Jubilee Editorial

Dietary fat and coronary heart disease

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Background

All the evidence relating dietary fat to plasma lipids or to coronary heart disease has been generated during the past 35 years. Not only are these topics not present in any issues of the *British Heart Journal* or Proceedings of the British Cardiac Society before 1953, but also there was scant reference to them elsewhere. Earlier, the *British Heart Journal* published several papers on arteriosclerosis and coronary arterial obstruction and their relation to myocardial ischaemia and infarction but these included very little consideration of the pathogenesis of coronary heart disease and no mention of blood lipids or dietary constituents—fats or others.¹⁻⁴ These papers associated the origin of coronary heart disease with hypertension and cigarette smoking and occasionally with heredity, but not with the other risk factor, blood cholesterol (or diet).

Weiss and Minot (1933) reviewed what was known about nutrition and arteriosclerosis⁵ and, although they gave an account of the early feeding studies in rabbits with cholesterol alone and cholesterol dissolved in sunflower seed oil,^{6,7} they were quite clear that there was no convincing evidence of such a relation in people. Such interest as there was, related to the possibility that a high protein diet, particularly meat consumption, might be harmful. Weiss and Minot concluded that, while statements that dietary fat might be connected with human arteriosclerosis were not lacking in published reports, none was based on controlled observations and most were strongly influenced by the imbibition theory of arteriosclerosis proposed by Virchow⁸ and amplified by Anitschkow.⁹ "Caution is necessary at this point lest we fall into the so often dangerously applied post hoc propter hoc method of reasoning". Regrettably, this form of reasoning continues today, particularly in the interpretation of epidemiological

correlations with coronary heart disease and intervention studies.¹⁰

It was not until 1940 that it was seriously suggested that the lipids in atheromatous plaques had their origin in plasma,¹¹ but even then the relations between disturbances of lipid metabolism and coronary atherosclerosis or coronary heart disease were only considered in the context of diabetes, hypothyroidism, and the nephrotic syndrome. Paul White, in the 1947 third edition of his book, writing on the cause of atheroma, stated, "faulty cholesterol metabolism, local arterial strain or overwork, hypertension, infection, allergy, endocrinopathy and heredity are among the many factors suggested, but none has been proved or consistently found."¹² Both he and Paul Wood (1950)¹³ repeated the orthodox views⁹ that there are "lipoid substances" in the arterial lesions but in their textbooks on heart disease, neither of them made the connection between blood cholesterol and coronary heart disease, let alone between dietary fat and blood cholesterol or dietary fat and coronary heart disease.

Blood cholesterol and coronary heart disease

Familial hypercholesterolaemic xanthomatosis was recognised as a cause of both coronary atherosclerosis and of coronary heart disease in 1948¹⁴ and the first paper in the *British Heart Journal* that clearly related raised serum cholesterol to premature coronary heart disease was published under the title "Tuberous xanthomatosis" by Leys in 1951.¹⁵ He stated "sudden death suggestive of cardiac disease below the age of 40 demands a study of sibs and particularly of the children." Thirty-six years later, many doctors still ignore this message.

While there were reports elsewhere indicating that patients with coronary heart disease often had raised blood cholesterol concentrations,¹⁶⁻¹⁸ the first paper on the plasma lipids and coronary heart disease, which appeared in the *British Heart Journal*, was to my surprise from my late colleague George Boyd and myself in 1953.¹⁹ We reported the relation between plasma cholesterol and plasma

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phospholipids in 200 consecutive patients with coronary heart disease and 200 miscellaneous controls. While identifying the importance of the relation of hypercholesterolaemia to coronary heart disease, we paid little attention to the influence of dietary factors and suggested that genetic and hormonal influences were of particular importance. I presented these results to the Newcastle meeting of the British Cardiac Society in April 1953 and, when the chairman (Sir William Hume) called for comments and questions, there was a stony silence. After about half a minute (it seemed like an hour) Paul Wood stood up and said, more or less, that he could not understand why we had been wasting time making biochemical measurements in patients with coronary heart disease when so much more needed to be known about haemodynamic function during and after acute infarction. This comment was made with characteristic acerbity and produced a general murmur of approval. The balance was redressed by Maurice Campbell, however, who said that he didn't understand why members of the Cardiac Society needed to be so harsh on a young man who had produced something new. "Given time, there might just be something in it" he said.

We followed this paper with an analysis of plasma lipoproteins in 50 healthy men and 50 men with coronary heart disease under the age of 50.²⁰ This was a painstaking analysis, achieved by paper zone electrophoresis with staining of globulin fractions with bromophenol blue and subsequent cutting of the paper strip into ten 1 cm sections for extraction and estimation of cholesterol—a lot of work. The α (high density)/ β (low density) lipoprotein ratio was significantly lower in the patients with coronary heart disease.

My studies of the subject were first stimulated when Rae Gilchrist suggested in 1950 that I should spend three months in the library and "find out about coronary disease". With a biochemical background and two years in the University Department of Biochemistry (under Professor Guy Marrian), George Boyd and I developed a joint programme of research which lasted 10 years. During this decade there was an explosion of interest and enthusiasm in the subject of blood lipids and dietary fat and coronary heart disease. This was described, under the title of Cholesterophobia, as "Seldom can so much have been written by so many and read by so few."²¹

The dietary fat story

The principal architect providing the foundations of the relation between dietary fat and coronary heart disease was undoubtedly the physiologist nutritionist Ancel Keys. His interest began in the late

1940s with the belief that "the physico-chemical characteristics of the individual should have predictive value" for coronary heart disease.²² This was the origin of "coronary risk factors". A fat free diet had earlier been shown to reduce blood cholesterol,²³ and in 1952 Keys identified the relation with coronary heart disease.²⁴ Probably the first convincing evidence that exogenous cholesterol can enter human arterial tissue also came in 1952 when it was shown that oral feeding of tritium-labelled cholesterol to men resulted in demonstration of the label successively in the plasma and aortic atherosclerotic plaques.²⁵ In the next year Keys focused attention on international differences in blood cholesterol, dietary fat, and coronary heart disease by indicating the possibilities of prevention through reduction of dietary fat.²⁶ The plasma lipid elevating effect of saturated fats and the lowering effect of polyunsaturated fats were described²⁷ and the Keys²⁸ and Hegsted *et al*²⁹ developed equations to provide a basis of relating blood cholesterol concentrations to the proportions of saturated and polyunsaturated fat in the diet. Keys also indicated that a reduction of saturated fat in the diet would have a greater effect on serum cholesterol than a reduction of dietary cholesterol or an increase in dietary polyunsaturated fats. The Seven Countries Studies showed that there was a strong positive correlation (0.73) between calories derived from dietary saturated fat and the incidence of coronary heart disease but found no other significant correlations between any other dietary component and coronary heart disease.³⁰ It soon became evident that the effects on plasma lipids of polyunsaturated fats (including fish oils) was approximately related to their degree of unsaturation. Consequently, the polyunsaturated:saturated (P:S) ratio was widely used in relation to the prevalence of coronary heart disease between countries and within communities, resulting in the observation that the lower the P:S ratio the greater the incidence of coronary heart disease.

Where do we stand now?

There are those who are immutably of the opinion that the high incidence of coronary heart disease in different countries is a result of eating too much fat and that a reduction of dietary fat will restore a normal lifestyle and reduce the incidence of coronary heart disease. And there are those who regard diet as making a minor or even coincidental contribution to coronary heart disease and who therefore recommend no action. Neither view is supported invincibly by scientific evidence.

While there are now many certainties about the influence of dietary fat on coronary heart disease, there are also many uncertainties and unknowns.³¹

CERTAINTIES

These must include the fact that the relation between serum cholesterol and coronary heart disease is now firmly established: it is curvilinear and continuous.³² A most convincing fact is that three long term trials have been consistent in showing that diets with a P:S ratio of > 1.5 given to men with very high serum concentrations of cholesterol were associated with less coronary heart disease than in the control groups.³³⁻³⁵ Collateral and supportive evidence comes from the Lipid Research Clinics—Coronary Primary Prevention Trial (1984) in which cholestyramine was used to lower serum cholesterol in low density lipoprotein in men in the top 5% of the cholesterol distribution.³⁶

UNCERTAINTIES

No major prospective controlled trial of a low fat diet has, however, ever been conducted, generally because of logistic and economic limitations.³⁷ A low fat diet applied with strict surveillance, even when combined with reduction of cigarette smoking and blood pressure, in three trials of multiple risk intervention led to little or no reduction in coronary heart disease in those who were healthy initially³⁸⁻⁴⁰; and the relation between alteration of the diet in the North Karelia Prevention Project with changes in serum cholesterol and coronary heart disease incidence is unimpressive and has recently been seriously questioned.⁴¹ Calculations based on Keys' equation²⁸ concerning the degree of reduction of dietary saturated fat or increase in polyunsaturated fat necessary to produce a given reduction in serum cholesterol have not been substantiated by the experience of long term trials of dietary intervention, possibly because of poor compliance and the independent influence of endogenous synthesis of cholesterol-rich lipoproteins. All the long term dietary intervention trials,⁴² and some of the bigger drug trials,⁴³ have been associated with a relative increase in non-cardiovascular mortality or no change in total mortality or both.

There have been no planned prospective studies in people to relate a given dietary constituent (such as saturated fat) at baseline examination to the subsequent development of coronary heart disease. Retrospective analyses based on crude dietary recall methods and without subsequent monitoring of compliance or change and with incomplete documentation of coronary heart disease events have been attempted.⁴⁴ The findings are unconvincing and no incontrovertible data to incriminate dietary saturated fat have resulted from these studies. There is no consistently significant relation between the constituents of the average daily diet and serum lipoprotein concentrations within populations or in individuals.

Also there are important exceptions that do not fit with the commonly held epidemiological view of a positive relation between dietary fat and coronary heart disease. For example, Sweden reports dietary changes resembling those in the United States, but there is an increase in coronary heart disease mortality. Japan has had a nearly two fold increase in the consumption of saturated fat over the past 10 years and yet at the same time coronary heart disease mortality has decreased by 23%. Israel appears to have a reduced coronary heart disease mortality and increased saturated fat consumption. The incidence of coronary heart disease in Asian immigrants in London is exceptionally high and so is their P:S ratio.⁴⁵ As is always the case with coronary heart disease, all the observed trends cannot be explained by one factor alone.

The decrease in coronary heart disease incidence in the United States is difficult to interpret merely in dietary terms because the contribution of fat calories to total energy has remained around 41-42% since 1957; although the type of fat in the food has changed, with the amount of polyunsaturated fat, particularly linoleic acid, increasing. While surveys of food consumption show that there has been a reduction in the intake of milk, eggs, beef, pork, and vegetable fats, amounting to a decline of 17% in total fat consumed, the data are more consistent with a protective effect of polyunsaturated fats than of a harmful effect of saturated fats.

UNKNOWNNS

It is really remarkable that there are still so many. A crucial question, not yet resolved, is whether reduction of serum cholesterol by reduction of dietary saturated fats (or an increase in polyunsaturated fats) can lead to regression of coronary occlusive atheroma in man. Despite encouraging results from studies in relatively young primates exposed to diets rich in saturated fats and identification of regression of lesions when these diets are withdrawn, the small and mostly uncontrolled trials of maximum treatment (of various types) in high risk men point only to slowing of progression of lesions. More cannot yet be said and convincing evidence of regression will have to wait for more knowledge about spontaneous changes in atheroma, improved imaging techniques, and studies of advanced coronary occlusive lesions. But there is encouraging evidence that repeated plasmapheresis for familial hypercholesterolaemia may prolong life by a few years,⁴⁶ and that drug treatment that lowers raised cholesterol retards the development of lesions after coronary bypass surgery.⁴⁷

There is still a lack of knowledge about the relation of various dietary constituents, particularly dietary fatty acids, to thrombogenesis in man. This

is partly because the cholesterol hypothesis, which relates primarily to atherosclerosis and not coronary heart disease, has been too dominant for too long and partly because of the lack of attention given to the weakness of the relation between atherosclerosis and the events that surround the onset of clinical manifestations of coronary heart disease.⁴⁸

The protective role of polyunsaturated fats has yet to be explored fully. We have been able to show from successive studies over the past 10 years that coronary prone populations and patients with coronary heart disease have lower than expected concentrations of the essential fatty acid, linoleic acid, in adipose tissue and platelets.⁴⁹ There is also evidence to suggest that, at least in the short term, linoleic acid is capable of reducing blood pressure.⁵⁰ There is emergent experimental evidence as well that linoleic acid may be antiarrhythmic. Thus there is at least as strong a case to be made for a lack of dietary polyunsaturated fats as one of the principal influences in the development of coronary heart disease as for an excess of saturated fats. This proposition has tended to be obscured by the use of the P:S ratio. The fact that a low P:S ratio is associated with coronary heart disease has been generally ascribed to the excess of saturated fat and far less commonly to a lack of polyunsaturated fats. Interest in the polyunsaturated fats in relation to vascular disease has been focused during the past decade on arachidonic acid because of its key role in the production of prostanooids and leucotrienes, and little attention has been given to its precursor fatty acids, other unsaturated fatty acids, and influences that modulate their biological availability.

We are now in a new phase of interest in the relation of diet to coronary heart disease, not only because of the identification of the importance of low linoleic acid concentrations but also because it has now become clear that the effects of monoenoic fatty acids (particularly olive oil) on plasma lipids are not neutral, and also because fish oils may be protective. Olive oil lowers raised serum cholesterol and low density lipoprotein concentrations and its effects are as impressive, if not more so, than the effects of polyunsaturated oils such as corn oil.⁵¹ In contrast to these fatty acids, a diet rich in olive oil does not reduce high density lipoprotein cholesterol, for example. Oleic acid may have other advantages in so far as it has a lower proportion of transfatty acids than polyunsaturated fats.

As early as 1953, Sinclair identified the paucity of atherosclerosis and coronary heart disease among Eskimos.⁵² The theoretical benefits of marine oils on haemostatic variables and serum lipids are well documented and have been extensively reviewed this year in the *British Heart Journal*.⁵³ Saunders rightly

concluded that "The association between modest fish consumption and protection from coronary heart disease requires confirmation."

British Cardiac Society's role

The British Cardiac Society produced its first report in conjunction with the Royal College of Physicians in 1977.⁵⁴ This was the first time that the society made recommendations on dietary fat. The Second Working Party reported earlier this year.⁵⁵

These reports are consistent in their advice. They reaffirmed dietary guidelines for a prudent diet, set out in numerous international and national reports, and the recommendations of the Committee on Medical Aspects of Food Policy in 1984.⁵⁶ These are that there should be a reduction in calories from fat from the current level of above 40% to below 35%, a reduction of saturated fats down to <15% of total energy with partial substitution of polyunsaturated fats, and no excess (>500 mg) of dietary cholesterol. For those identified as being at increased risk of coronary heart disease the recommendations should be stricter⁵⁷ with no more than 30% of calories from fat and no more than 10% from saturated fats and an increase of polyunsaturated fats to raise the P:S ratio towards 1.0. In these high risk individuals <250 mg of cholesterol should be taken each day.

But we recognised that the evidence is not so strong that it is mandatory for government or the food industry to introduce such changes, and we eschewed the most radical and strident tones of the so-called National Heart Lung and Blood Institute consensus⁵⁸ and of its disciples. There are other health priorities, even within the field of vascular diseases, such as the elimination of cigarette smoking. It should also be clearly understood that the number of lives likely to be saved by the introduction of these dietary measures in adult life is small. Reduction of serum cholesterol by one decile is likely to benefit only about 8 per 1000 over a 10 year period⁵⁹ and no promise can be offered to any individual that he or she will be one of the eight.

Finally, the advantages or disadvantages of a low fat diet for growing children have recently been examined by the American Academy of Pediatrics and the view is taken that it seems prudent not to recommend changes in the current dietary patterns for the first two decades of life without first assessing the effects on growth, development, and nutritional adequacy.⁶⁰

Conclusion

Evidence of a relation between eating habits and

blood lipids, and between blood lipids and coronary heart disease, did not emerge until about 30–35 years ago. From then, the emphasis has been on the adverse effects of a diet rich in saturated fats and less attention has been given to the possibility that diets low in polyunsaturated fats might be equally harmful.

Not only is the case against dietary saturated fat not closed, but more basic and clinical research is needed into the effects of individual dietary fatty acids on the mechanisms leading to coronary heart disease and on its incidence.

Meanwhile, it is good sense to recommend diets that increase the ratio of polyunsaturated to saturated fat as a general measure and as a particular measure for those at high risk because of hypercholesterolaemia.

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