Coronary heart disease remains the leading cause of death in the industrialized countries and, ever since the epidemiological relationship between this disease and hyperlipidaemia was observed, the search for an effective lipid-decreasing agent has occupied many scientists throughout the world. The perennial question as to whether a decrease in serum lipids is efficacious or even necessary in the prophylaxis or treatment of coronary disease is beyond the scope of this paper. For the purposes of this review, therefore, the decrease of serum lipids in human populations will be accepted as being clinically desirable.

The current most popular drug that serves as a yardstick for the assessment of newer agents is clofibrate [Atromid-S, ethyl 2-(4-chlorophenoxy)-2-methylpropionate]. This compound has been successful as a hypotriglyceridaemic agent, but falls short of the ideal in terms of hypocholesterolaemic activity. In clinical terms, clofibrate is of value in the treatment of Type IV and possibly Type IIb hyperlipoproteinaemias, but of questionable significance in Type IIa patients, in which cholesterol concentrations are abnormally high. This is borne out by the results of the Coronary Drug Project Research Group (1975), who report that clofibrate decreased cholesterol and triglycerides by 6.5% and 22.3% respectively in a group of several thousand post-infarction patients followed up for periods of up to 8.5 years. The marginal decreases in serum cholesterol obtained in this trial make apparent our need for an effective hypocholesterolaemic agent.

Although this review is mainly concerned with more recently reported hypolipidaemic agents, brief consideration of the suggested mode of action of existing agents will serve to illustrate some of the possible mechanisms for decreasing serum cholesterol and triglycerides.

The mode of action of clofibrate is still not completely understood. A primary mechanism appears to involve the inhibition of hepatic triglyceride synthesis (at the level of acetyl-CoA carboxylase, EC 6.4.1.2) and cholesterol synthesis (at the level of β-hydroxy-β-methylglutaryl-CoA reductase, EC 1.1.1.34). Other effects reported include the displacement of thyroxine from serum albumin, inhibition of adipose tissue lipolysis and stimulation of lipoprotein lipase. The mode of action of clofibrate has been reviewed by Havel & Kane (1973).

Other agents used in the past and currently in use include d-thyroxine, which is thought to act by increasing the catabolism of cholesterol to bile acids (Kritchevsky, 1960), and nicotinic acid, which inhibits the mobilization of free fatty acids from adipose

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Hypolipidaemic Agents: Current Status and Recent Developments

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Coronary heart disease remains the leading cause of death in the industrialized countries and, ever since the epidemiological relationship between this disease and hyperlipidaemia was observed, the search for an effective lipid-decreasing agent has occupied many scientists throughout the world. The perennial question as to whether a decrease in serum lipids is efficacious or even necessary in the prophylaxis or treatment of coronary disease is beyond the scope of this paper. For the purposes of this review, therefore, the decrease of serum lipids in human populations will be accepted as being clinically desirable.

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tissue (Carlson & Orö, 1962). Finally, there are the bile acid-sequestering resins, such as cholestyramine, Colestipol and DEAE-Sephadex.

It is pertinent, at this point, to consider the properties of the ideal hypolipidaemic agent, so that we might assess the relative merits of the drugs discussed in this paper.

1. The compound should be effective in decreasing plasma triglycerides and cholesterol in the most prevalent forms of hyperlipoproteinaemia (Types IIa, IIb and IV).

2. The compound should be capable of oral administration in a form acceptable to the patient.

3. As treatment will undoubtedly involve taking the drug for long periods of time (perhaps for the lifetime of a patient), side effects should be minimal or, preferably, non-existent.

4. There should be no tachyphylaxis.

From the point of view of those in the pharmaceutical industry, criterion 3 is probably the most difficult to satisfy.

**Novel agents**

The number of so-called 'novel hypolipidaemic agents' appearing in the literature is legion. However, many such agents disappear from view after initial reports of their activity in laboratory animals. One can only assume that most synthetic agents are too toxic to be of value in human therapy. Rather than merely list the recently reported agents, therefore, it would be more useful to discuss those compounds that have actually reached the stage of administration to man.

**Probucol (DH-581)** \([4,4'-(iso~ropylidenedithio)-bis-(2,6-t-butylphenol)]\) (structure I; Fig. 1). This compound is of a novel structure in terms of hypolipidaemic agents and has been administered to humans, without deleterious side effects, in a number of clinical trials. Harris et al. (1974) administered 1 g of probucol/day to 50 men for 12 months. The mean decreases in serum lipids observed were 19% for cholesterol and 16% for triglycerides. In general, lipoprotein patterns tended to return to normal in Type I1 patients and not in Type IV patients, in spite of the fact that the hypocholesterolaemic effect was less in Type I1 than in Type IV patients. This is the only study with probucol to show a decrease in serum triglycerides. A similar study by Parsons (1972) showed that, in Type IIa patients, probucol lowered cholesterol by 17% after 8 weeks' treatment, while having no effect on triglyceride concentrations. The compound also lowered cholesterol marginally in Type IIb (8%) and Type IV patients (9%). Again, no effects were seen on triglycerides. Clinically, therefore, probucol could form a useful adjunct to clofibrate in the treatment of mixed hyperlipoproteinaemias.

With respect to its mode of action, probucol has no consistent effect on lipogenesis in animals (Barnhart et al., 1970), but Miettinen (1972), in studies using familial hypercholesterolaemics, demonstrated a decreased endogenous synthesis of cholesterol. In addition, Miettinen (1972) suggests that inhibition of intestinal cholesterol absorption or re-absorption contributes to the hypocholesterolaemic effect of probucol.

An interesting structural variant on probucol is the di-t-butyl-4-hydroxyphenylthioalkanoic acid DH-990 (structure II; Fig. 1), described by Wagner et al. (1974). This compound, unlike probucol, decreases triglycerides significantly in rats. Serum cholesterol is lowered in rats, Rhesus monkeys and cholesterol-fed rabbits.

**Tibric acid (structure III; Fig. 1).** Tibric acid has been shown to be a well tolerated substance in humans and lowered triglycerides in Type IV patients when given over 6 months, at a dose of 500–1000 mg/day (Sirtori et al., 1974). Marginal decreases in triglyceride were seen in Type IIb patients, but no cholesterol-lowering activity was seen at all. These observations were confirmed in a trial conducted by Bielmann et al. (1975). Clinically, therefore, tibric acid seems to have no advantage over clofibrate.

The suggested mode of action of tibric acid (Sirtori et al., 1974) is that the compound stimulates the hepatic mitochondrial enzyme \(\alpha\)-glycerophosphate dehydrogenase (EC 1.1.99.5). This enzyme catalyses the oxidation of the fatty acyl acceptor \(\alpha\)-glycerophosphate, thereby decreasing the rate of hepatic triglyceride synthesis. In rats, tibric
acid stimulates RNA and protein synthesis in liver mitochondria and the consequent increase of α-glycerophosphate dehydrogenase may persist for some days.

Compound CL-720 (structure IV; Fig. 1). Little information has been published on this compound, other than that it lowered serum cholesterol by 24% in Type II patients and serum triglycerides by 51% in Type IV patients. No side effects were observed (Blumenthal et al., 1975). The decrease in cholesterol reported is somewhat greater than that
claimed for most other drugs and we await further details on compound CL-720 with interest.

\textit{p-Aminosalicylic acid} (structure V; Fig. 1). Barter et al. (1974) administered 6–8 g of \textit{p}-aminosalicylic acid per day for 12 weeks to groups of Type IIa and IIb patients. Decreases in serum lipids obtained were of the order of 16\% for cholesterol and 10–21\% for triglycerides. A similar study carried out for 12 months showed that the effectiveness of the drug did not decrease with time. In the past, \textit{p}-aminosalicylic acid has been poorly tolerated by patients and has often led to a malabsorption syndrome and steatorrhoea. However, the latest preparations have been highly purified and seem to be well tolerated. It is suggested that the compound acts by inhibiting lipid absorption from the gut, although the hypocholesterolaemic effect does not correlate with the degree of steatorrhoea seen in the past.

\textit{Aryloxyalkanoic acids}. Many aryloxyalkanoic acids, structurally related to clofibrate, have been reported to be hypolipidaemic in animals and in man (reviewed by Howe, 1974). Although none of these derivatives has so far proved to give a significant advantage over clofibrate, several are worthy of mention.

Nafenopin (SU-13437, structure VI; Fig. 1) has a greater effect on triglycerides than on cholesterol. Like clofibrate, its mode of action involves inhibition of hepatic triglyceride synthesis. However, the compound was withdrawn owing to hepatotoxicity in long-term studies on rats.

Halofenate (MK-185, structure VII; Fig. 1) markedly lowers serum triglycerides and uric acid concentrations, but has little effect on cholesterol.

Compound SaH-42348 (structure VIII; Fig. 1) was shown to be effective in man (Berkowitz, 1969), but no recent results have been reported.

The structure of clofibrate (structure IX) has been included in Fig. 1 for comparison.

\textit{Linoleamides}. The most potent of this series of compounds, moctamide (structure X; Fig. 1), has been tested in man. The compound inhibited dietary-induced hypercholesterolaemia at doses of 300 mg/day. This indicates that, as in animals, moctamide acts in man by inhibiting cholesterol absorption (Takeuchi & Yamamura, 1974).

\textit{Naturally occurring agents}

Many natural agents are purported to have hypolipidaemic effects in humans. Among those enjoying current popularity is dietary fibre. It is hypothesized that dietary fibre is hypocholesterolaemic by virtue of its binding capacity for bile acids. The effects of fibre are difficult to assess, as the substances used in various experiments are, by nature, heterogeneous. Further, many different types of fibre have been used for investigation. However, in spite of encouraging results in animals, results in humans have been generally disappointing. For example, Morgan et al. (1974) showed that sugar-cane fibre (bagasse) increased faecal bile acids and hepatic cholesterol 7α-hydroxylase in rats, whereas Walters et al. (1975) were unable to demonstrate serum lipid changes in humans fed on this substance, although faecal bile acid output was increased.

\textit{Conclusions}

In considering the problem of treating hyperlipidaemias it is becoming increasingly obvious that we must think in terms, not merely of a single abnormality, but of several metabolic malfunctions contributing to a variety of elevated lipoprotein patterns. No single agent yet in clinical trials is capable of correcting all the major hyperlipoprotein-aemias. It may well be that combination therapy will emerge as the only effective treatment. For example, it may be advantageous to combine a bile-acid-sequestering agent with a systematically acting agent. Howard & Hyams (1971) reported that clofibrate and DEAE-Sephadex acted synergistically in decreasing cholesterol concentrations, as did the combination of cholestyramine and nicotinic acid (Moutafis et al., 1971). Duncan & Best (1973) reported that, in rats, a combination of probucol and clofibrate had greater activity in decreasing serum cholesterol than did either compound alone.
In the final analysis, the true test of any hypolipidaemic agent must lie in its ability to decrease morbidity and mortality from occlusive vascular disease in man. It is only when we have at our disposal a clearly efficacious and safe agent capable of substantially lowering both cholesterol and triglycerides and maintaining such activity over a long period of time that we can begin to resolve the question of the relevance of blood lipid concentrations to occlusive vascular disease.

Parsons, W. B., Jr. (1972) Circulation 46, Suppl. 2, 16

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Plasma Lipoproteins in Liver Disease

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The lipoproteins of normal plasma can be divided on the basis of particle size and density into chylomicrons, VLD lipoproteins,* LD lipoproteins and HD lipoproteins. Chylomicrons and VLD lipoproteins transport triglyceride from the intestine and liver to the tissues where it is hydrolysed by lipoprotein lipase. The function of LD lipoproteins is not known; their cholesteryl ester may represent the transport of tissue cholesterol to the liver for conversion into bile acids. HD lipoproteins act as substrate and as activator for phosphatidylcholine-cholesterol acyltransferase. This plasma enzyme transfers fatty acid from the β position of phosphatidylcholine to the 3β-hydroxyl group of free cholesterol; cholesteryl ester and lysophosphatidylcholine are produced (Glomset, 1968). This reaction accounts for most of the turnover of plasma cholesteryl esters. HD-lipoprotein apoprotein also activates lipoprotein lipase.

If the activity of phosphatidylcholine-cholesterol acyltransferase was decreased one would expect that free cholesterol and phosphatidylcholine would accumulate in plasma and that lysophosphatidylcholine and cholesteryl ester would decrease. These changes are found with familial deficiency in this enzyme (Norum et al., 1972); they

* Abbreviations: VLD lipoprotein, very-low-density lipoprotein; LD lipoprotein, low-density lipoprotein; HD lipoprotein, high-density lipoprotein.

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