechanism of action:** Cholesterol is converted by the liver to bile salts, but otherwise it is not significantly degraded in the human body. An exception to this generalization is the conversion of cholesterol to other steroids in the adrenal gland. The major pathway for the elimination of cholesterol is through the biliary excretion of neutral (i.e., cholesterol) and acidic (i.e., bile acids) steroids and their subsequent loss in the feces. Cholestyramine forms an insoluble com-
plex with the bile acids, and its administration results in increasing the loss of acidic sterol in the stool by approximately tenfold [20-31,35-36]. To compensate for this loss, the hepatic synthesis of bile acids is decreased. The net effect of administering cholestyramine is to achieve an increased catabolism of bile acids and, secondarily, of cholesterol. In order to maintain new steady-state concentrations, a net increase in the hepatic synthesis of both cholesterol and bile acids occurs. Presumably, the increased rate of catabolism of cholesterol is reflected in the catabolism of LDL, as the concentration of both cholesterol and LDL in serum is decreased. Cholestyramine, at the usual dosage administered, does not decrease cholesterol absorption [29]. Langer et al. [37], in a study of the catabolism of LDL, reported that people who are heterozygotes for familial type II hyperlipidemia or familial hypercholesterolemia have a reduced rate of LDL catabolism. In these patients, the reduced catabolism was partially corrected by the administration of cholestyramine. Goldstein and Brown [38] have proposed that the cellular defect in this disorder is a deficiency or defect in the cell receptors that bind LDL. A decreased binding of LDL to cells could decrease its rate of degradation and clearance.

Side effects and interaction with other drugs: Since cholestyramine is not absorbed in the gastrointestinal tract, its major side effects are limited to the gut. These consist mainly of bloating, excessive gas production and constipation. The first two symptoms often disappear after the subject has been receiving the medication for three or four days. In some cases, the administration of antacids is helpful. Approximately 20 per cent of subjects reported having constipation with cholestyramine [29,32,34]. Usually, this symptom can be controlled with the use of a stool softener such as dioctyl sodium sulfosuccinate (Colace®, Mead Johnson). In some instances, however, the gastrointestinal symptoms are of such severity that the patient is unable to tolerate the medication. The drug should not be used in patients who have had an ileal bypass operation or in those with steatorrhea or other malabsorption syndromes. We are not aware of reports of hypersensitivity to the medication. Four cases of pancreatitis have been described in patients taking cholestyramine [29,32,34]. Rarely, calcification of viscera, particularly in the upper right quadrant of the abdomen has been noted [29,39], the etiology of which is not known. Cholestyramine may interfere with the absorption of any drug that is negatively charged, such as thyroxine [29,34,40-42]. The absorption of other medications such as digoxin, coumadin, thiazides, phenylbutazone, phenobarbital and antibiotics may also be disturbed. As a general rule, other medications should be taken one hour before cholestyramine [29,32,34,40]. At the usual dosage, cholestyramine does not interfere with the absorption of dietary fat, calcium or the fat-soluble vitamins. At dosages greater than 24 g/day, disturbances of the absorption of fat-soluble vitamins have been observed. It is recommended that determinations of plasma levels of the fat-soluble vitamins be made periodically in patients who are receiving cholestyramine for a period of a year. In children, oral supplementation of the fat-soluble vitamins is advisable.

Dosage and mode of administration: Cholestyramine usually is given in divided doses of 16 to 24 g/day. Patients may take 4 or 8 g at one dosage. Available commercial preparations are Questran® (Mead Johnson) and Cuemid® (Merck, Sharp and Dohme). The resin should be mixed with liquid and left for a minute so that fluid may be absorbed prior to ingestion. The palatability of the medication is increased in many subjects by having them take it with lemonade, orange juice, soft drinks or even apple sauce. The commercial preparation, Questran, is orange flavored and has had a high general level of acceptance by patients [32,34].

Indications and patient selection: Cholestyramine is clearly the drug of choice for subjects with primary type II hyperlipidemia. Although cholesterol and LDL-cholesterol levels are lowered by 20 to 25 per cent, over and above the effect of diet, the level of serum triglycerides may be initially elevated after starting the medication. This effect is usually transient. This medication has little efficacy in other types of hyperlipidemia [16,32,43,44].

The drug was only relatively recently approved by the Food and Drug Administration for treatment of hypercholesterolemia and type II hyperlipidemia, but, owing to its safety and efficacy, it has found an important place in the treatment of type II hyperlipidemia. The use of this medication has greatly changed the outlook for treatment of subjects with this form of dyslipidemia as patients may now be treated effectively over a period of years without the development of tolerance or loss of efficacy of the medication. The drug has been administered to growing children without reported side effects. There is no significant systemic toxicity of the medication. Questran is currently being used in a nation-wide double blind trial by the Lipid Research Clinics Program of the National Heart and Lung Institute to test whether lowering cholesterol and LDL-cholesterol levels in healthy men with type II hyperlipidemia will protect them against death from myocardial infarction and coronary heart disease. This is a primary prevention trial, the results of which are awaited with great interest [18]. If the
result obtained is positive, it will give new hope to patients with type II hyperlipidemia who are at great risk of the development of accelerated atherosclerosis.

**Clofibrate.** Clofibrate (Atromid-S®, Ayerst) is the branched chain fatty acid ester chlorophenoxyisobutyrate (CPIB) (Figure 2). In 1962, Thorp [45] first showed that this drug has a lipid lowering action in mice. The original drug, Atromid®, contained the ethyl ester of chlorophenoxyisobutyrate (now Atromid-S) and andosterone. Thorp [46] showed in monkeys that chlorophenoxyisobutyrate reduces the serum cholesterol level and is the active chemical substance in Atromid-S. The hypocholesterolemic effect of clofibrate was also shown by Oliver et al. [47], Best et al. [48] and Nestel [49]. Barrett et al. [50] and Cendella et al. [51] found that clofibrate causes a reduction in the plasma unesterified fatty acid levels in rats for a sustained period of time. Clofibrate was the first drug to be approved by the FDA for the treatment of hyperlipidemia following the withdrawal of MER-29 from the market. It is well tolerated by most subjects, is relatively safe and has now been in use for more than 10 years.

**Metabolism:** Clofibrate is essentially completely absorbed from the gastrointestinal tract. In the plasma, it is immediately hydrolyzed to chlorophenoxyisobutyric acid [45], which is then bound to albumin [20]. The albumin-clofibrate complex is excreted largely by the kidney. The drug has a decay time in man of approximately 10 to 12 hours [20].

**Mechanism of action:** The mechanism for the hypolipidemic action of clofibrate is not well understood, despite the relatively long time the drug has been in use. Clofibrate is mainly effective in decreasing the concentration of endogenously synthesized triglycerides of VLDL, causing a reduction of 20 to 25 per cent. It is much less effective in reducing serum cholesterol and LDL levels, the extent of the lowering varying from 4 to 10 per cent. The most important action of clofibrate is thought to be an inhibition of the synthesis and/or secretion of VLDL by the liver [20,32,34,45,52–54]. Gould et al. [55] found that hepatic triglyceride synthesis is reduced by clofibrate. In animals, clofibrate decreases the alcohol-induced hepatic accumulation of triglycerides [20,68,69] and increases the activity of microsomal alpha glycerophosphatedehydrogenase in the liver [20,58–60]. The enhancement of this enzyme might lead to a reduction in the availability of precursor glycerol for the synthesis of triglyceride. If the drug inhibited the synthesis of apoprotein synthesis or apoprotein-binding to lipid [20,61–64], then an accumulation of hepatic triglyceride might be expected whereas the opposite effect is observed. Other hepatic inhibitors of lipoprotein synthesis such as ethanol or orotic acid do lead to an hepatic accumulation of triglyceride [65,66]. Under normal conditions essentially all the plasma triglyceride in man is formed by esterification of plasma unesterified fatty acid in the liver. After the administration of clofibrate, however, only 50 per cent of the triglycerides are derived from unesterified fatty acids, the rest presumably being formed by hepatic lipogenesis [67]. In vitro evidence suggests that clofibrate inhibits acetyl CoA carboxylase, thought to be the rate-limiting enzyme in the biosynthesis of fatty acids [59].

Another way in which clofibrate could decrease the hepatic synthesis of VLDL is through an antilipolytic effect in adipose tissue, thus blocking the release of fatty acid precursors of triglyceride. An antilipolytic effect of clofibrate observed after the administration of epinephrine may be related to a decrease in the intracellular availability of cyclic adenosine monophosphate (AMP) [68]. Since most of the plasma LDL is thought to be derived from VLDL, it is not clear why the reduction of circulating levels of VLDL should not also be reflected in a reduction of LDL. As the latter does not occur, the possibility is raised that the drug might in some way enhance the conversion of VLDL to LDL. Such an effect could be exerted through the activation of tissue lipoprotein lipase [66,69].

Clofibrate has been shown to inhibit the hepatic synthesis of cholesterol at two sites, one between acetyl CoA and mevalonate and the other between mevalonate and isopentenyl pyrophosphate [20,52–54,70]. Only the first of these would likely be rate-limiting with respect to over-all hepatic synthesis of cholesterol. However, as already noted, the effect of clofibrate on the level of serum cholesterol is relatively minor.

In animals, clofibrate appears to increase the biliary excretion of cholesterol as neutral steroids [20,52]. Grundy et al. [52] have observed that despite the fact that clofibrate has only a minor effect on serum cholesterol, it may nonetheless in some patients decrease the size of xanthomas or xanthelasmas over a period of time, presumably due to a mobilization of body stores of cholesterol. Clofibrate has recently been reported to block the arginine-in-
duced stimulation of insulin and glucagon secretion by the pancreas and to decrease insulin secretion in man [71]. Whether such an effect is related to the hypolipidemiac action of the drug is not known [71].

In summary, the major site of action of clofibrate is thought to be in the liver, perhaps exerted through a decrease in triglyceride synthesis. The precise hypolipidemic mechanism of clofibrate is not understood. Several potential effects of the drug are known, which may act individually or in concert. These include a decrease in the concentration of plasma unesterified fatty acids, an increased activity of hepatic α-glycerol phosphatase [69], inhibition of hepatic synthesis of fatty acids [45, 48], acetyl CoA carboxylase [59, 72] and carnitine acyltransferase enzymes activation [73]. The relative importance of these effects to the action of clofibrate in ameliorating endogenous hypertriglyceridemia requires further study.

**Side effects and interrelationship with other drugs:**

Many patients have taken clofibrate for as long as 10 years. The drug has a high degree of acceptance and the incidence of side effects is relatively mild and most frequently limited to the gastrointestinal tract. A few of the side effects are quite serious but these, fortunately, are rare. In the recently completed Coronary Drug Project, the use of clofibrate was associated with a small increase in the incidence of nonfatal pulmonary emboli, angina pectoris, intermittent claudication and cardiac arrhythmias [28]. Nausea and abdominal discomfort are the most common side effects attributed to this medication [20, 28, 32, 34]. A decrease in libido and breast tenderness may also occur in men [28, 74, 75]. The symptoms usually abate quickly after administration of the drug is discontinued. Transient and reversible abnormalities in liver function tests also occur [20, 28, 32, 45, 75]. In rats the medication causes an increase in liver size. A small degree of weight gain is not uncommon in man [20, 32, 76], possibly due to the antiuretic properties of the drug [77].

Dryness of the skin, brittleness of hair and alopecia have all been described as reactions to clofibrate [20, 28, 32]. Skin eruptions and urticaria caused by hypersensitivity to clofibrate have been reported but are quite rare. An uncommon, interesting side effect is a "myositis-like" syndrome first described by Langer and Levy [78], accompanied by diffuse muscular pain, stiffness, malaise and an increased sedimentation rate and serum creatinine phosphokinase. The syndrome is reversible and is dose-related [20, 78, 79]. Another symptom complex is more flu-like with arthralgia as the prominent symptom, and it is accompanied by muscle aching, weakness and malaise [20, 78, 79]. At the present time preexisting muscle disease is not considered to be a contraindication to the use of clofibrate. The occurrence of a lupus-like syndrome [80] has been described in a 66 year old woman who had weakness, malaise, fever, arthralgia, an increased sedimentation rate, a low serum complement value and a positive antinuclear antibody [80]. All the manifestations disappeared after administration of the drug was discontinued.

Another side effect described in a single patient is the induction of a severe ventricular arrhythmia [81]. The effect was completely reversible. Clofibrate is not known to exacerbate diabetes and is not contraindicated in the treatment of such patients. It may be used in both adult onset and juvenile onset diabetes [17, 20, 32, 34]. In the recent Coronary Drug Project, the incidence of gallstones was increased by about twofold in patients receiving clofibrate as compared with those receiving a placebo [28]. The reason for this effect is not known, although it could be related to an alteration in the composition of the bile [20, 82, 85].

An important consideration when using clofibrate is its potential interaction with other medications, particularly with the warfarin group of anticoagulant drugs, the actions of which are potentiated. The mechanism of this effect is not known, but it may be related to an increase in the smooth endoplasmic reticulum in the liver. Another potential way in which clofibrate could increase the activity of anticoagulants is in displacing the agent from a plasma carrier protein [20, 84], as it probably does to thyroxine, which is displaced from its binding site to a plasma protein.

Clofibrate may also affect the coagulation system by increasing fibrinolytic activity [20, 85–87]. A reduction in the fibrinogen level usually occurs between the sixth week and fourth month of treatment, thereafter, it returns to normal [20, 88–90]. A potentially important effect of clofibrate is a decrease in the adhesiveness of platelets and a decrease in platelet turnover [20, 88–91]. Abnormalities in platelet function in patients with familial type II hyperlipidemia, e.g., an increased tendency to aggregate in the presence of adenosine diphosphate (ADP), is partially reversed after treatment with clofibrate [90]. As a general rule, the dosage of the anticoagulant agent should be decreased by about one-half if the administration of clofibrate is started [20, 32, 34].

**Dosage and administration:** Clofibrate (Atromid-S, Ayerst) is given orally in a daily dosage of 2 g, usually in two divided doses. Each capsule of clofibrate contains 500 mg of drug. Very large dosages of the drug, usually exceeding 3 to 4 g/day, may cause an elevation in blood lipid levels [12, 20]. The drug is very well absorbed from the gut.
Selection of patients and indications: Clofibrate is unquestionably the drug of choice in the treatment of type III hyperlipidemia. Used in conjunction with diet, the drug normalizes plasma lipids in practically all patients with this type of dyslipidemia [16,20,32,34,92]. When a drug is required for the treatment of type IV hyperlipidemia, clofibrate is the first choice [16,20,32,34]. It has variable and usually relative little efficacy in type V hyperlipidemia and has no place in the treatment of type I hyperlipidemia. In type II hyperlipidemia, clofibrate may cause a 6 to 10 per cent reduction in the level of serum cholesterol [16,20,32,34]. Several observers have found that LDL-cholesterol may actually increase in some subjects who are treated with clofibrate [93,94]. The combination of neomycin and clofibrate has been suggested as a useful one in the treatment of subjects with type II hyperlipidemia. The combined effects of these agents have not been well studied and their mechanism is speculative at present. One possibility is that clofibrate could enhance increased hepatic excretion of neutral steroids whereas neomycin would increase the elimination of cholesterol in the feces [20,32,34].

Clofibrate and the Coronary Drug Project (summing up): A large, double-blind, secondary prevention trial with clofibrate, referred to as the Coronary Drug Project, has just been completed in the United States [28]. Most of the patients received the medication for five to seven years. The subjects were men who already had one or more myocardial infarctions. In a dosage of 2 g/day, clofibrate caused only about a 6 per cent reduction in serum cholesterol levels, but it did reduce triglyceride levels by approximately 22 per cent. Only about one-half of the subjects had an increase in serum cholesterol of over 250 mg/100 ml at the beginning of the study. In two earlier studies [22,23], clofibrate had been reported to reduce either new myocardial infarctions or death from coronary heart disease in subjects with angina pectoris. The beneficial effects were not seen in patients without angina pectoris regardless of whether they had had a previous myocardial infarction or not. However, these beneficial effects of clofibrate were not observed in the Coronary Drug Project [28]. There was no reduction in the incidence of either new myocaridial infarctions or deaths from coronary heart disease in the treated subjects as compared with the control subjects in this study. When an analysis was made of subjects who did have angina pectoris, again no beneficial effect was found in the patients treated with clofibrate [20]. The group treated with clofibrate did have a significantly higher incidence of thrombophlebitis, pulmonary emboli, congestive heart failure and gallstones as referred to [28].

Who, then, should be given clofibrate? Unfortunately, it is not possible to answer this question at the present time. The study cannot be extrapolated to patients who have not had a myocardial infarction. Based on the results of the Coronary Drug Study, the medication should not be given haphazardly to all patients who have had a myocardial infarction. The drug may still have a place in the treatment of endogenous hypertriglyceridemia (type IV hyperlipidemia). In patients with type IIb hyperlipidemia, clofibrate usually causes a reduction in triglyceride levels if cholestyramine is the primary agent used for treatment of the hypercholesterolemia. We would recommend that patients with type III hyperlipidemia be treated with clofibrate. Its advantages are the ease with which it can be taken, its relatively low incidence of side effects and the fact that it does not complicate the management of diabetes mellitus.

Nicotinic Acid or Niacin. Nicotinic acid, or niacin (Figure 3), is a member of the vitamin B group of compounds and has been used for many years for the treatment of pellagra. Altschul et al. [95] first described in the 1950's the hypolipidemic effect of nicotinic acid, which required a much higher dosage than that necessary for the vitamin effect. Nicotinic acid is a very potent agent for lowering cholesterol, triglyceride, LDL and VLDL levels.

Mechanism of action: The mechanism of action of nicotinic acid in reducing lipid levels is not understood. Its effects on triglycerides and VLDL occur within 48 hours, which is earlier than the time required to lower cholesterol and LDL levels [32,34,96]. One of the most potent actions of the drug is in reducing the level of circulating unesterified fatty acids by inhibiting lipolysis in adipose tissue [97]. This effect may be exerted through decreasing cyclic AMP in the adipose tissue cell [98]. A reduction in the quantity of fatty acids available to the liver for triglyceride synthesis would be expected to decrease triglyceride. These actions would not explain the more rapid reduction in the levels of VLDL and triglyceride as compared to those of LDL and cholesterol [96]. From isotopic studies with 1125-labeled LDL, Levy et al. [99] observed that nicotinic acid decreases the rate of synthesis of LDL, which could be a consequence of the decreased supply of
fatty acids to support VLDL formation. A direct hepatic effect on the synthesis of VLDL is also a possibility [96,99].

A number of studies have focused on the effect of nicotinic acid on the hepatic synthesis of cholesterol. Both in vivo studies with human subjects [96,100,101] and in vitro studies with rat liver slices or homogenates [96,102,103] point to an inhibition by nicotinic acid of cholesterol synthesis, possibly at the level of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase [96,103–106].

Catabolic effects of the drug have been noted, for example, an increase in cholesterol oxidation [96,107] and an enhanced clearing of chylomicrons and VLDL [94]. Hirschorn [108] has suggested that nicotinic acid may increase lysosomal permeability and lead to an activation of lipoprotein lipase, which could clear chylomicrons and VLDL from the plasma. An effect of nicotinic acid on the catabolism of VLDL-triglyceride not involving the conversion to LDL would be consistent with the earlier action of the drug on triglyceride as compared to cholesterol and LDL.

**Side effects and contraindications:** Although nicotinic acid has a number of side effects, the adherence in the Coronary Drug Project to this drug was quite good, although not as good as to clofibrate [28]. The most common side effect is an initial cutaneous flush, which usually occurs in the upper part of the body within 1 to 2 hours after taking the medication. The cause of this phenomenon is not understood [32,34,96,109–111], but it generally disappears after taking full doses of the medication for several days, and occurs in practically everyone who takes the medication, even in dosages as low as 50 mg. The flushing may be decreased by taking the medication with food. Many patients who have been receiving the drug for prolonged periods of time will have inexplicable episodes of flushing at intervals. Other cutaneous manifestations, which are less common, include dryness of skin and an increased pigmentation, resembling acanthosis nigricans. These pigmentary changes are usually localized to the axilla or groin, but rarely may be diffuse in the upper extremities, antecubital fossa or popliteal fossa [32,34,96,109,112,113]. They are reversible upon discontinuance of the medication and are not associated with significant morbidity. Unless the initial flushing does not abate after reaching the full dosage of the drug, the skin manifestations do not often necessitate discontinuance of the drug [32,34,96,109,112].

Gastrointestinal symptoms are very common in patients who take nicotinic acid. They include nausea, diarrhea and abdominal pain and may be lessened by taking the medication with meals [34,96,109,111]. Nicotinic acid may aggravate the symptoms of peptic ulcer disease [114]. Increased urinary frequency and dysuria have also been associated with this drug.

Of the more serious side effects of the medication, one of the most common is a disturbance of liver function and necessitates periodic testing of liver function. Liver biopsies performed in patients in whom hepatic dysfunction developed during treatment with nicotinic acid have shown ultrastructural alterations in the endoplasmic reticulum and mitochondria, the significance of which is not known [34,96,109,112,115–117]. A few overt cases of clinical jaundice were reported. These seem to be more common at dosages greater than the maximum now recommended, i.e., 3 g [96,112,118,119]. In addition to hepatic dysfunction, nicotinic acid may induce other metabolic disturbances, especially hyperuricemia and glucose intolerance. Patients not overtly diabetic may show a reduction in glucose tolerance with occasional glycosuria. Patients with overt diabetes may be more difficult to control. It is not known whether the induced glucose intolerance represents the unmasking of latent diseases [34,96,109,112,115,120,121]. Nicotinic acid has recently been shown to reduce the release of glucagon, which might be exerted through a decrease in the circulating level of unesterified fatty acids or possibly through a decrease in the level of pancreatic cyclic AMP [68].

Interaction with other drugs is not usually a problem, although nicotinic acid may enhance the vasodilating and hypotensive effects of ganglionic blocking agents. For this reason, ganglionic blocking agents, if used to treat hypertension, should be administered with great caution. This medication does not enhance the coagulant action [96,111,122]. Hyperuricemia may also occur and, occasionally, acute episodes of gouty arthritis may be precipitated [115,123].

There are a few absolute medical contraindications for the use of nicotinic acid. These include overt diabetes mellitus, pre-existing liver disease, active peptic ulcer disease, hyperuricemia with a history of gouty arthritis and the development of severe idiosyncratic reactions. It is still possible to administer the medication to subjects with certain of these conditions but close medical supervision must be instituted and administration of the drug may have to be discontinued on short notice if severe aggravation of the condition occurs [16,17,96].

**Dosage and mode of administration:** Nicotinic acid is given orally in the form of a tablet; these are available in 100, 250, 500 and 1,000 mg tablets. We prefer the use of 500 mg tablets in patients who are receiving the usual maintenance dosage of 3 g/day.
The side effects are much more common at higher dosages. We begin with 250 mg orally with meals three times a day on day 1, increasing to 500 mg three times daily on day 2, and 1 g three times daily with meals on day 3.

Various analogs of nicotinic acid have been tried in order to minimize the side effects. Nicotinamide has been found to be less effective than nicotinic acid [34,96,119].

**Indications and selection of patients:** The group receiving nicotinic acid in the Coronary Drug Project [28] had a five year mortality of 21.2 per cent as compared to 20.9 per cent in those receiving the placebo. The five year rate of coronary death for the group receiving nicotinic acid was 15.9 per cent versus 16.2 per cent for the group receiving the placebo. No subgroup receiving nicotinic acid could be identified in which there was a significant reduction in five year mortality. However, nicotinic acid did reduce the five year incidence of nonfatal myocardial infarctions from 12.2 to 8.9 per cent. The results might have been of greater significance if the patients had been preselected for the occurrence of hyperlipidemia or had had a lesser degree of atherosclerosis. The reduction in cholesterol was about 10 per cent in those receiving nicotinic acid and in triglyceride approximately 26 per cent. Since nicotinic acid lowers cholesterol, triglyceride, LDL and VLDL levels, it will reduce plasma lipid levels in all types of hyperlipidemia, except type I. It is probably the most effective drug for type V hyperlipidemia, but has the limitation that it exacerbates diabetes mellitus. It is also very effective in types III and IV hyperlipidemia, but it has more side effects and a lesser degree of patient acceptability than clofibrate. In types IIA or IIB hyperlipidemia, nicotinic acid will reduce in the levels of LDL and cholesterol about 10 to 15 per cent. In type IIB hyperlipidemia, the drug has the additional benefit of decreasing triglycerides as well. Nicotinic acid is not the drug of choice for the treatment of type II hyperlipidemia, but it may be used in conjunction with cholestyramine or in place of cholestyramine for patients who cannot tolerate this medication.

To summarize, nicotinic acid is a very useful lipid-lowering drug, which is most frequently used in types II and V hyperlipidemia. It may also be used in type IV hyperlipidemia when adequate control is not obtained by clofibrate or when there is an adverse reaction to the latter medication. The main drawbacks to nicotinic acid are the side effects and adverse reactions. Fortunately, most of these are reversible and dose-related. The efficacy of nicotinic acid in preventing coronary heart disease, myocardial infarction and cardiovascular death remains to be established. It was one of the four medications used in the Coronary Drug Project, a secondary prevention trial already referred to.

**Sodium Dextrothyroxine (D-1,3,5,7-tetralodothyroxine).** This is the sodium salt, dextroisomer of levothyroxine, the normally occurring thyroid hormone (Figure 4). The rationale for use of this medication is that it has a hypolipidemic action out of proportion to its general effect on increasing metabolism. Administration of the naturally occurring thyroid hormones in dosages sufficient to cause a significant reduction of serum lipids will often produce a hypermetabolic state. The hyperlipidemia associated with hypothyroidism is well known; this most often produces a type IIa or IIb hyperlipidemia pattern. Severe myxedema has rarely presented as a type I hyperlipidemia pattern. Of the thyroid isomers tested, dextrothyroxine shows the widest ratio between the dosage required for the hypocholesterolemic and metabolic effects [32,34,110,124].

**Mechanism of action:** Both hypothyroid and euthyroid patients respond to treatment with desiccated thyroid with a reduction in plasma cholesterol and LDL levels [34,124]. Thyroid hormones increase the hepatic synthesis and catabolism of cholesterol; probably the latter is disproportionately increased. The increased cholesterol catabolism would produce an expected increase in the intestinal excretion of both neutral and acidic sterols [32,34,124-128] and a concomitant lowering of serum cholesterol levels. Thyroid hormone also reduces serum triglyceride [124,129,130], but to a lesser extent than cholesterol.

**Side effects and contraindications:** Overt hyperthyroidism does not usually occur at a daily dosage of 2 to 6 mg of dextrothyroxine. However, mild increases in basal metabolic rates have been noted at these dosages. Uptake of $^{131}$I is depressed, but this effect is reversed within 10 days of discontinuing the medication. Rarely, frank hyperthyroidism is induced [39,124,125-127,129,131-134]. Dextrothyroxine was one of the four medications used in the Coronary Drug Project [28], but it was discontinued because of untoward effects [28,136]. Patients with more than one previous myocardial infarction or with a previous infarction complicated by a sustained arrhythmia, shock, cardiac arrest, congestive heart failure, extension of infarction, pericarditis or thromboembolism had a higher incidence of new myocardial infarcts.
dial infarctions, of fatal arrhythmias, and a higher over-all mortality with dextrothyroxine than if with the placebo. Thus, the major contraindication which limits the usefulness of dextrothyroxine is that of coronary heart disease. Other disorders of the heart may also disqualify patients from using this medication; these include congestive heart failure, tachycardia, paroxysmal atrial tachycardia and other arrhythmias even without a history of coronary artery disease. Advanced liver or kidney disease and hypertension are also relative contraindications. The drug is not recommended for use by pregnant women. Since dextrothyroxine has been found to aggravate diabetes mellitus [124], plasma glucose values should be followed closely in patients with known carbohydrate intolerance.

The only known significant interactions of dextrothyroxine with other drugs are a tendency to potentiate digitalis-like agents and anticoagulants [124,128]. Owen et al. [137] were the first to show the latter effect, the mechanism of which is not understood. The medication should be given with caution to patients receiving anticoagulants; prothrombin time and other blood coagulation parameters should be closely monitored. A history of iodism is also a contraindication to the use of dextrothyroxine. The dosage of the anticoagulant should be reduced by approximately one-third when the thyroid analog is added [124,128,138].

Indications and patient selection: Although the major effect of the drug is in reducing LDL and LDL-cholesterol levels, dextrothyroxine may also be used on occasion in patients with endogenous hypertriglyceridemia. Reports on the reduction in VLDL and triglyceride levels are variable, but there is a consensus that at least in some patients the medication is effective [124]. The drug has to be considered as a second line choice for the treatment of hyperlipidemia because of its contraindications and side effects, and particularly because of the danger in using the medication in patients with known coronary artery disease. In our opinion, the use of dextrothyroxine should be limited primarily to younger patients who are unable to take cholestyramine and who have no signs or symptoms of coronary artery disease. It has been used in a few children and adolescents for a year or more without adverse effects on growth. We require a negative exercise electrocardiogram before using this medication in any patient. Safer and simpler methods of treatment are available for control of hypertriglyceridemia [32, 34,110,124].

**Dosage and administration:** Dextrothyroxine (Choloxin®, Flint) is given orally in tablets containing 2 or 4 mg. The initial dosage in adults should be 1 to 2 mg/day, increasing by 1 to 2 mg at approximately one month intervals to a total dosage of 6 mg. It may be given as a single daily dose. The dosage should not be increased more frequently than once a month. If the patient is hypothyroid and if the dextrothyroxine is being used to partially replace levothyroxine, the initial dosage should be 1 mg and the monthly increment should not exceed 1 mg. For pediatric patients, the initial dosage should be about 0.05 mg/kg; this is increased by 0.05 mg/kg at monthly intervals to a maximum dosage of 4 mg. The drug is well accepted and well tolerated by children [32,34,110,124].

To summarize, dextrothyroxine is a potent cholesterol and LDL reducing agent which is approved by the Food and Drug Administration. Because of the results of the Coronary Drug Project, its use will probably be restricted primarily to children, adolescents and young adults with types IIA or IIB hyperlipidemia who are free of organic heart disease.

**Beta Sitosterol (Cytellin®, Lilly).** Sitosterols are plant sterols with structure similar to cholesterol (Figure 5) — beta sitosterol and stigmasterol. In the mid-1950's it was found that these sterols are not

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**Figure 5.** β-sitosterol molecule.
well absorbed and lower serum cholesterol levels, presumably through an interference in its absorption [34,110,139–142]. Although normal subjects absorb only very small quantities of beta sitosterol, an interesting syndrome has recently been identified, betasitosterolemia, in which significant quantities of the plant sterols are absorbed and are found in the circulation [143].

Cytophlin is an oral preparation in which each 15 ml of the suspension contains about 3 g of the sitosterols. The usual dosage is 3 to 6 g immediately before meals. The preparation may be mixed with a beverage, such as tea or fruit juice, to increase palatability. The major side effect is diarrhea, but other gastrointestinal symptoms such as nausea or bloating may also occur. This medication is useful only in type II hyperlipidemia; it does not reduce triglyceride levels but it does lower plasma cholesterol and LDL concentrations by about 10 per cent. It should be considered as a second line medication in the treatment of hypercholesterolemia [32,34,110,139].

Drugs Not Approved by the Food and Drug Administration for Lowering of Plasma Lipids

Hormonal Preparations. Three types of hormonal preparations will be discussed: estrogens, progestational agents, and anabolic steroids.

Estrogens: The rationale of treating patients with hyperlipidemia and coronary artery disease with estrogens was based on animal studies in which estrogen preparations appeared to protect against atherosclerosis and the observation that estrogens tend to lower levels of plasma LDL and to raise those of HDL. As compared to males, premenopausal females are known to have lower levels of LDL, higher levels of HDL and a significantly lower rate of coronary artery disease and myocardial infarction. There were some early encouraging reports concerning the use of estrogen preparations in the treatment of hyperlipidemia and atherosclerosis [144–146]. Unfortunately, these benefits have not been borne out in man. In the first place, in order to reduce the serum cholesterol level, it often is necessary to use a dosage that produces feminization in the male. Intravascular clotting and thromboembolic phenomena also occur as side effects of estrogen treatment [28,34,110,146–147]. In the Coronary Drug Project, one of the original regimens was 5 mg of diethylstilbestrol administered daily. It was discontinued because the group receiving treatment had an increased number of nonfatal cardiovascular endpoints as compared to the group receiving placebos [28,148]. The group receiving treatment had no comparative decrease in total mortality. Subsequently, the trial was terminated in a second treatment group receiving 2.5 mg of estrogen per day when the data suggested that there was a higher incidence in thromboembolism and mortality from cancer in this group than in the group receiving the placebo [28,149]. Also, the group receiving treatment had a slightly higher over-all mortality than the group receiving the placebo. In addition to lowering LDL and raising HDL concentrations, estrogens also increase levels of VLDL and of serum triglycerides, although usually not above the normal limits. The increase is not usually considered of pathologic significance [150]. However, in susceptible patients with type IV or type V hyperlipidemia, the use of estrogen may elicit a marked increase in triglycerides and even result in bouts of abdominal pain and acute pancreatitis.

Progesterone agents: Glueck et al. [151] reported in 1969 that four female patients with type V hyperlipoproteinemia responded with a significant decrease in their hypertriglyceridemia after treatment with a progestational agent, norethindrone acetate (Norlutate®, Parke-Davies) at a dosage of 5 mg/day. The results have subsequently been confirmed by others [21,34,110].

The mode of lipid-lowering by progestational agents may be through an activation or an increase in the activity of postheparin lipolytic activity, thus promoting the clearance of chylomicrons and of VLDL from the plasma [34,110,151]. The drug may be given orally in one daily dose. Disturbance of endocrine and liver function may occur. Preexisting uterine fibroma and carcinoma may increase in size. Cholestatic jaundice has been reported as a very rare complication. Some patients have tenderness, enlargement and secretion of the breasts. Fluid retention is a common side effect. Conditions influenced by fluid retention such as epilepsy, migraine, asthma, renal dysfunction and congestive heart failure may be exacerbated by these agents. Epithelial closure may be caused and the drugs should not be used in young patients in whom bone growth is not completed. Patients with psychic aberrations may have an exaggeration of the symptoms by progestational therapy. Since a decrease in glucose tolerance has been observed occasionally, diabetic patients should be monitored carefully. Gastrointestinal symptoms, including nausea and loss of appetite, may occur [152].

The drug is used mainly in females with type V hyperlipidemia, who are unresponsive to clofibrate or who cannot tolerate nicotinic acid. The total number of patients treated is too small to estimate the overall benefit of the drug.

Anabolic Steroid Preparations. The anabolic steroid, oxandrolone, was found by Sacks in 1968 to have an hypolipidemic effect [153] in patients with hypertriglyceridemia. Subjects with hypercholesterol-
emia showed either no change or a mild increase in plasma cholesterol. Glueck et al. [154] confirmed the effect and observed a significant decrease in tri-
glyceride levels in 18 of 20 patients with types IV and V hyperlipidemia. The fall in triglyceride levels was
associated with a decrease in both the chylomicron and VLDL fractions [154].

Mechanism of action: As with progestational agents, the mechanism of action of anabolic steroids is
thought to be related to an enhancement of the pe-
ripheral hydrolysis of triglycerides via postheparin il-
polytic activity [153,154].

Side effects: Virilism may occur in females; hence, the use of oxandrolone is restricted to males. If the
drug is given to growing children it may retard growth
by affecting epiphyseal closure. Disturbed liver func-
tion, leukopenia, water and sodium retention, and
aggravation of carcinoma of the prostate have been
described. The drug is contraindicated in patients
with prostatic carcinoma. It does not exacerbate dia-
abetes mellitus and is usually tolerated better than nic-
otinic acid.

Dosage and patient selection: Oxandrolone (Anav-
ar®) is given in 2.5 mg tablets, usually three times
daily. The drug is useful in males with type V hyperli-
pidemia who cannot tolerate nicotinic acid or who
have one of the contraindications for use of this
drug. It is usually very well tolerated. It may be tried
in conjunction with nicotinic acid in type V hyperlipi-
demia if the latter drug does not give an acceptable
reduction of triglycerides at the dosage tolerated.

Colestipol. Colestipol is an investigational bile acid
sequestrant similar to cholestyramine. The drug was
introduced by Parkinson et al. [155] in 1970 in a
search for bile acid sequestrants which were better
tolerated than cholestyramine. It is an anion ex-
change resin and resembles cholestyramine in its ef-
ficacy, potency, side effects and patient acceptance
[156]. The daily dosage of colestipol varies from 15
to 25 g given in individual doses of 5 g.

Neomycin. Neomycin sulfate is an antibiotic pro-
duced from a streptomyces. Its hypocholesterolemic
effect, which is present when administered orally,
was first noted by Samuel et al. [139,157–159], who
showed that long-term administration has a signifi-
cant cholesterol reducing action. The mechanism of
this effect remains unknown. Suggested mecha-
nisms have included a change in the intestinal flora
[159], alterations in intestinal mobility [160] and
formation of insoluble complexes with bile salts in
the intestine [160,161] with a concomitant in-
crease in fecal neutral sterol excretion and a de-
crease in cholesterol absorption [160]. It is not pos-
able at the present time to choose between these
various possibilities. It has been noted that neomycin
is a useful adjunct to clofibrate in patients with type II
hyperlipidemia [32,36,110]. On a theoretic basis,
clofibrate and neomycin might exert a synergistic ef-
fact in lowering serum cholesterol levels through
combined increased excretion of cholesterol in the
bile, produced by clofibrate, coupled to an increased
loss of cholesterol from the intestine, promoted by
neomycin [32,34].

The main use of neomycin sulfate is in treating
type II hyperlipidemia, preferably in conjunction with
2 g of clofibrate daily. This combination is useful in
patients who cannot tolerate either cholestyramine
or nicotinic acid [34,139]. Neomycin sulfate
(Squibb) is given orally as 350 mg tablets, three or
two times daily with meals. The most common side
effects are related to the gastrointestinal tract, either
vague abdominal discomfort and/or mild diarrhea.
Although the drug is largely not absorbed, it does
have the potential of inducing ototoxicity and nephro-
毒性 if absorbed. It should not be used in patients
who have preexisting otologic or renal insufficiency.
Close monitoring of renal function and of audiograms
is necessary for patients receiving long-term treat-
ment. Neomycin should not be given when diuretic
agents such as furosemide or ethacrynic acid, or
when other ototoxic or nephrotoxic agents, such as
streptomycin, kanamycin or gentamicin, are adminis-
tered.

Para-aminosalicylic acid (PAS). Para-aminosalicy-
cyclic acid is a well known antitubercular drug. It was
found to be a potent hypocholesterolemic agent in
the 1950’s in the long-term treatment of tuberculosis
[162]. This observation has been confirmed by oth-
ers [163–165] who found it to be useful in treating
patients with type IIA or B hyperlipidemia. PAS can
reduce cholesterol or LDL-cholesterol levels by 15 to
20 per cent. It can also reduce triglyceride levels by
25 per cent. PAS has been badly tolerated by pa-
tients in the past because of severe gastrointestinal
symptoms and a steatorrhea-like syndrome. A rela-
tively new preparation, PAS-C (Hellwig), which is
a highly purified aminosalicylic acid, is reportedly better
tolerated. Barger et al. [165] treated groups of pa-
tients with this preparation for 12 months with mini-
mal side effects and very good cholesterol and tri-
glyceride lowering action. Most of these patients had
been receiving other hypolipidemic drugs previously.
Most of them found it easier to tolerate PAS-C than
cholestyramine.

The daily dosage of PAS-C is 6 to 8 g in one or
two doses. The drug is supplied as 500 mg tablets.
The most common side effects are nausea, vomiting
and diarrhea. The medication should be discontinued
at the first indication of a hypersensitivity reaction,
such as fever, skin eruption, malaise, leukopenia,
jaundice or hemolytic anemia. Fortunately, this is a rare occurrence. An unusual endocrine manifestation is that of goiter, with or without clinical evidence of hypothyroidism. In the presence of renal or hepatic insufficiency or of a gastric ulcer, the medication probably should not be used for the treatment of hyperlipidemia [165].

The mechanism of action of PAS is not understood. Barter et al. [165] suggested that it causes a selective impairment of cholesterol absorption.

**Halofenate.** 2 Aceto-Amido-ethyl (P-Chlorophenyl)-(M trifluoro-methyl-phenoxy) acetate (MK-85) is structurally related to clofibrate. Its main efficacy is in lowering VLDL and endogenous triglyceride levels in subjects with type IV hyperlipidemia. This drug also has the additional useful effect of reducing hyperuricemia, which commonly accompanies endogenous hypertriglyceridemia [166–169]. It is still investigational and its use has been attended with several instances of severe gastrointestinal bleeding. More study is needed before a decision can be made concerning the safety of this drug for human use. There are a number of other drugs related to clofibrate still under investigational use [166,169], some of which contain sulfur at the (2) position.

**Tiberic Acid.** Tiberic acid is a 2-chloro-5 (cis 3,5 di- methyl piperidonosulfanyl) benzoic acid. It is a new agent which was found to reduce plasma lipid levels in rats in doses as low as 5 mg/kg/day. The drug was also found to be active in dogs. Its applicability to human subjects is still unknown [166,170].

**Miscellaneous Drugs.** Colloid substances, such as metamucil, which by bulk effect produce diarrhea, have a mild cholesterol lowering effect, but their use has been relatively limited [139]. The antibiotic amphotericin B, has been found to lower plasma lipid levels in rats. However, because of the nephrotoxicity of this drug, it is unlikely to be used to treat hyperlipidemia in man [171]. Drugs of the sulfonl urea group have been reported to lower plasma triglyceride levels in patients with type V hyperlipidemia and diabetes mellitus [139].

**SUMMARY AND CONCLUSIONS**

The epidemic of cardiovascular deaths in our society, the association of hypercholesterolemia and hypertriglyceridemia as risk factors, the popularization of a phenotyping system for classification of hyperlipidemia, and the development of effective regimens for lowering plasma lipid levels have all contributed to an increased interest and awareness in the use of pharmacologic agents for the treatment of hyperlipidemia. Five such agents are approved by the Food and Drug Administration: Clofibrate, cholestyramine, nicotinic acid, D-thyroxin and beta sitosterol. The addition of a drug should only be used after it has been established that the subject has primary hyperlipidemia, after the phenotype has been identified, and - after treatment with diet has not produced satisfactory lowering of lipid levels. A clear-cut indication for therapy is the patient with severe chyomicronemia, abdominal pain and pancreatitis. The most frequent indication is for protection against arteriosclerosis and cardiovascular disease, although it has not yet been proved that control of hyperlipidemia will reduce the risk. No drug is currently available for the treatment of type I hyperlipidemia. The drug of choice for the treatment of type II hyperlipidemia is cholestyramine; if this drug is not well tolerated, nicotinic acid is the second choice. Dextrothyroxine may be useful in younger patients without organic heart disease. It is contraindicated in the presence of coronary artery disease or arrhythmias. Clofibrate, in conjunction with neomycin sulfate, may also lower LDL and cholesterol levels in these subjects. PAS-C and beta sitosterol are second line agents: in subjects with type IIB hyperlipidemia, nicotinic acid causes a reduction in triglyceride levels as well as in cholesterol levels. Clofibrate may be used in hypertriglyceridemia as well. For type III hyperlipidemia, clofibrate is clearly the drug of choice. Type IV hyperlipidemia may often be controlled by weight reduction, limitation of alcoholic intake and reduction in consumption of free sweets. Clofibrate is probably the first drug that should be tried if dietary control fails. Nicotinic acid is effective, but it has more side effects. In the treatment of type V hyperlipidemia, norethindrone acetate in women and oxandrolone in men are usually efficacious and have fewer adverse effects than nicotinic acid. Nicotinic acid is quite effective, but it exacerbates diabetes, has gastrointestinal and hepatic toxicity, and causes flushing [16,17,32,34,110,172].

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