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SYMPOSIUM ON 'DIETS IN TRANSITION: HUMAN HEALTH AND ANIMAL PRODUCTION'

Nutrition, coronary heart disease and preventive medicine

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Since it is some 14 years since the appearance of the first report of the Committee on Medical Aspects of Food Policy (Department of Health and Social Security, 1974), it is appropriate that the present Symposium include a review of progress that has been made toward a reduction of coronary heart disease in this country by nutritional means. During that period three other major sets of recommendations have been put forward with the same goal. A comparison of age-standardized mortality rates for coronary heart disease in Western countries, based on World Health Organization statistics from 1980–82 offers little reassurance to those responsible for public health in the UK (Pyorala, 1987). Contrasting with their position in the rank order 10 years previously, the highest mortality rates from coronary heart disease in the world have come to be those in Scotland and Northern Ireland. These rates are no less than eight to ten times greater than those found in another industrialized country, Japan. In Japan, many of the classical risk factors for coronary heart disease (cigarette smoking, hypertension) are no less prevalent than in the UK and may indeed be even more common.

Since the epidemiological studies of Keys (1980), we have recognized that environmental factors, and in particular nutrition, are major determinants of international differences in coronary disease rates. Keys' (1980) major conclusion was that such differences are largely mediated by differences in serum cholesterol distribution in different countries, this approximate aetiological factor being determined in turn by intake of saturated fatty acids. A particularly close-fit was obtained between coronary mortality and an index taking into account intakes of saturated and polyunsaturated fatty acids and of cholesterol (Keys, 1980). That ethnic differences in serum cholesterol are largely mediated by diet was established more than 25 years ago in South Africa (Antonis & Bersohn, 1962) in an institutional cross-over feeding experiment.

This does not exclude the possibility that a minority of international differences in risk-factor levels may have a genetic basis. International differences exist in the frequency of polymorphisms for two apolipoproteins, apo E and apo B, that may be associated with differences in lipoprotein metabolism. It is conceivable that an increased prevalence of the E₄ phenotype of apolipoprotein E contributes to a small extent to the high mean serum cholesterol level in adults in Finland. Apolipoprotein B is the structural protein of three of the major lipoprotein classes of human plasma, low-density (LDL),

intermediate-density and very-low-density lipoproteins. Genetic polymorphisms of this apoprotein have been described, one of which is demonstrated by cleavage of DNA with the Xba1 restriction enzyme. Houlston *et al.* (1988) have shown that the fractional catabolism of LDL is significantly less in subjects who are homozygous for the X2 polymorphic form. My colleague Dr Richard Houlston has shown (unpublished results), in another large population study, that a 4% variation in serum cholesterol levels is associated with this polymorphism. The molecular basis of this effect probably stems from small differences in the binding affinity of the polymorphic forms of apo B for the LDL receptor that mediates most of the catabolism of LDL. But it must be emphasized that the magnitude of these genetic effects appears small compared with that of the effects of dietary differences on LDL-cholesterol concentration.

Secular changes in coronary heart mortality are informative in generating hypotheses as to environmental causes of coronary heart disease, and in describing the effectiveness of public health measures directed to such causes. Since 1968 coronary heart disease mortality has fallen by about 40% in the USA (Havlik & Feinleib, 1979) and by almost half in Australia. This trend is shared by many developed countries. In the USA and Finland it has been established that this decrease is associated with a fall in the incidence of coronary heart disease and not only in case fatality. In England and Wales and in Scotland there is the suggestion of a small decrease in coronary heart disease mortality since about 1977 (Office of Population Censuses and Surveys, 1984). Total coronary deaths occurring between the ages of 30 and 59 years have shown a relatively marked decline during this period, but the majority of UK deaths, occurring in older people, have shown little trend.

No single change in health-related behaviour has been identified that would uniquely explain these decreases in coronary heart disease deaths. The contribution of risk-factor change to change in coronary heart disease mortality has been studied in some depth in the USA. Food disappearance findings attest a marked and prolonged steady increase in the use of polyunsaturated (*n*-6) fats, and a more recent decrease in dietary cholesterol, also substantial (Havlik & Feinleib, 1979). Surprisingly the most important single recommendation of every expert committee, reduction in the use of saturated fats, has not been complied with by the American public. Monounsaturated fatty acid intake has possibly increased slightly. Recently it has become possible to answer the question, to what extent has this change in food consumption altered the proximate risk factor, serum cholesterol? Comparison of Health and Nutrition Education Surveys (HANES), 20 years apart, indicate an average fall for serum cholesterol in the USA of about 4% (National Center for Health Statistics - NHLBI Collaborative Lipid Group, 1987). It may be predicted from this change in serum cholesterol that between one-fifth and one-third of the decline in coronary heart disease mortality in the USA may be explained by nutritional change leading to a fall in serum cholesterol levels. To explain the rest of the decline in mortality, changes in the detection and management of high blood pressure, in cigarette use, in exercise habits, in acute coronary care and in coronary vascular surgery may all contribute.

In the UK, as mentioned, such a downturn in coronary heart disease as may have occurred started later and has to date been substantially smaller than that in many other industrialized countries. In addition, Marmot (1987) has demonstrated that the decrease has been smaller, and has commenced from a higher level, in manual workers than in non-manual workers. Whatever the bases for this downturn, they have been least operative in the segment of the population that most requires them. Nutritional trends in the UK are reviewed by Dr David Buss in the present Symposium. A little information is available on trends in serum cholesterol in the UK. In our factory survey conducted in

1972–73, mean serum cholesterol in the age range 20–69 years was 5.8 mmol/l in males and 5.9 mmol/l in females in London. The far larger British Regional Heart Study, conducted at the beginning of the present decade in England, Scotland and Wales indicated a mean serum cholesterol of 6.3 mmol/l in men aged 40–59 years (Thelle *et al.* 1983). Most recently Mann *et al.* (1988) have examined a population based on general practices of 12000 men and women in England and Scotland, samples being collected in 1985–86. Mean serum cholesterol in the age range 25–59 years was 5.9 mmol/l in men and 5.8 mmol/l in women; in the subset aged 40–59 years, mean serum cholesterol was 6.1 mmol/l in both sexes. The methods used in the first and last of these studies were referable to the same Abell-Kendall reference method. Nevertheless the sampling frames in the three studies are slightly different. For this reason interpretation of these values must be somewhat cautious. Nevertheless they do not indicate any conspicuous decrease in mean serum cholesterol in the UK between the early 1970s and the present time.

Mechanisms linking nutrient intake and coronary heart disease

By far the most extensive body of information relates to the triangular relation between intake of dietary lipids, serum cholesterol concentration and coronary heart disease rates (Keys, 1980; Pyorala, 1987). Nevertheless serum cholesterol, or to be more precise LDL-cholesterol, should not be regarded as the only proximate mechanism by which diet influences coronary heart disease risk. Intake of saturated and, in the opposite direction, polyunsaturated fatty acids also modify blood pressure, another well-defined coronary heart disease risk factor. Further, intake of saturated fatty acids, and (in the opposite direction) polyunsaturated fatty acids of the *n*-6 *n*-3 series modify platelet function and thrombotic tendency.

The serum cholesterol–coronary heart disease incidence relation is a very striking, consistent and powerful one. Repeatedly demonstrated, it is most remarkably attested by a longitudinal study on 361 000 middle-aged men screened for entry into the Multiple Risk Factor Intervention Trial (MRFIT) (Martin *et al.* 1986). The twenty quantities of serum cholesterol range from about 4 to 8 mmol/l. Within this wide range, there is no evident threshold level of serum cholesterol below which the positive association between serum cholesterol and coronary heart disease risk disappears. The increase in risk, associated with the increase in serum cholesterol, is certainly conspicuous from a level of 5 mmol/l, and it appears to become substantially steeper as levels exceed 6.5 mmol/l. These observations have considerable bearing on our definition of what comprises a desirable level of serum cholesterol, and on the selection of action limits defining therapeutic approaches to hypercholesterolaemia. The cholesterol–coronary heart disease relation in longitudinal studies is attenuated by errors consequent on the fact that the cholesterol level is measured only once in each person. In fact the slope of the relation is steeper than expressed in longitudinal studies of this type. This does not negate the importance of other mechanisms linking coronary heart disease with nutrition, namely the independent risk factors of obesity, hypertension and abnormalities of the coagulation system. In addition, and independently of serum cholesterol concentration, longitudinal studies of the fatty acid composition of plasma lipids and adipose tissue have affirmed an inverse predictive relation between the percentage of linoleic acid and coronary heart disease rates (Miettinen *et al.* 1982; Wood *et al.* 1987); no significant trend was discernible for the percentage of oleic acid, while a statistically non-significant inverse relation was present between the *n*-3 fatty acid eicosapentaenoic acid in adipose tissue and coronary heart disease.

Prevalence of hypercholesterolaemia in the UK

In the discussion of the longitudinal study of MRFIT screenees (Martin *et al.* 1986) it was concluded that risk of coronary heart disease is increased when serum cholesterol concentration exceeds 5 mmol/l, and that risk increases with a steeper slope as levels exceed 6.5 mmol/l. Such cut-off points are remarkably prevalent in the UK. In our study of men and women aged 25–59 years in England and Scotland (Mann *et al.* 1988) 65% had cholesterol levels exceeding 5.2 mmol/l and 25% had levels exceeding 6.5 mmol/l. Levels exceeding 8 mmol/l, which are commonly due to genetic disorders of lipoprotein metabolism, occurred in 4% of this population sample.

Several groups of experts have in the past few years examined the concept of desirable levels of serum cholesterol, with a view to defining action limits for therapy (NIH Consensus Development Panel, 1985; Assmann *et al.* 1987; National Cholesterol Education Program Expert Panel, 1988). The European Atherosclerosis Society statement on prevention of coronary heart disease (Assmann *et al.* 1987) has proposed that serum cholesterol levels exceeding 5.2 mmol/l deserve consideration for treatment, such treatment comprising dietary counselling and advice concerning many associated risk factors. Levels exceeding 6.5 mmol/l require treatment, also by nutritional means alone in the first instance, in a clinical setting. The goal of therapy in these and other recent recommendations is to achieve a cholesterol level of 5.2 mmol/l or less.

The effect of various sets of dietary recommendations on mean serum cholesterol levels in the population can be calculated from well-known regression equations such as that of Keys (1980). Using such estimates, the effect of various dietary recommendations on the prevalence of cholesterol levels exceeding either of the above cut-off points can be estimated. Even full compliance by the adult population to the dietary changes recommended, for example by the American Heart Association would still leave a large number of people with cholesterol levels exceeding 6.5 mmol/l. More realistically, moderate dietary change by most of the population would have a smaller effect and hyperlipidaemia would be expected to persist in quite considerable numbers of people. To minimize the prevalence of lipid-related risk factors, it follows that a minimalist strategy will not be adequate to make serious inroads on the present extraordinary high prevalence of risk-promoting levels of serum cholesterol. Thus diligent public education over a large number of years is going to prove necessary if an adequate degree of dietary re-education is to be established.

The feasibility of substantial change in lipoprotein-mediated risk of coronary heart diseases by nutritional change is well established. In an institutional feeding experiment with normal subjects, we have shown that the effect of dietary lipid modification is additive with that of supplementation by soluble fibre, and that used together, these dietary changes will lead to a fall of no less than 34% in LDL-cholesterol (Lewis *et al.* 1981). In an ambulant hyperlipidaemic population followed at our lipid clinic, this diet produced a 22% reduction in serum cholesterol and a 25% reduction in LDL-cholesterol. It is important that a diet for widespread use should differ in as few respects as possible from the present food preferences of the population. For this end, my colleagues Dr G. Watts and Dr J. Quiney and I have examined, in ambulant patients attending the lipid clinic, the effect of consuming a lipid-lowering diet including moderate quantities of very lean meat. Baseline serum cholesterol averaged 8 mmol/l and triglyceride 3.5 mmol/l. The intervention diet led to an 18% fall in serum cholesterol and a fall of almost 24% in LDL-cholesterol.

In designing an optimal pattern of diet for the population, and also for the hyperlipidaemic patient in clinical care, certain controversies remain and further

rigorous feeding experiments are desirable. In some recent publications the importance of dietary cholesterol has been questioned. Nevertheless, dietary cholesterol and serum cholesterol are correlated. One recent feeding experiment indicated that moderate changes in dietary cholesterol do indeed influence serum and LDL-cholesterol levels, and that this effect remains evident even when dietary fat content is modified (Zanni *et al.* 1987). Over and above the effect of dietary cholesterol on serum cholesterol (i.e. on LDL-cholesterol chiefly), there appears to be a relatively potent effect of dietary cholesterol on one of the atherogenic fractions of serum cholesterol, i.e. that transported in intermediate lipoproteins or 'remnant particles'. Variation in these particles is not detected by changes in total serum cholesterol concentration.

Further, it is possibly misleading to look at mean changes in serum cholesterol in response to dietary cholesterol, for there is a very wide individual variation in the magnitude of the serum cholesterol response to this nutritional change. This chiefly reflects variation in the ability to repress cholesterol synthesis in response to a high-cholesterol diet. Some individuals, as has emerged from a collaborative study by Dr M. B. Katan and ourselves, increase the rate of production of LDL-apolipoprotein B in response to an increase in dietary cholesterol, while others show little such increase. Thus there is a variation in the effectiveness of the homeostatic response to dietary cholesterol. If one is designing a diet of maximum effectiveness in reducing the risk of coronary heart disease, it is unwise to ignore the role of dietary cholesterol; the mean response is not inconsiderable, and some individuals show a very pronounced response.

The optimal polyunsaturated fatty acid:saturated fatty acid intake is also worthy of discussion. Similar changes in serum cholesterol can be achieved by a marked reduction in saturated fatty acid intake, with substitution by carbohydrate, and by a more modest reduction in saturated fatty acid intake with partial substitution by polyunsaturated fatty acids of the *n*-6 series. In one controlled feeding experiment a considerably larger change in serum cholesterol was produced by the latter pattern of dietary change than by the former (Brussaard *et al.* 1982). To achieve maximum change in serum cholesterol level while conserving conventional patterns of food selection, it appears that a modest increase in polyunsaturated fatty acid intake should accompany substantial reduction in saturated fatty acid intake.

The status of monounsaturated fatty acids in the recommended diet is being re-examined at the present time. Epidemiologically, Eastern Mediterranean populations with a low intake of saturated fat and a substantial intake of olive oil have relatively low mortality rates from coronary heart disease (Keys, 1980). Some recent feeding experiments have questioned the view that the serum-cholesterol-lowering effect of *n*6 polyunsaturated fatty acids is greater than that of monounsaturated fatty acids, when substituted for saturated fatty acids. However, the conventional view is supported by careful feeding experiments in substantial numbers of individuals, and until rigorous experiments have established the appropriateness of diets rich in monounsaturated fatty acids it seems inappropriate to modify conventional dietary recommendations. It should be pointed out, however, that reduction in the use of fats of animal origin, necessary to decrease intake of saturated fatty acids, will also reduce intake of oleic acid. Introduction of modest quantities of olive oil into a lipid-lowering diet would therefore leave unchanged the total intake of monounsaturated fatty acid.

The status of polyunsaturated fatty acids of the *n*-3 series is being actively examined at the present time. There is no doubt that dietary supplementation with marine oils potently reduces serum triglyceride levels. At very high intakes (20–30 g/d) such diets can also lower concentrations of LDL-cholesterol. However, at more moderate intakes, particularly in hypertriglyceridaemic individuals, a fall in plasma triglyceride is

accompanied by an increase in LDL concentration (Sullivan *et al.* 1986). The role of LDL in increasing the risk of coronary heart disease is undoubted, while that of triglyceride-rich lipoproteins is less well defined at the present time. The net effect of *n*-3 fatty acids on lipoprotein-mediated risk of coronary heart disease is therefore uncertain. Long-term trials in man have yet to be performed; and there is also a dearth of long-term studies on the toxicology of diets enriched in marine oils. When such oils are used in clinical practice for the treatment of hyperlipidaemia it is strongly recommended that the patients be monitored for untoward changes in LDL concentration. There is at present inadequate evidence to justify their widespread use in the population, where of course the potential for such effects could not be monitored. A fairly consistent epidemiological finding has been the inverse relation between fish consumption and coronary heart disease mortality. Whether this relation is mediated by differences in intake of *n*-3 fatty acids remains to be shown. It appears justified to recommend an increased use of fish in diets designed to minimize risk of coronary heart disease, but judgement must be deferred as to the value otherwise of a large change in intake of *n*-3 fatty acids.

Finally, a brief mention has been made of qualitative changes in lipoproteins that may modify the rate of development of atherosclerosis, and of a possible role of nutrition in lessening such changes. A characteristic event in atherosclerosis is the accumulation of cholesterol, derived from plasma, in macrophages of the vessel wall, these becoming converted to foam cells. Studies *in vitro* have failed to show that macrophages accumulate large quantities of lipid when incubated in the presence of normal plasma LDL. Interestingly, however, LDL that has undergone lipid peroxidation is readily taken up by the macrophage, and macrophage conversion to foam cells is well documented under such circumstances. Shaikh *et al.* (1988), working with samples of artery removed during the course of reconstructive vascular surgery, have shown that modified LDL, derived from plasma LDL, can be demonstrated in the arterial wall. It will prove of the greatest interest to ascertain whether natural lipid-soluble antioxidants in the diet are capable of interfering with peroxidation of lipoproteins in the vessel wall, hence preventing a process that appears central to the development of the atherosclerotic plaque.

The plasma concentration of high-density-lipoprotein (HDL)-cholesterol shows a clear inverse relation with the incidence of coronary heart disease. Nevertheless there is no information from intervention studies in man to indicate that this association represents cause and effect, or that measures that increase concentrations of HDL-cholesterol will decrease the risk of coronary heart disease. Therefore it appears premature to take into account effects of nutrient intake on HDL concentration, when designing diets to minimize the risk of coronary heart disease.

Conclusions

Since coronary heart disease mortality is declining in a number of countries in which mortality rates have been gravely high, the present approach to preventive strategy appears worth continuing. This involves patient efforts at public education directed to maximize compliance with recommendations for dietary change. Similarly, there are grounds for continuing to encourage the food industry to make available products that conform with these dietary guidelines. Other aspects of health-related behaviour require equal attention.

The high prevalence of seriously elevated levels of serum cholesterol in the population justify the parallel strategy of identification of individuals at particular risk because of the presence of such levels, with a view to their treatment by individual clinical care. This is by no means an alternative strategy to public education. Since the individual and

population strategies are interdependent, the former requires to be introduced in parallel with the population strategy. By so doing, a proportion of the population requiring individual care will be much reduced by implementation of measures directed to the population as a whole (Lewis *et al.* 1986). By simultaneously directing efforts to the population as a whole, and to the case-finding and management of people at particularly high risk, the prospect of substantially reducing the present high mortality from coronary heart disease is excellent.

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