Regular Review

Dietary prevention of ischaemic heart disease—a policy for the '80s

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The two daughters of the Greek god of healing, Asklepios, represent contrasting attitudes to medical care: Panacea's name has been translated as "Cure-all" and Hygieia's as "Health." Neither approach alone could overcome the problem of ischaemic heart disease, which led to 156 000 deaths in England and Wales in 1976, proportionately more in Scotland, and much acute and chronic sickness. The valued contributions of coronary care units and of coronary artery surgery in individual management of patients have been estimated to reduce overall mortality from ischaemic heart disease by 4% and (on generous assumptions) 4-5% respectively.^{1 2} Medium-term trials indicate a place for drug treatment with beta-adrenergic blockers,³ and sulphinpyrazone⁴ and aspirin⁵ may possibly reduce the risk of reinfarction in patients with ischaemic heart disease. But the need for primary prevention is inescapable.

This review assesses the quality of the evidence that changes in plasma lipids induced by diet may reduce the risk of heart disease. In the past quarter-century few subjects have undergone such intense scrutiny by epidemiologists, clinicians, and laboratory scientists. In dealing with lipids and ischaemic heart disease I am isolating for discussion one aspect of a multifactorial disease.⁶ In practice any policy for prevention must be directed against all modifiable risk factors.

Mortality in men and women from ischaemic heart disease more than doubled in England and Wales between 1950 and 1974⁷; and the progressive rise recorded during this century is unlikely to be an artefact unless William Osler, Thomas Lewis, and James McKenzie habitually attributed coronary deaths to fatal indigestion. Such a rapid change establishes that environmental factors are important in the aetiology of ischaemic heart disease. Corroboration has come from studies of migrating population groups,⁸ such as the rising mortality from ischaemic heart disease in Japanese who migrated via Honolulu to California⁹ and in Yemenites who settled in Israel.

Three sets of evidence relate ischaemic heart disease to abnormal lipid metabolism: *association*, which is no longer seriously debated, evidence of *mechanisms* by which such associations could be causally linked, and *experimental data* which support the cause-and-effect interpretation (table).

Evidence of association

The clinical example of heterozygous familial hypercholesterolaemia is informative. This disorder, which confers a tenfold excess risk of ischaemic heart disease in affected men,^{10 11} is due to a mutant gene causing a single abnormality,

Lipoproteins as causal factors in IHD

EVIDENCE OF ASSOCIATION

- Clinical
- Case-control
- Interpopulation
- Predictive
- Angiographic

MECHANISMS OF ACTION

- LDL and cholesterol deposition
- LDL as mitogen
- HDL and cholesterol mobilisation

EXPERIMENTAL EVIDENCE

- Induction of atheroma in primates
- Regression of atheroma in primates including man
- Controlled trials of IHD prevention

a deficiency or defect of low-density lipoprotein receptors on the surface of peripheral cells.¹² As a result the plasma concentration of cholesterol is increased twofold or threefold. The arterial lesion of heterozygous familial hypercholesterolaemia is typical atherosclerosis.¹³

Epidemiological evidence abundantly confirms this clinical association. Two large interpopulation comparisons have shown strong positive correlations between plasma cholesterol concentrations and both mortality from ischaemic heart disease¹⁴ and the extent of coronary atherosclerosis.¹⁵ These variables correlate, in turn, with consumption of fat, notably saturated fat. Several within-population prospective studies have established that the risk of subsequent ischaemic heart disease increases directly with the plasma concentration of cholesterol. One of these⁶ followed 12 381 men in the United States for up to 10 years: when the influence of age was excluded by bivariate analysis there was a striking, progressive increase in the risk of ischaemic heart disease with each increment in cholesterol from the lowest to the highest. The strength and linearity of the association are reminiscent of the dose-response relationships of pharmacology; and the high cholesterol concentration antedates the heart disease by several years, the sequence to be expected of a cause-and-effect relationship.

Though measurement of plasma cholesterol concentrations is informative, far more can be learned from analysis of the different lipid-bearing particles in plasma, the lipoproteins, which have distinct physiological and pathological roles.¹⁶ Low-density lipoprotein (LDL) transports about 70% of the plasma cholesterol, whose concentration chiefly reflects LDL. Cells in peripheral tissues probably acquire most of their cholesterol content by uptake of LDL, a process largely mediated by receptors with a high affinity for this lipoprotein. High-density lipoprotein (HDL), bearing some 15% of the

plasma cholesterol, may well have the opposite physiological role,¹⁷ transporting cholesterol away from the periphery, carrying it (directly or indirectly) to the liver for excretion, and limiting cellular uptake of LDL. Very-low-density lipoproteins (VLDL) and chylomicrons bear most of the circulating fat or triglyceride, yielding up this energy-rich cargo in muscle and other tissues; in part, VLDL is then converted by the liver to LDL.

Average levels of lipoproteins are abnormal in patients with ischaemic heart disease; concentrations of LDL and VLDL lipids are raised, while the HDL cholesterol is low.¹⁸ Patients with both ischaemic heart disease and peripheral vascular disease present clinically at a significantly earlier age when they have raised concentrations of LDL or VLDL or both than when their lipoproteins are typical of the healthy population,¹⁸ suggesting that the course of these disorders is accelerated in the presence of hyperlipoproteinaemia. Longitudinal epidemiological studies have shown that the risk of heart disease rises with increasing plasma concentrations of LDL and with decreasing ones of HDL cholesterol.¹⁹ Raised triglyceride concentrations, reflecting VLDL, are also predictive of a high risk of heart disease²⁰; to some extent this relation may be due to the tendency of persons with hypertriglyceridaemia to have low concentrations of HDL.

When atherosclerosis is assessed by coronary arteriography, its severity correlates directly with plasma concentrations of cholesterol²¹; it is inversely related to the amounts of HDL cholesterol,²¹ especially in the HDL₂ subclass.²² In earlier studies of this type these relations were not always apparent; since atherosclerosis is related to non-lipoprotein risk factors such as smoking, hypertension, and age, failure to take these into account could explain the lack of lipoprotein correlations in some series.

The association between secondary hyperlipidaemias and ischaemic heart disease is less consistent. McMichael²³ has cited negative reports, including one on only eight patients with iatrogenic hypothyroidism. While positive reports may also be cited, the main reason for rejecting his interpretation of the negative findings is that since secondary hyperlipidaemia is of shorter duration than primary hyperlipidaemia its effects on the artery would be expected to be less severe.

Mechanisms

Hence there is abundant evidence of associations between lipoprotein abnormalities and ischaemic heart disease. An important contribution to our understanding of atherosclerotic disease comes from evidence indicating mechanisms by which these associations could be causal in nature. From Virchow's observations, and in ever-increasing detail since, raised atheromatous plaques have been shown to be rich in lipid, containing five to 10 times more cholesteryl ester than normal artery from aging persons, and 100-fold more than that from adolescents.²⁴ Lipids comprise 50-60% of raised plaques.²⁴ Yet little cholesterol is synthesised by human arterial cells^{25 26} (though some sterols may be produced). On the other hand, cholesterol, and the cholesterol-rich LDL, readily enter the arterial intima from plasma^{24 25 27 28}; the amount of LDL in an atheromatous artery (at necropsy²⁹ and in surgical specimens³⁰) correlates directly with its plasma concentration. The rate at which LDL transfers from plasma to intima (the "net flux") also correlates strongly with plasma concentrations of LDL and cholesterol.³¹ Hence there are grounds for believing that cholesterol, a major component of the plaque, is derived

largely from plasma LDL (though other lipoproteins may contribute), and that its rate of accumulation is proportional to plasma concentrations of LDL and cholesterol over a wide range. This is one mechanism by which hypercholesterolaemia could promote growth of plaques; the process may in fact be self-accelerating, for flux into plaques is about 10 times faster than into normal artery.³² Not only the accumulation of cholesterol but also the smooth muscle hyperplasia so characteristic of atheroma may be due in part to influx of LDL; this lipoprotein, or a subclass of it, is one of the substances which stimulate mitosis of cultured arterial smooth muscle.³³

On physiological grounds, and on the basis of these observations, it is reasonable to expect high concentrations of LDL to promote deposition of cholesterol in the artery and other tissues. The inverse relationship between concentrations of HDL and the risk of ischaemic heart disease would also be expected on present physiological concepts; in fact, the grounds are even stronger, for the size of the two tissue cholesterol pools has been shown to be inversely related to plasma concentrations of HDL cholesterol.³⁴

Experimental data

Since 1912 we have known that lesions resembling atherosclerosis develop in animals (most species used in laboratories) when plasma concentrations of cholesterol are sufficiently raised by a high dietary intake of cholesterol or saturated fat.^{35 36} The lesions are often not identical with human atherosclerosis, and deposition of lipid may occur in reticulo-endothelial tissues as well as in arteries. These differences are probably immaterial: extravascular lipid deposits (xanthomas) are also a feature of severe hyperlipidaemia in man, and modest differences between human and experimental atheroma are not surprising in view of the compressed time course of the latter and the appreciable differences in the lipoprotein pattern in the species studied. Experimental atheroma in primates slowly regresses when plasma lipid concentrations are reduced,^{37 38} a potent argument for a causal role of hyperlipidaemia. This has been shown in several studies; not only is there histological regression but the amounts of lipid, calcium, and collagen also fall. Regression occurs even when the plasma concentration of cholesterol is reduced to 5 mmol/l (193 mg/100 ml), not an unusually low figure in man. There is impressive but as yet incomplete evidence that in man, too, reduction in lipid concentrations is followed by regression of atheroma.³⁸⁻⁴⁰

Design criticisms may be levelled at all the numerous published trials of the effect of reducing plasma concentrations of cholesterol on the frequency of ischaemic heart disease; those which yielded negative results and those indicating benefit are equally challengeable.⁴¹ Intervention and control groups were inadequately matched in some positive trials; advanced age at recruitment and inadequate reduction of cholesterol concentrations are valid criticisms of some negative ones. Nevertheless, three differently designed early trials of primary prevention of ischaemic heart disease or "all cardiovascular events" by diet were consistent in indicating a beneficial trend.⁴²⁻⁴⁴ Three recent drug trials have also given positive results: the clofibrate trial which showed reduced morbidity, but not mortality, was the first to use adequate sample size but was limited by a meagre 9% fall in plasma cholesterol⁴⁵; two smaller trials which recorded benefit were characterised by substantial reduction in cholesterol level.^{46 47}

When 14 reported trials are ranked by the extent of the reduction achieved in concentrations of cholesterol, a tendency is seen for their outcome to relate to this rank order. In some negative trials the mean fall in cholesterol concentrations was as little as 6%; a feature of most positive trials was the substantial reduction in the plasma cholesterol, up to 21%. Trials in which much of the intervention group remains hyperlipidaemic are inadequate to test the lipid theory.

Concept of normal and optimal lipid concentrations

Defining optimal lipid concentrations, and hence hyperlipidaemia, is a difficult but not insuperable problem. The usual statistical devices for deriving ranges from a population sample, valuable in defining normal amounts of sodium or haemoglobin, are inapplicable, for mean concentrations of cholesterol vary over an almost twofold range in healthy populations on different diets.⁴⁸ Cross-over feeding experiments^{16 49} and studies of migrant groups⁹ have established that these differences are of environmental origin. Other sources are available of normative data for concentrations of cholesterol and LDL—epidemiological studies of populations and population subgroups at low risk of ischaemic heart disease and lipid concentrations producing regression of experimental atheroma in primates—and from the kinetics of lipoprotein transfer into the human arterial intima the plasma concentration of LDL can be predicted which would be associated with minimal net transfer of this lipoprotein into the vessel wall. A multidisciplinary workshop⁴⁸ recently showed remarkable unanimity in suggesting optimal mean concentrations of cholesterol in adults of about 4.5 mmol/l (174 mg/100 ml) with an upper limit of 5.5 mmol/l (212 mg/100 ml).

In defining lower limits for an optimal range there are many sources of information.⁴⁸ The neonate's plasma concentration of cholesterol of about 2 mmol/l (77 mg/100 ml)⁵⁰ meets the need of growth and rapid synthesis of cell membranes; in genetic hypolipidaemias leading to abnormalities of the cell membrane concentrations are even lower.⁵¹ Cell culture studies suggest that the affinity of lipoprotein receptors for LDL is so great that an adequate supply of cholesterol may be obtained when the concentration of LDL protein in the tissue fluid is as little as 13 µg/ml⁵²; this corresponds to a plasma concentration of cholesterol of the order of 2.5 mmol/l (97 mg/100 ml).

Death rates in groups with very low cholesterol concentrations do not generally suggest that such levels increase the risk of non-cardiovascular disease, though more detailed study is needed. In the very large United States Co-operative Pooling Project there was no excess of total mortality or cancer deaths in the lowest quintile for plasma cholesterol.⁴⁸ Suggestions have been made of an excess of carcinoma of the colon in a low-cholesterol subgroup of a British population,⁵³ and of non-cardiovascular deaths in a small series of Maoris⁵⁴ (some of whom had cholesterol concentrations as low as 2.5 mmol/l); but, since statistical significance of these findings disappears⁵⁵ or decreases⁵⁴ when deaths in the first two years of follow-up are excluded, the low cholesterol concentrations were probably a consequence of disease rather than an antecedent. Most cogently, in those Mediterranean countries in which mean concentrations of cholesterol conform with the suggested optimal range, and in which fat provides 25-30% of dietary energy (it is 42% in Britain), total mortality and mortality from cancer are both lower than in the United States, England and Wales, and Scotland.⁵⁶

A policy for the '80s

If it is accepted that raised concentrations of LDL cholesterol are one of the causes of ischaemic heart disease, what action is merited? Continuing research certainly, but the size of the problem of heart disease demands immediate action to reduce risk if this is both practicable and safe.

Plasma concentrations of cholesterol and LDL are influenced by many environmental factors, including several nutrients; genetic determinants appear to play a part, though estimates of its size vary from negligible to 40% of the variance of plasma cholesterol.^{57 58} While the amount and type of dietary fat are the most powerful and best studied determinants of plasma concentrations of cholesterol,^{14 16} dietary recommendations including multiple small changes in food habits seem to provide the best chance of attaining optimum mean concentrations of cholesterol and LDL⁴⁸: reduced energy intake in the obese; reduced total fat intake to 28-30% of food energy, with roughly equal proportions of saturated, monounsaturated, and polyunsaturated fatty acids; reduced cholesterol intake; increased fibre (pectins, oat bran); and an increased ratio of vegetable to animal protein. These conclusions are largely based on comparisons of national populations and of small closed population groups with varying dietary habits and on feeding experiments. At least two within-population studies have shown moderate correlations between fat intake (and in one instance fibre, too) and plasma cholesterol.^{59 60} Morris, Marr, and Clayton have studied the relation between the dietary pattern of fatty acids and subsequent experience of ischaemic heart disease. In the first report of their prospective study the association of the ratio of polyunsaturated to saturated fatty acids in the diet with ischaemic heart disease incidence was significant ($p < 0.05$) at five years' follow-up, but not overall.^{61 62} They now tell me that accumulation of further cases has resulted in a significant association ($p < 0.03$) over the whole period of observation.

The evidence that modest changes in energy, fat, fibre, and cholesterol intake will reduce mortality from ischaemic heart disease is persuasive but incomplete; the case must not be overstated. The rigorous proof demanded by Ahrens in a recent review⁶³ may never be attained, and the criterion of quality of evidence must be balanced against the gravity of the public health problems. Ahrens has also criticised the dietary proposals on the grounds that inadequate experience has been gained with them. To those who would intervene against ischaemic heart disease, the experience of millions living in Mediterranean countries on diets similar to the proposed pattern is both adequate and reassuring. Acceptance of the demand for rigorous proof of benefit would have effects on the practice of preventive medicine which few would endorse: we should cease treating obesity, allow the cigarette habit to go unchecked, and stop advocating physical exercise. We lack controlled trials of benefit from these measures, and are unlikely to obtain such evidence.

Recent British statistics on deaths from cardiovascular disease are no advertisement for conservatism in preventive medicine.⁶⁴ The fall in mortality from ischaemic heart disease in the United States, Australia, Belgium, Finland, Canada, and the Netherlands began some years ago and is now substantial.⁶⁵ Rates in Britain are, at best, flattening. Our present rates of mortality from heart disease may be seen as the side effect of inactivity.

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