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Lipids and atherosclerosis in man

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Probably the main contribution which a physician can make to this symposium is an assessment of the aetiological and therapeutic importance of animal and vegetable fats in terms of human disease. Although it has been speculated that a deficiency of essential fatty acids might contribute to various diseases in man, atherosclerosis is the disease in which animal and vegetable fats have been most closely implicated and is the only disease which will be considered here. The object of this discussion is to examine briefly the nature of certain associations and the strength of certain relationships which may exist between dietary fat and human atherosclerosis rather than to review them in any detail; several comprehensive reviews have been published recently (Hilditch & Jasperson, 1959; Katz, Stamler & Pick, 1959; Oliver, 1960*b*; Sinclair, 1960).

Arterial lipids and atherosclerosis

The earliest visible lesions in human arteries are fatty streaks on the intimal surface. There is little or no associated fibrosis in these early lesions which are present in many by the age of 5 years and in the majority of 10-year-olds in this country. The fat in these lesions is mostly esterified and free cholesterol, and these lipids increase greatly with the severity of atherosclerosis mainly at the expense of the phospholipids and triglycerides; this is so for the coronary and cerebral arteries and is particularly striking in the aorta. Although there are differences between these arteries, with increasing atherosclerosis the polyunsaturated fatty acids of cholesterol esters also increase while those of phospholipids decrease (Böttcher, Boelsma-Van Houte, Ter Haar Romeny-Wachter, Woodford & Van Gent, 1960).

Cholesterol can be synthesized in the arterial wall, but this property decreases with advancing age and most of the esterified and free cholesterol is derived from the plasma. In addition to the evidence from experimentally induced atherosclerosis that the level and duration of plasma hypercholesterolaemia is roughly responsible for the extent and degree of atheromatous-like lesions, there is adequate evidence from studies with isotopes in man that cholesterol in the plasma passes across the

vascular endothelium into the vessel wall. When hypercholesterolaemia is present, as in xanthomatosis, atheromatous lesions are more extensive and florid and consequences such as the development of ischaemic heart disease are more common. This much is reasonably certain but the nature of the relationship between the plasma lipids and atherosclerosis or ischaemic heart disease is far less clear.

Plasma lipids and atherosclerosis

At present, no abnormality that can be regarded as indicative of the presence of atherosclerosis has been found in the plasma lipids in man. This may be due partly to the fact that in man the atherosclerosis process begins spontaneously at a very early age and by adult life all of us have developed some arterial lesions. Since we are unable to detect those who have very few or only early lesions, it is impossible to say with certainty that any particular plasma lipid pattern represents or is near to normality. Until the normal is known, degrees of abnormality cannot be recognized but, in patients who have developed features of ischaemic heart disease, divergence from the expected pattern of the plasma lipids is often found. This divergence is particularly common in those who develop clinical features of ischaemic heart disease before middle age and is less frequently found in older patients (Oliver, 1960*a*). Elevation often occurs of the concentration of plasma ester and free cholesterol, of the plasma phospholipids, of the β-lipoprotein cholesterol or low-density lipoproteins and of the plasma triglycerides, and postprandial lipaemia persists longer than usual. Recent reports suggest that certain fatty acids may be present in abnormal concentration in the plasma lipids in some patients with ischaemic heart disease. It should be emphasized that the plasma lipid pattern does not deviate from the expected in more than a minority of patients with ischaemic heart disease. The most that can be said is that the majority of young men with ischaemic heart disease have some abnormality of their plasma lipids. Yet there is good evidence that apparently healthy individuals with significant elevation of the plasma cholesterol level have an increased risk of developing ischaemic heart disease (American Heart Association: Co-operative Study of Lipoproteins and Atherosclerosis, 1956; Dawber, Moore & Mann, 1957). Familial hypercholesterolaemia, whether xanthomatosis is present or not, is also associated with increased susceptibility to ischaemic heart disease. On the other hand, there is no relationship between survival and the concentrations of plasma cholesterol and of low density lipoproteins once myocardial infarction has occurred (Roe, Little & Schanoff, 1960).

Thus, all one may conclude is that some form of association exists between the presence of abnormal plasma lipid patterns and ischaemic heart disease. There is nothing to indicate the nature of this association in man although there is suggestive evidence that there may be a causal relationship between hypercholesterolaemia and the early development of atheroma. Whether it is mediated by increased passage of lipid across the vascular endothelium or by production of a thrombotic tendency is not a subject for discussion here and has been considered in some detail recently (Oliver, 1960*c*).

Dietary fat and coronary heart disease

Much of the interest concerning a possible relationship between dietary fat and coronary heart disease has been the result of studies of the dietary habits and incidence of ischaemic heart disease in different populations. The results of such studies are often difficult to interpret since surveys of the incidence of ischaemic heart disease in different races and populations are likely to be less reliable than similar surveys of the incidence of communicable diseases, trauma and nutritional disorders in which one group of the population is clearly affected and the other is clearly not affected. The vital statistics for ischaemic heart disease are based on the incidence of angina and myocardial infarction, which are poor indicators of the degree of coronary atheroma. They can, moreover, be misleading as a result of inaccurate diagnosis, a varying awareness of ischaemic heart disease in different countries and the lack of any standardized nomenclature. Accurate estimation of diet is also exceedingly difficult; national returns seldom give an adequate account of the habits of particular groups of the community and they are often based on questionnaires on food habits which are notoriously misleading. Yet serious studies of many different populations (Keys, 1956; Keys & White, 1956) have mostly supported the thesis that the intake of fat and the level of cholesterol in the plasma and the incidence of ischaemic heart disease can be positively correlated. For various reasons, some of which have been mentioned, these views cannot be accepted unreservedly and it is probably wise to conclude that the racial and geographical differences in the incidence of ischaemic heart disease and serum cholesterol levels are not due either solely or principally to differences in the total intake of dietary fat.

Ten years ago saturated and unsaturated fats were believed to have the same effect on the level of plasma cholesterol and other lipids. Kinsell, Partridge, Boling, Margen & Michaels (1952) reported that the addition of large quantities of unsaturated fats to the diet reduced the plasma cholesterol level. It is now recognized that saturated fats raise and unsaturated fats reduce the plasma cholesterol level. Whether the effect of reducing the serum cholesterol level which follows the intake of excess unsaturated fats is related to the total degree of unsaturation and chain length of the fatty acids (Ahrens, Insull, Hirsch, Stoffel, Peterson, Farquhar, Miller & Thomasson, 1959) or to the essential-fatty-acid content (Kinsell, Michaels, Friskey & Splitter, 1958) of unsaturated fats is not yet settled.

There have been many studies of the effects of animal and vegetable fats on in vitro tests of coagulation and fibrinolysis but none have clearly shown that the degree of saturation of the fat influences these systems. They are, of course, poor measures of the formation of intravascular thrombi and much work is obviously required in this direction.

Therapeutic implications

Though it has been shown that a diet low in saturated fats but high in unsaturated fats reduces the plasma lipid levels, the importance of this finding cannot be assessed accurately until it is known whether reduction of the serum lipids is beneficial.

No controlled and adequate study of the effect of a change in diet on morbidity and mortality in ischaemic heart disease has yet been reported, although a study being undertaken in the Central Middlesex Hospital indicates that the first $2\frac{1}{2}$ years of reducing the plasma cholesterol by a diet low in saturated fats has not altered the prognosis of such patients (K. Ball, 1961, personal communication). Thus, our present knowledge is too incomplete to recommend any major dietetic changes for the prevention and treatment of ischaemic heart disease. It might be argued, however, that dietary recommendations are justifiable for those considered to be particularly at risk, such as apparently healthy men with hypercholesterolaemia and a family history of ischaemic heart disease. It is not difficult to devise a diet with complete exclusion of all dairy products and fatty meats and the substitution of vegetable oils, such as maize (corn) oil, soya-bean oil or sunflower-seed oil, for frying, roasting, salad oils and pastries (Pilkington, Stafford, Hankin, Simmonds & Koerselman, 1960).

A 5-year study recently completed has shown that reduction of abnormal plasma lipid levels by the use of oestrogens does not alter the prognosis in men who have recovered from their first myocardial infarct (Oliver & Boyd, 1961). A similar conclusion has been reached from a comparable study by Stamler, Katz, Pick, Lewis, Page, Pick, Kaplan, Berkson & Century (1960). These results infer, but certainly do not prove, that continued reduction of the level of serum lipids by any means does not reduce the incidence of further non-fatal or fatal myocardial infarction in men who have developed ischaemic heart disease. It would not be particularly surprising if subsequent more comprehensive dietetic studies failed to show any improvement in prognosis of patients once they have developed the clinical features of ischaemic heart disease. One only has to consider the extensive structural changes that are present in the coronary arteries of such patients to wonder how reduction of the lipid levels in the plasma could make much difference at this stage in their disease. Indeed, it may be completely unsound to test the efficacy of cholesterol-lowering diets or drugs in patients with clinically manifest coronary disease. Further, since most apparently healthy adults have more or less severe structural damage in their arteries, reduction of the level of plasma lipids may ultimately prove to be of little value unless through a decrease in intravascular thrombus formation. Nevertheless, long-term studies on prognosis should be conducted in individuals who are still healthy but are most at risk and in whom the disease is less advanced. The substitution over a 5-year period of unsaturated fatty acids for saturated fats in the diet of otherwise healthy men would require much co-operation and close surveillance but should be attempted since it is the only available means of obtaining a definite conclusion as to whether reduction of elevated serum cholesterol levels reduces the risk of developing myocardial infarction. Such studies may raise certain ethical considerations and would have to be conducted on very large numbers in such a way as to disturb the subjects' lives as little as possible. This aim would be best achieved through the administration of an otherwise bland and non-toxic substance in tablet or capsule form without relying on any change in diet.

Conclusion

There is suggestive evidence for a causal relationship between abnormal plasma lipid patterns and the early development of atheroma both experimentally and in man.

There is a weak association of unknown significance between abnormal plasma lipid levels and ischaemic heart disease.

Geographic differences in the incidence of ischaemic heart disease cannot be related causally to quantitative differences in the intake of fat. Saturated fats raise and unsaturated fats decrease the plasma cholesterol level and it is easy to devise a diet rich in unsaturated fats and low in saturated fats.

Two 5-year studies in which oestrogens were used have shown that reduction of the plasma lipids is not associated with any improvement in prognosis in men who have had one myocardial infarct. The benefit of reducing the plasma lipids by dietetic means has not yet been adequately tested in patients with coronary heart disease, or in healthy individuals at risk.

In order to decide whether reduction of plasma lipid levels decreases the risk of developing ischaemic heart disease, it will be necessary to substitute unsaturated for saturated fats for several years in a large group of healthy individuals. Such a trial presents many difficulties.

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