Therapy of lipid disorders

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The Background

It is first necessary to distinguish between lipid disorders that require treatment in their own right because of symptoms directly related to their occurrence, and the much larger problem of the possible prevention of complications like vascular disease. Patients with those disorders associated with chylomicronaemia (types I and V hyperlipoproteinaemia of Fredrickson, Levy, and Lees, 1967) may present with attacks of abdominal pain, and there can be no doubt of the importance of direct and immediate treatment aimed at the control of symptoms. Similarly, eruptive xanthomas in hypertriglyceridaemia also require treatment. The larger and more difficult problem, which is much debated, is that of the prevention of long-term vascular complications of the hyperlipidaemias. As we have heard, there is a clear association between the hyperlipidaemias and the occurrence of myocardial ischaemia and peripheral vascular disease, but in the majority of those prone to or affected by these the aim of therapy is naturally wider. The whole person must be considered and this introduces immense complications due to the multifactorial aetiology of cardiac ischaemia and peripheral vascular disease. Another problem is that so many of the patients in whom these abnormalities are present—whether of the lipids or otherwise—may be asymptomatic. Some may actually request and accept preventive therapy, but often such motivation is of brief duration. In many others the advice may actually be resented, and there are few more difficult problems than persuading an unenthusiastic individual to carry out such instructions. The business executive who has a check up usually wants to hear that all is well, not that he has to rearrange his life by dietary restrictions, giving up smoking, and taking more exercise. The asymptomatic maturity-onset diabetic, discovered perhaps by a routine examination for insurance purposes or by population screening, is similar. A diabetic or a patient with cardiac disease who presents with symptoms may, for a time, willingly follow appropriate instructions, but no sooner has the average

sufferer lost his symptoms than he slides back. The occurrence of angina or a cardiac infarct, on the other hand, may well induce willingness to accept measures for secondary prevention. Alas, the first heart attack is fatal too often to recommend waiting for it before undertaking preventive measures.

This, therefore, brings us to consider whether manipulation of the level of lipids in the blood influences the tendency to develop ischaemic heart disease, and whether further episodes can be prevented in the patient who has already had one ischaemic episode. It is not possible to be dogmatic on these points but there is some evidence that makes advice of this sort sensible, and it is on this basis that I propose to discuss the approach to the therapy of these disorders.

Obviously, in underlying disorders that may have an inherent short life expectancy, eg, some cases of renal disease and certain forms of cholestatic jaundice, the hyperlipidaemia may not be so easily amenable to therapy, and other problems may be more important. If however, the nephrotic syndrome persists for a long time, the likelihood of ischaemic heart disease is increased, so measures designed to produce reduction in blood lipids are desirable.

Until recently our approach was based on the reports by Turpeinen, Miettinen, Karvonen, Roine, Pekkarinen, Lehtosuo, and Alivirta (1968) and Dayton, Pearce, Goldman, Hamish, Plotkin, Shickman, Winfield, Zagar, and Dixon (1968) which suggested that the prevalence of ischaemic heart disease could be decreased by diets which lower the plasma cholesterol of otherwise well men in whom it had been raised. Provided the patient can be offered a safe and effective method of lowering the plasma lipids, this seems highly desirable. Even though secondary prevention after the onset of an ischaemic cardiac episode is more difficult, it may nevertheless be valuable (Leren, 1966) and should be attempted.

The long-awaited results of the Finnish trial are now available (Miettinen, Turpeinen, Karvonen, Elosuo, and Paavilainen, 1972) and are most instructive. The patients in two mental hospitals

were subjected to a 12-year clinical trial by means of a cross-over study, wherein for the first six years one hospital had the cholesterol-lowering diet and the other had the normal diet: during the second six years the diets were reversed. The main difference between the experimental and normal diets was that, in the former, ordinary milk was replaced by 'filled milk' consisting of an emulsion of soya-bean oil in skimmed milk, and instead of butter and conventional margarine, a margarine high in polyunsaturated fatty acids was used. This resulted in a polyunsaturated/saturated fatty acid ratio of approximately 1.5 : 1 in the experimental diet, and 0.25 : 1 in the normal diet. They were able to show that biopsied adipose tissue from those on the experimental diet contained more linoleic and less myristic acids, which are respectively derived from soya-bean oil and milk fat, thus proving adherence to the diet. The experimental diet produced a decrease in the mean serum cholesterol levels of 12 to 18%. It was thus shown that under these particular circumstances such a diet was feasible, and that a moderate reduction in the serum cholesterol could be achieved. Furthermore, the effects on health were clear cut in men, showing very definitely reduced mortality from coronary heart disease. Interestingly, total mortality was also lower. In women, although the results did not achieve significance, the mortality from coronary heart disease was likewise lowered during the diet period, though total mortality was unaffected. There are various reasons why women might be expected not to show a response so easily, mainly because coronary heart disease is less frequent in them so that the expected numbers would be smaller. There was certainly no excess of deaths from other causes, eg, carcinoma, which had been suggested by Pearce and Dayton (1971). This trial appears strongly to support the policy of advising a cholesterol-lowering diet in all who have hypercholesterolaemia, in the expectation that it will achieve normal cholesterol levels in at least the mild cases, and that the death rate from coronary heart disease will be diminished. It seems reasonable to give this advice to women as well as to men, even though the benefits were less obvious in women than in men.

With an institution population of this sort it is relatively easy to modify the diet and to ensure that it is taken. It is much more difficult with the population at large, especially as we are unable to adopt the advertising methods employed by certain food industries. People do not like changing dietary habits any more than they like giving up smoking, but this should not prevent the appropriate advice being given and consumption of foods likely to be

beneficial encouraged at the expense of saturated fats.

Meade and Chakrabarti (1972) emphasize that the known risk factors for ischaemic heart disease do not explain the occurrence of all cases, which we do not deny (Krikler and Lewis, 1972). However, their theoretically based pessimism conflicts with the more definitive report by the Finnish group who showed clearly that the sequence of reduction of dietary lipid, lowering of blood cholesterol, and decrease in mortality from ischaemic heart disease is a genuine one. I am unaware of any similar demonstration in relation to certain other suggested risk factors such as car and television ownership, though I concede that indirect associations can be implied; for instance, if we had fewer cars and television sets we might take more exercise.

While Yudkin (1964) has been a great protagonist of the aetiological role of dietary sugar, this has not been exposed to therapeutic trials like those of Miettinen *et al* (1972), and few others have been as enthusiastic. The evidence seems to me far weaker than that linking saturated fats with ischaemic heart disease, and in the absence of therapeutic proof we cannot incriminate sugar except in relation to hypertriglyceridaemia, obesity, or diabetes.

Whether to advise dietary change or medication for all who are at risk needs careful consideration. Too often an elderly patient in whom hypercholesterolaemia is a chance finding, is given a diet and/or tablets; this is quite uncalled for as long-term prevention is needless. We want as far as possible to treat the young whose arteries are still supple, and the younger the better; if this means that healthier eating habits become more widespread, this is all to the good. Indeed, when making dietary recommendations it is reasonable to extend them to the whole family; this at least eases the housewife's task and also makes it easier for the patient by removing the temptation to break his diet.

Diet

In the patient with mild type I hyperlipoproteinaemia it is essential to restrict the dietary triglyceride, and this will promptly diminish the chylomicronaemia. Ordinarily this means a shift to a greater consumption of carbohydrate, but the diet can be better balanced if medium-chain triglycerides are given. These are not transported as chylomicrons and are carried to the liver in the portal vein and there metabolized. Unfortunately they are not very palatable. A similar approach will be helpful, at least in part, in dealing with type V hyperlipoproteinaemia. Where

eruptive xanthomas are a problem other dietary modifications may also be required.

As previously indicated, the main reason for treating hyperlipidaemia is the prevention of the life-threatening vascular complications apparently associated with it. While precise classification of a hyperlipidaemia is not always essential it is very useful, and generally both the cholesterol and triglyceride levels are required before the appropriate dietary measures can be recommended. What is suitable for patients with hyper- β -lipoproteinaemia may be quite undesirable for those with hyper-pre- β -lipoproteinaemia. However, a general purpose diet can be designed to suit both, as discussed below.

The biggest problem concerns elevation of the plasma cholesterol, ie, β -lipoprotein. It is perfectly feasible to lower cholesterol values by sharply decreasing the amount of saturated fat in the diet and substituting highly unsaturated oils. The National Heart Foundation of New Zealand (1971) recommends that fat should not provide more than 35% of the calories, and that the ratio of polyunsaturated to saturated fats should exceed 1 : 1. The cholesterol intake should not exceed 300 mg a day. To a limited extent many members of the population themselves already attempt this in a variously enthusiastic fashion.

In prescribing a diet high in unsaturated fats and low in saturated fat and cholesterol it is necessary to ensure that it will be both palatable and effective. The response may be extremely good, particularly if the patient's previous diet was grossly unsatisfactory, but unless the diet is simple and palatable its acceptability, and therefore the response to it, may be poor. To keep the saturated fat content down, dairy products should be eliminated as far as possible, insofar as they contain fat. Thus skimmed milk and its derived products will be acceptable, eg, cottage cheese and fat-free yoghurt. Milk, in the small amounts usually added to tea or coffee, may be permitted for milder cases, but otherwise, or if any doubt exists, fat-free milk should be taken; this may be dried, or obtained by discarding the top creamy layer of unhomogenized milk. Butter can be replaced by suitable soft margarines, making sure that the particular brand is designed for this purpose; not all are. Fish, chicken, and turkey are the best sources of protein, and the more fatty meats, including most pork products, are best avoided entirely. In restricting meat, all visible fat should be trimmed from it before cooking: if it is prepared with a lubricant, no solid fat should be used and only a highly polyunsaturated oil, like corn oil or sunflower-seed oil, should be used for roasting, frying, and the like. Even if the meat appears to be lean, those who eat large amounts may well thereby

ingest a considerable quantity of saturated fat invisible to the naked eye, so this aspect must be watched. Other unsuitable foods include full-cream cheeses, ice cream, saturated oils (eg, coconut) and chocolate, and it is also prudent to restrict foods that have a high cholesterol content, eg, egg yolks (no more than two a week), liver, and shellfish. Unfortunately many favourite foods may have to be curtailed, but, provided the patient is not overweight, others, such as carbohydrate, alcohol, and nuts need not be restricted. Green vegetables and salads can be permitted in plenty, together with the appropriate oils. The American Heart Association issues diet guides which cover these points, and in this country a number of diet cookery books provide suitable recipes attuned to local taste (Nilson, 1967).

It is my personal preference to start the patient off on a fairly strict diet. With periodic observation the patient's response can soon be assessed and may later be possible to relax the dietary controls slightly. It is most important to interview the wife to explain to her the important points about food selection and cooking. Our dietitians are most valuable associates in this field. Such diets do indeed lower the serum cholesterol (Miettinen *et al*, 1972) and one of the best general reviews of the evidence that by the National Heart Foundation of New Zealand (1971). Diet alone will, however, rarely suffice when the initial cholesterol values exceed 350 mg/100ml, but below this level it is often possible to achieve reduction into an apparently normal range; however each case has to be followed individually. The suggestion that the incidence of carcinoma is increased by a diet high in polyunsaturated oils has not been corroborated by a number of studies, including those of Ederer, Leren, Tuohi, and Frantz (1971) and Miettinen *et al* (1972).

When the triglyceride is raised the dietary approach is different, because this component tends to be more dependent on the intake of carbohydrate. A low carbohydrate diet is extremely useful and effective in lowering the serum triglycerides. Simple sugars seem to be more dangerous than complex starches, and should be eliminated as far as possible. Fruit should not exceed three servings per day because of the fructose content. Starches are of course restricted, and alcohol is permitted to a total of no more than six drinks² a week. Patients in whom the serum triglycerides are raised are often obese, and provided they follow the diet, weight and triglycerides will fall together.

For those in whom there is elevation of both

¹A 'serving' is one apple, peach, etc.

²A 'drink' is one tot of spirits, one glass of table wine or the equivalent.

triglycerides and cholesterol, a known high-risk combination (Carlson and Böttiger, 1972), both dietary approaches should be combined. Hulley, Wilson, Burrows, and Nichaman (1972) have modified the standard American Heart Association fat-controlled diet by decreasing its carbohydrate content and yet providing 35% of calories from carbohydrate, 40% from fat, and 25% from protein. There is a high ratio of polyunsaturated to saturated fats and a low ratio of simple to complex carbohydrates (1 : 2). In addition to what has already been mentioned skimmed milk is restricted to two cups a day because of its lactose content. This diet can be quite palatable; indeed we have used one like it for some years in the treatment of similar cases, ie, obese patients with pure hyper- β -lipoproteinaemia. Dietary manipulation is, however, so major a factor and so unpleasant to a number of people that success can only be expected from those who are highly motivated.

Medications

While diet should be the mainstay of the therapeutic approach, appropriate medication must be considered for those who need it. This is not a substitute for dietary control as, in my experience, few patients who fail to follow a diet will religiously consume tablets over a prolonged period. Furthermore none of the available medications is entirely effective in hypercholesterolaemia and this is especially true for patients in whom the levels are very high. The various agents available will now be considered.

CLOFIBRATE

In this country, clofibrate is the most widely used drug for hyperlipidaemias. The manufacturers are clearly aware of its indications, usefulness, and limitations, but a very large number of practitioners equate the treatment of hyperlipidaemia with the use of this substance. Indeed, many patients are given clofibrate when dietary advice, or indeed reassurance, would be more suitable; and it is used for patients whose cholesterol elevation may not reflect a condition inherently responsive to clofibrate.

The precise mode of action remains unclear, but clofibrate is especially helpful in disorders in which the triglycerides are elevated. It is of the most specific value in patients with 'broad beta' disease (see page 35) and also helps those with predominant hypertriglyceridaemia. Many of the latter will respond to a low-carbohydrate diet, but some may not respond completely. Before using clofibrate the causes of secondary hyperlipidaemia which require specific treatment, eg, diabetes, should be excluded.

With a dose of 1500 to 2000 mg daily, the triglyceride response is usually very satisfactory, often of the order of 40% reduction or more. Tolerance is usually extremely good, nausea being a rare complaint. Some years ago there was concern because of myalgia together with transient elevation of the serum aspartate and alanine aminotransferases (EC 2.6.1.1; EC 2.6.1.2) and creatine kinase (EC 2.7.3.2) (Langer and Levy, 1968); I have seen only two such patients. There have been only a few subsequent reports of myalgia and it appears that the creatine kinase may be raised without elevation of the aminotransferases (Sekowski and Samuel, 1972). If the serum albumin is low, as in the nephrotic syndrome, the toxicity of clofibrate is enhanced and the dose should be reduced (Bridgman, Rosen, and Thorp, 1972).

Clofibrate has less effect on the plasma cholesterol, but when this component is only moderately elevated the response to clofibrate may be adequate; the usual reduction is about 11% (Stone, 1972). Possible benefits of clofibrate in ischaemic heart disease, not attributable to its hypolipidaemic effect, are puzzling and intriguing (Dewar and Oliver, 1971) but are beyond the scope of this review.

CHOLESTYRAMINE

This ion-exchange resin is rather more popular in the United States than in Britain. It binds bile salts in the intestinal lumen and thereby impairs their reabsorption so that the enterohepatic circulation is disrupted. As bile salts are synthesized from cholesterol the latter is lost from the body. If the patient will accept this drug the effect is satisfactory, with a decrease in the serum cholesterol averaging 28% (Stone, 1972). It must be remembered that fat-soluble drugs and vitamins require bile salts for their absorption, so that such medications should be taken several hours after cholestyramine. I am not aware that metabolic bone disease has occurred with cholestyramine therapy but it seems possible that this might occur after prolonged consumption, especially if the dietary intake of vitamin D and calcium is low. Current preparations are more palatable than those hitherto available, but many patients still find the dose (16 grams a day) unpleasant to take; virtually all complain of varying degrees of constipation and some develop duodenal ulcers, perhaps due to an effect on the duodenal pH (Thompson, 1972).

NEOMYCIN

It is not its antibacterial activity that impairs the absorption of lipids, but rather its ability to disrupt the micelles within the intestine: neomycin precipi-

tates cholesterol inside the lumen and thus enhances its excretion in the stools (Thompson, 1972). Other similar polybasic, but non-antibiotic, compounds can induce malabsorption in the same way. Because it is poorly absorbed, neomycin is usually safe except in those in whom poor renal function will impair the excretion of the small amounts that are absorbed. So far there have been no reports of deficiency of fat-soluble vitamins after long-term therapy but, as in the case of cholestyramine, this is theoretically possible. The recommended dose is 1-2 grams a day.

DEXTHROTHYROXINE

The serum cholesterol tends to be elevated in hypothyroidism, and the fact that this can be corrected by replacement therapy with thyroid hormone drew attention to the possible usefulness of thyroxine in patients with hypercholesterolaemia due to other factors. Such patients can be given thyroid hormones in order to produce a net increase in cholesterol catabolism (Krikler, 1972). The increased metabolic activity resulting from laevothyroxine therapy is particularly inappropriate in patients already suffering from coronary artery disease; any increase in the demands on the myocardium may be deleterious, whether by precipitating arrhythmias or inducing or aggravating angina, and in some it may lead to cardiac infarction. Dextrothyroxine, on the other hand, appears rather safer as it has a relatively lower calorogenic effect and a shorter half-life. By itself it may produce evidence of myocardial ischaemia in those with latent ischaemic heart disease, though this is less likely than with laevothyroxine. We have shown (Krikler, Lefevre, and Lewis, 1971) that the addition of a β -adrenergic blocking agent, propranolol, provides a safe and effective way of obviating this problem. We generally find that 8 mg of dextrothyroxine and 40-80 mg of propranolol daily will suffice, and this can be divided into two equal doses. A reduction in the serum cholesterol of the order of 20 to 25% may be anticipated. We have been reminded of the important protective properties of the β -blocker in some patients who have discontinued it but have carried on with the dextrothyroxine alone, and who have then suffered a recrudescence of angina that had previously been effectively suppressed.

In a trial in the United States an increased death rate was noticed in a small group of men with coronary artery disease who, before they entered the trial and were given dextrothyroxine, had multiple extrasystoles (Coronary Drug Project Research Group, 1970). Consequently these workers regard extrasystoles as a contraindication to dex-

trothyroxine: we feel that the addition of a β -blocker neatly copes with this particular problem.

NICOTINIC ACID

Nicotinic acid in doses of 3 to 6 grams daily can reduce the serum cholesterol concentration by roughly 20%, apparently by partially inhibiting free fatty acid release, by decreasing the synthesis of low-density lipoproteins, and also in other ways not clearly understood. It is also effective in hypertriglyceridaemia. These doses, however, tend to cause flushing and pruritus which may upset patients sufficiently to make them stop the treatment. More rarely abnormalities of liver function may be noted and, although to some extent effective, nicotinic acid has not proved widely acceptable in this country.

COMBINED THERAPY

A combination of different agents is often needed in the treatment of severe hypercholesterolaemia in hyper- β -lipoproteinaemia, especially in the homozygous type, which has a bad prognosis. At present the best available therapy is the combination of diet, cholestyramine, and nicotinic acid (Moutafis, Myant, Mancini, and Oriente, 1971). Any possible benefit must be balanced against the tendency to liver damage or other complications in patients whose outlook is in any case gloomy.

Conclusion

In the past twenty years knowledge of hyperlipidaemias has increased to the extent that safe and effective treatment, by diet and/or medication, can be offered to the milder cases with a reasonable expectation of averting vascular complications in a proportion of them. Precisely how early such measures should be started is not known and more knowledge is required before the more severe cases can be treated effectively. Hypolipidaemic therapy is, of course, only a part of the prevention of ischaemic heart disease, and other identified risk factors must also be treated. Most important, it must be accepted that only known or suspected risk factors can be treated and that others, as yet unknown, may turn out to be of major import. Nevertheless today our task is to make the best use of present knowledge while seeking opportunities to extend the preventive approach by further investigations.

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