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SYMPOSIUM ON
'DIET AS A RISK FACTOR IN CARDIOVASCULAR DISEASE'

Diet in the epidemiology of coronary heart disease

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The term coronary heart disease (CHD) includes three distinct but overlapping syndromes in middle-age: myocardial infarction, angina pectoris, and sudden death. Virtually all CHD occurs on the basis of severe atherosclerosis, although not every person with severe atherosclerosis necessarily suffers from CHD. We are thus concerned to understand both the aetiology and pathogenesis of atherosclerosis, and the pathogenesis of CHD, which can be regarded as a complication of severe atherosclerosis.

Fig. 1 depicts a hypothesis concerning CHD and in the main it presents the 'nutritional-metabolic' concept of atherosclerosis and CHD (Stamler, 1967). In this

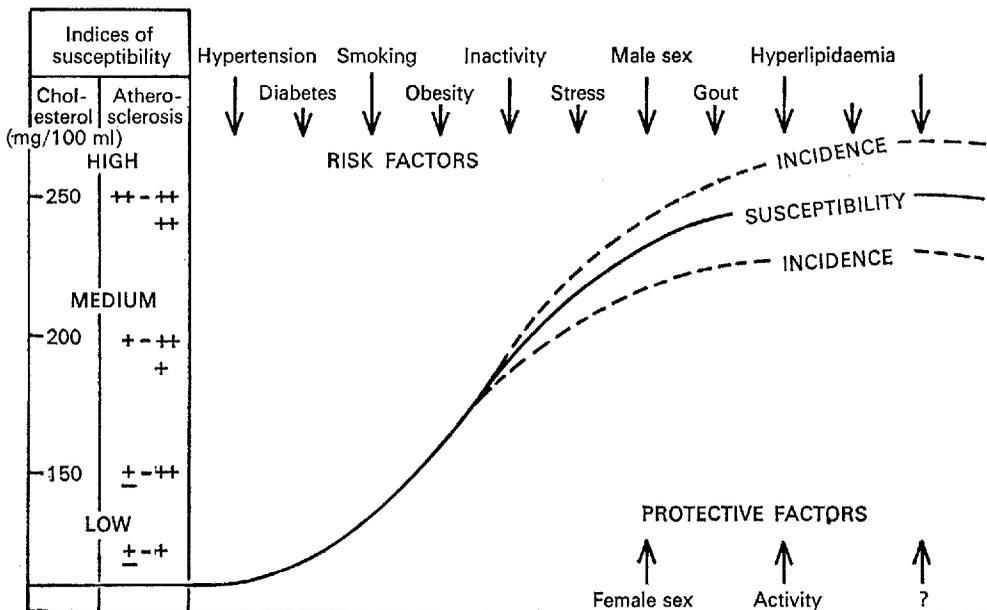


Fig. 1. Community susceptibility and incidence of coronary heart disease.

diagram, the curve represents increasing community susceptibility to CHD, and the dotted lines represent the variable incidence of CHD. On the left-hand side of the diagram are shown two main indices of community susceptibility to CHD, namely coronary atherosclerosis and the blood cholesterol concentration. Both of these indices are for the greater part nutritionally determined. The prevalence of atherosclerosis in the coronary arteries is determined at necropsy and the mean blood cholesterol concentration is that seen in apparently healthy middle-aged males in the community. A variety of factors which might increase or diminish the risk of CHD in susceptible communities are depicted above and below. These 'risk' factors and 'protective' factors may be effective by virtue of their action on atherosclerosis or on the blood cholesterol concentration or on both of these indices, or they may be effective through other mechanisms, for example myocardial function, fibrinolytic activity, platelet or leucocyte function, or blood pressure.

Atherosclerosis, CHD and diet

There are striking international and regional variations in the occurrence of severe coronary atherosclerosis and this has been shown in many studies, the most comprehensive being the International Atherosclerosis Project (IAP) (McGill, 1968). Communities with little or no severe atherosclerosis have virtually no CHD, and an increase in the extent of coronary atherosclerosis is accompanied by an increase in the susceptibility to CHD. It is also evident from international studies that communities with similar necropsy patterns of coronary atherosclerosis may have very different prevalence and incidence levels of CHD. The hypothesis allows for this situation by emphasizing that coronary atherosclerosis is an index of susceptibility and not of incidence.

Comparison of published information on diet with the findings in the IAP indicates that the severity of atherosclerosis is closely associated with the serum cholesterol concentration and with the proportion of total energy derived from fat. There is a vast literature of clinical, pathological, and animal experimental work to support the epidemiological finding that dietary factors are fundamental to the development of severe atherosclerosis. In particular, severe atherosclerosis would appear to be closely associated with the dietary pattern seen in the affluent countries of the world, characterized by a high intake of energy, total fat, saturated fat, and cholesterol.

Blood cholesterol, CHD, and diet

In the economically advanced countries of the world, the blood cholesterol concentration in males rises progressively with age until the sixth decade and then declines moderately. From prospective community studies in many countries we know that these increasing levels of blood cholesterol are associated with a progressively increasing risk of CHD, even from concentrations which many would regard as absolutely normal, such as 200 mg/100 ml. The mean total cholesterol concentration is perhaps the most powerful predictor of individual risk.

We also know that what is true within the coronary-prone communities holds

good when international comparisons are made. Communities with low mean concentrations of blood cholesterol in middle-aged men (e.g. 150–180 mg/100 ml) are virtually free from severe atherosclerosis and from CHD. At moderate concentrations (200–220 mg/100 ml) a community has a moderate degree of susceptibility and at higher concentrations (250 mg/100 ml) or more the susceptibility to CHD is marked.

What determines the community level of blood cholesterol? The main determinant of the mean blood cholesterol level in a community is dietary and relates to the quantity and proportion of the total energy supplied by saturated fats and polyunsaturated fats. In man, the blood cholesterol concentration can be altered by changes in the amount and kind of fat in the diet, and the average response in the blood is predictable from information about the dietary fatty acids. Saturated fatty acids in the diet raise the blood cholesterol concentration whereas polyunsaturated fatty acids have the opposite but weaker effect. The cholesterol-raising effect of saturated fatty acids is practically restricted to those with twelve to sixteen carbon atoms, thus incriminating, in particular, lauric, myristic, and palmitic acids (Keys, 1969). Stearic acid and other saturated fatty acids with more than eighteen carbon atoms in the chain appear to have little effect on the blood cholesterol concentration, although this does not necessarily render them free from other effects. Recent animal experimental studies suggest that, in the presence of a high cholesterol intake, certain long-chain saturated fatty acids, principally arachidic and behenic, may be markedly atherogenic without raising the blood cholesterol concentration (Kritchevsky, Tepper, Vesselinovitch & Wissler, 1971). There is also experimental evidence in man indicating that stearic acid and the saturated fatty acids with fewer than twelve carbon atoms (mainly caprylic and capric) produce significant rises in blood triglyceride concentrations (Grande, Anderson & Keys, 1972).

Studies in which dietary cholesterol has been restricted suggest that the reduction in blood cholesterol concentration obtained by lowering only the dietary cholesterol intake is limited but it is quantitatively important and in some individuals it may be critical. Manifestly, there are factors, other than fatty acids and cholesterol, which play a role in determining both the community and individual concentrations of blood cholesterol, and these probably include the fibre content of the diet (Trowell, 1972).

Risk factors in CHD

Both of the main indices of susceptibility should be regarded as essential prerequisites for CHD, but it is a well-established epidemiological principle that an essential factor may not be a sufficient cause in itself. Where CHD is endemic there are certain characteristics present in the population or in their environment which can considerably affect the incidence of CHD. These include hypertension, cigarette smoking, and diabetes mellitus, as well as obesity, physical inactivity, raised uric acid concentrations, emotional stress, and soft drinking-water. The presence of these factors can produce significantly different incidences of CHD in communities with the same degree of basic susceptibility. As the theme of this symposium con-

cerns diet as a risk factor in cardiovascular disease, we shall briefly examine those additional risk factors which may have a nutritional basis.

Blood pressure. In susceptible communities, high blood pressure is almost as powerful a predictor of CHD as the blood cholesterol concentration. It should be emphasized that it is only in communities already susceptible to CHD that hypertension effectively increases the risk of CHD (Shaper, 1972*a,b*).

Notwithstanding the introspective preoccupation of our society with 'stress' as being responsible for high blood pressure and CHD, we should be reminded that there is a nutritional hypothesis for essential hypertension. Considerable epidemiological and experimental evidence suggests that the dietary sodium intake may play a critical role in determining the community pattern of blood pressure, although genetic factors are apparently of considerable importance in determining the individual response to sodium intake (Dahl & Love, 1954; Dahl, 1967). There is also evidence suggesting that a low-calcium intake might accentuate the hypertension-producing effects of sodium (Langford, Watson & Douglas, 1968). In countries, like the UK, with a wide range of water hardness, the dietary sodium and calcium relationship may be of considerable importance.

Obesity. This appears to be of little direct importance as a risk factor in CHD (Keys, 1970). It almost certainly matters more by which dietary pathway you become fat, than whether you become fat. Becoming fat in our society has implications for lipid metabolism which do not arise in societies becoming fat on high-carbohydrate, low-fat diets.

Diabetes mellitus. It is generally held that diabetics are more prone to atherosclerosis, and especially to CHD and peripheral vascular disease. Epidemiological studies indicate that there is a consistent relation between the prevalence of diabetes and an excess of energy intake in relation to energy expenditure, regardless of the source of the energy (Jarrett, 1970). Dietary factors thus play a further (but indirect) role in the development of CHD through their effect on the prevalence of diabetes mellitus. Again, it should be emphasized that it is only in communities already susceptible to CHD that diabetes mellitus effectively increases the risk of CHD.

Triglyceridaemia. It has been suggested that triglyceride concentrations are better predictors of subsequent CHD than cholesterol concentrations. From a study in Stockholm it is now claimed that plasma triglycerides and plasma cholesterol are risk factors for CHD independent of each other (Carlson & Böttiger, 1972). In that study, a 'normal' concentration of cholesterol is one which is less than 280 mg/100 ml. As we know that there is a progressive increase in risk of CHD from concentrations of even 200 mg/100 ml upwards, it is difficult to accept their conclusion. The results provided (their Table II) suggest that raised plasma triglycerides are a risk factor in subjects already susceptible to CHD, rather than an independent factor.

Sucrose. Sucrose has been put forward as an important and possibly vital factor in the development of CHD (Yudkin, 1957; Cleave, Campbell & Painter, 1969). In the study 'Coronary Heart Disease in Seven Countries' (Keys, 1970), the incidence of CHD was significantly related to the percentage of energy supplied by

dietary sucrose, and was even more significantly correlated with the percentage of dietary energy supplied by saturated fatty acids (Keys, 1970). The correlation between sucrose and saturated fatty acids in the diet was high, and was considered to be adequate to explain the observed relationship between sucrose and CHD. The known biological effects of sucrose do not support the concept of a primary role in CHD, although the effect of dietary sucrose on obesity, diabetes mellitus, and triglyceridaemia are certainly of secondary importance.

Objections and exceptions to the hypothesis

(1) *The missing link.* Within the susceptible communities, it has not been possible to demonstrate clearly a correlation between the habitual diet of the individual and his blood cholesterol level or his risk of developing CHD. This piece of missing evidence is regarded by some as being of sufficient importance to make the whole hypothesis untenable. Individuals do manifest apparently spontaneous variation in their blood cholesterol concentrations from time to time without obvious changes in diet or other aspects of their way of life (Keys, 1962). When one adds to this individual variability, the difficulty of estimating the exact composition and amount of the diet in free-living individuals, the lack of this piece of information in a community with a limited dietary variation is hardly surprising. However, there is no doubt that manipulations of the fatty acids in the diet can lower or raise blood cholesterol concentrations in an individual or in a community in a predictable way (National Diet-Heart Study Research Group, 1968; Grande *et al.* 1972).

(2) *Exceptional communities.* There are certain communities whose life-patterns and experience of CHD appear to challenge the nutritional-metabolic hypothesis, such as the Ceylonese and the nomadic Masai of East Africa. The Ceylonese are said to have a high incidence of CHD associated with a low-fat diet and low concentrations of blood cholesterol. The Masai are free of CHD and have low blood cholesterol concentrations despite their traditional diet of milk, meat, and blood. The situations in these communities have recently been reviewed (Shaper, 1972*a,b*), and there is not sufficient evidence to regard any of these groups as exceptional and outside the framework of the hypothesis.

(3) *Modification of the diet and reduction in the incidence of CHD.* There are several primary prevention studies in progress (Anonymous, 1972). Some are single-factor studies with an emphasis on dietary modification and others are multifactorial, with treatment of a wider range of risk factors. Preliminary reports on some of the single factor-dietary studies are encouraging but not conclusive and the lack of this conclusive evidence is regarded as a serious objection to the dietary hypothesis. Indeed, there are those among us who consider that primary prevention trials involving dietary modification are not worth pursuing in middle-aged men and are logistically impossible in younger people.

Conclusion

Diet is an essential factor in the causation of hypercholesterolaemia, atherosclerosis, and CHD. Specifically, a diet high in saturated fats and cholesterol is implicated. The concept of duration of effect is critical to an appreciation of this

situation, and for this diet to be of importance to a community it must represent a habitual and possibly lifelong pattern. All other factors are synergistic to this essential process, although many of these synergistic risk factors may also be nutritionally determined.

The blood cholesterol concentration measured at any particular time in the life-span is only a general indicator of the individuals lifetime dietary experience or of his whole cholesterol metabolism, and an equally general indicator of his degree of coronary atherosclerosis. Nevertheless, surprisingly and significantly, it remains the most powerful predictor of subsequent CHD in individuals and communities. In the ultimate analysis, we shall be concerned not with blood cholesterol or triglyceride concentrations, but with specific fatty acids in the diet, and in the blood and tissues. Not only are these specific fatty acids involved in determining hypercholesterolaemia and atherosclerosis, but they may affect other processes involved in CHD, for example the coagulation and fibrinolytic mechanisms

Though the ideal in prevention would be to have a community with lifelong low concentrations of blood cholesterol, there seems little hope of persuading society to make such fundamental changes without providing clear evidence that dietary changes will lower the incidence of CHD. Such studies are only feasible in middle-aged or elderly men with an unknown but probably well-established degree of atherosclerosis, in whom some degree of susceptibility to CHD will remain present. Nevertheless, because the blood cholesterol concentration is such a good general indicator of CHD risk, it would seem potentially valuable to change the community dietary pattern known to be responsible both for the raised blood cholesterol concentrations and for the risk of CHD. If dietary modification and blood cholesterol reduction do result empirically in a reduction in the incidence of CHD, we shall still have to determine precisely how this has been achieved!

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