Modification of the diet in primary prevention trials

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Several epidemiological studies have indicated that the risk of developing coronary heart disease (CHD) is increased with high blood pressure, high serum cholesterol concentration, and cigarette smoking. In some studies, additional risk factors have emerged.

The evidence incriminating serum cholesterol is massive. In prospective studies, the risk increases all over the range of serum cholesterol values. In countries with a high coronary mortality, a serum cholesterol concentration 50 mg/100 ml lower than the average is roughly equivalent to a risk 50% of that of the average population (Kannel, Dawber & McNamara, 1966; Truett, Cornfield & Kannel, 1967). The role of cholesterol as a risk factor has become more firmly established in men than in women, both because CHD is more frequent among men and because fewer studies have been conducted on women.

Both individual and population differences are observed in serum cholesterol concentrations. Though the individual variation is largely endogenous and only partly ascribable to individual differences in dietary habits, the population differences are closely correlated with the amount of saturated or total fats in the diet (Keys, 1970; Fejfar, 1971).

Experimental modification of the diet

Fatty acid content. Human experiments with formula diets have indicated that serum cholesterol concentrations may be decreased by reducing the proportion of food energy provided by saturated fatty acids, or by increasing the intake of polyunsaturated fatty acids or by both procedures. Variation in the amount of monounsaturated fatty acids alone has no effect. The influence of a change in the saturated fatty acid content of the diet is roughly twice as large as that of an equally great but opposite change in the polyunsaturated acids (Keys, Anderson & Grande, 1965*b*). The greatest effect is obviously attainable by replacing saturated fatty acids by polyunsaturated ones.

Dietary cholesterol. Another factor of importance is cholesterol in food. When the dietary intake of cholesterol is changed, the serum cholesterol concentration changes in the same direction. The change in serum cholesterol in mg/100 ml equals 1·5 times the square root of the change of intake as expressed as mg/1000 kcal (4·184 MJ) (Keys, Anderson & Grande, 1965*a*).

Ascorbic acid. Some other constituents of the diet may also influence the serum cholesterol. Of special interest is ascorbic acid; in subjects whose ascorbic acid intake is low, but not necessarily low enough to cause other manifestations of deficiency, serum cholesterol may rise (Ginter, 1970). Possibly a marked seasonal variation of serum cholesterol observed in some rural populations (e.g. Keys, Karvonen & Fidanza, 1958) is partly due to a marginal intake of ascorbic acid.

Effect of vegetable oil supplements. As the cholesterol-lowering effect of polyunsaturated fatty acids became known, it was hoped that their use as dietary supplements might result in effective prevention of CHD. Some trials were launched, but their results did not reward the optimism. The incidence of CHD was not reduced in primary prevention trials, nor was the progress of already manifest disease retarded. A critical analysis of the supplementation trials reveals that little effect was indeed to be expected in them. A moderate addition of polyunsaturated fatty acids to the daily diet will produce only a slight suppression of the serum cholesterol concentration. If the intake of other energy foods is not correspondingly reduced, body-weight will increase, which again tends to raise the serum cholesterol.

Specific effects of vegetable oils, such as their possible influence on blood clotting, have also been studied. However, up to now there seems to be no definite evidence for ascribing to the vegetable oils any other significant role in the prevention of CHD than their effect on the serum cholesterol.

Long-term intervention through change of diet

The decrease of serum cholesterol attainable with the aid of formula diets under laboratory conditions is not directly applicable to long-term intervention studies, and even less to the general population.

Two different approaches and their combinations have been used. One of them is to instruct and motivate each person involved deliberately to choose cholesterol-lowering foods. This approach has been employed with considerable success in secondary prevention trials (e.g. Leren, 1966), and in the New York Anti-Coronary Club trial of primary prevention (Christakis, Rinzler, Archer & Maslansky, 1966; Christakis, Rinzler, Archer, Winslow, Jampel, Stephenson, Friedman, Fein, Kraus & James, 1966). A basic principle of the study diet was to provide approximately equal quantities of saturated, monounsaturated and polyunsaturated fatty acids. In fact, ratios of polyunsaturated to saturated fatty acids in the diet (P:S ratios) of 1·25–1·5 were achieved, as against the values of 0·3–0·4 characteristic of the American diet. Beef, mutton or pork were limited to four meals per week; poultry and veal were consumed four or five times a week, and a minimum of four fish meals weekly was required. Butter and hydrogenated shortenings were replaced by a 'soft' margarine and a minimum of approximately 30 g of vegetable oil daily. Ice-cream, hard cheeses and pastry were to be avoided. Whole milk was replaced by skim milk. The diet contained 30–33% of total energy as fat. Overweight subjects were placed on a reducing diet, until the desired weight was reached.

The other approach is the centralized provision of cholesterol-lowering foods to the subjects. This has been done in the Helsinki Mental Hospital Study

(Turpeinen, Miettinen, Karvonen, Roine, Pekkarinen, Lehtosuo & Alivirta, 1968) and in the Los Angeles Veterans Study (Dayton, Pearce, Hashimoto, Dixon & Tomiyasu, 1969), which were both concerned with patients in institutions.

The National Diet-Heart Study Research Group (1968), in the USA, which conducted a feasibility study for primary prevention, combined the two approaches. In it, a great effort was laid on the introduction of cholesterol-lowering foods by the food industry, and on modifying individual cooking and choice of foods to attain suppression of serum cholesterol, according to a double-blind plan, the cholesterol-lowering diet being indistinguishable by the subjects from the control diet.

In the Helsinki study (Turpeinen *et al.* 1968), the diet of male patients was changed in one mental hospital (Hospital N), and another hospital (Hospital K) was used as a control. After 6 years the roles of the hospitals were exchanged (Table 1). The aim was to attain a marked decrease in serum cholesterol, but the choice of foods and the taste of individual dishes was to be retained as close to the customary

Table 1. *Plan of experiment*

Year	Hospital N	Hospital K
1958	Normal diet	Normal diet
1959–65	Experimental diet	Normal diet
1965–71	Normal diet	Experimental diet

Finnish cooking as possible. The main changes instituted were: replacement of milk by an emulsion of soya-bean oil in skimmed milk; replacement of butter and

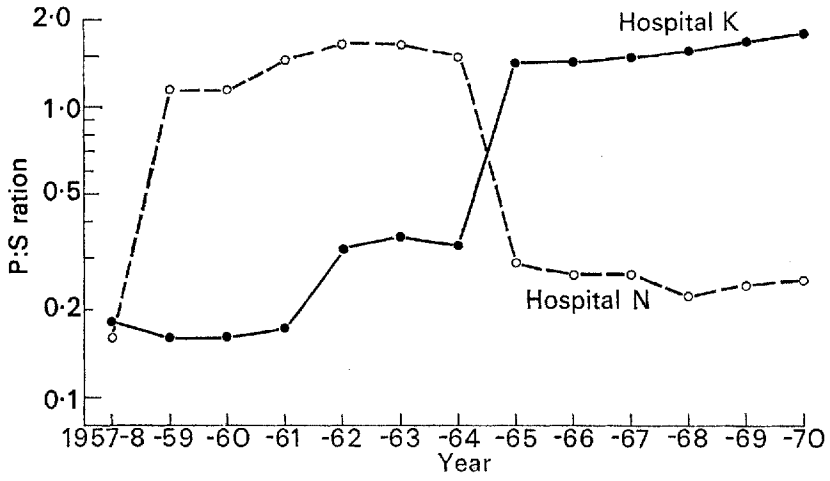

Fig. 1. The ratio of polyunsaturated to saturated fatty acids (P:S ratio) in the diet of men in two hospitals, K and N, before the experiment (1957–8) and during two stages of the dietary intervention.

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standard margarine by a margarine with a high content of polyunsaturated fatty acids; avoidance of fat meats, and generous use of vegetable oils in cooking. These changes resulted in an almost total replacement of the milk fat by vegetable oils, mainly soya-bean oil. The intake of polyunsaturated fats increased and that of the saturated fatty acids decreased in the hospital on the experimental diet. The P:S ratio increased from around 0·25 up to 1·5 (Fig. 1). The annual mean cholesterol intake has varied from 190 to 390 mg daily in the experimental diet, and from 400 to 540 mg daily in the control diet.

Results of dietary intervention studies

Serum cholesterol

In all the main primary prevention trials a significant suppression of the serum cholesterol was achieved. In the New York Anti-Coronary Club, a drop of 30 mg/100 ml from the mean starting value of 260 mg/100 ml was observed 1 year after the beginning, and a further decrease of 5 mg/100 ml ensued over the next 4 years. Controls showed no systematic change. In the Los Angeles veterans trials (Dayton *et al.* 1969), the mean serum cholesterol of the experimental men was 29·5 mg/100 ml lower than that of the controls. The US National Diet-Heart study (National Diet-Heart Study Research Group, 1968) attained a mean suppression of serum cholesterol from the base-line by 25·4–27·6 mg/100 ml in men living in their homes, and by 31·3–40·0 mg/100 ml in men living in institutions. In the Helsinki study (Turpeinen *et al.* 1968), the mean for patients in the experimental hospital was 51·3 mg/100 ml lower than among the controls during the first 6 years (Fig. 2). After the reversal of the diets, the serum cholesterol concentrations crossed, but the difference has remained smaller, approximately at 30 mg/100 ml.

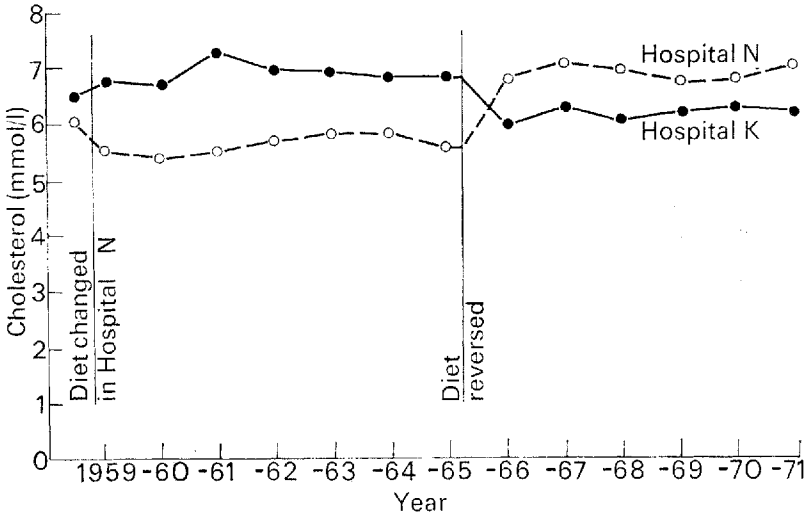

Fig. 2. Mean serum cholesterol concentration during two stages of the dietary intervention in men in two hospitals, K and N.

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Fatty acid composition of adipose tissue

The adherence to a vegetable-oil diet may be assessed with the aid of a fatty acid analysis either of a sample of the adipose tissue, or of the red cell lipids. The red cell lipids were used in the National Diet-Heart study, and adipose tissue samples have been analysed both in the Los Angeles Veterans Study and in the Helsinki study.

A sudden change in the diet initiates a slowly progressing change in the composition of the adipose tissue (Fig. 3). In 5 years, the linoleic (18:2) acid has risen so that it now makes approximately 30% of the total fatty acids. Myristic (14:0) acid, which is essentially derived from milk fat, has gradually decreased. It may be mentioned that the proportion of linoleic acid among the dietary fatty acids has lately been 37% in the experimental and 11% in the control diet. Myristic acid has correspondingly contributed 1·3 and 7·3% of the dietary fatty acids.

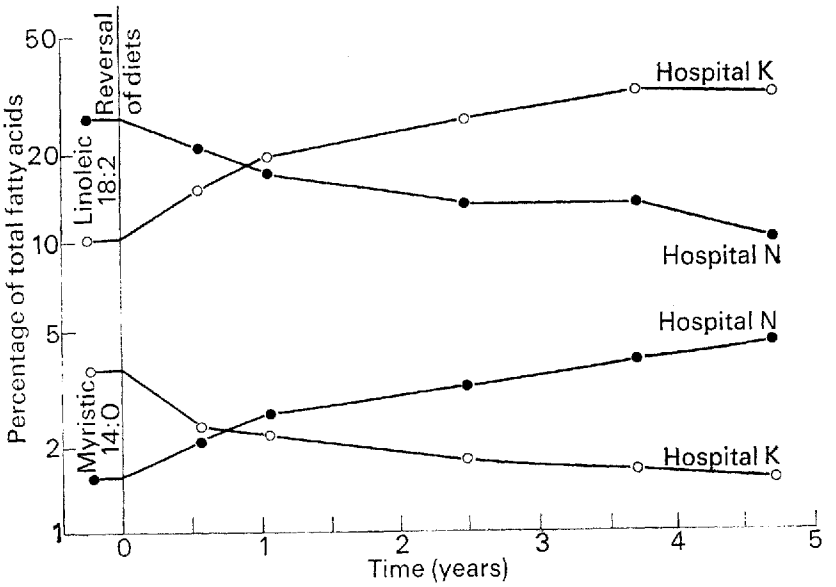

Fig. 3. Changes in the myristic (14:0) and linoleic (18:2) acid contents as a percentage of total fatty acids in men in two hospitals, K and N, after the reversal of the diets.

CHD

The three main trials have each separately demonstrated a statistically significant decrease in the incidence of the clinical or electrocardiographic manifestations, or both, of atherosclerosis. In the New York (Chrisakis, Rinzler, Archer & Maslansky, 1966; Chrisakis, Rinzler, Archer, Winslow *et al.* 1966) and the Helsinki (Turpeinen *et al.* 1968) studies this applies to CHD separately, and in the Los Angeles study (Dayton *et al.* 1969) to CHD and cerebral infarction as pooled together.

In the Los Angeles study (Dayton *et al.* 1969), in which the mean age of the subjects was quite high, over 65 years at the beginning of the study, the 8-year total incidence of primary and secondary end-points was as high as 47·7% among the controls and 31·3% in the experimental subjects ($P=0·02$).

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In the New York study (Chrisakis, Rinzler, Archer & Maslansky, 1966; Chrisakis, Rinzler, Archer, Winslow *et al.* 1966), which comprised men initially aged 40–59 years, the annual incidence of new coronary events was 0·98% among the controls and 0·34% in the subjects on diet ($P=0·02$).

Table 2. *Incidence of new coronary heart disease (CHD) per 1000 during 6-year study periods (O. Turpeinen, M. Miettinen, M. J. Karvonen, P. Roine, P. Pekkarinen, R. Elosuo and E. Paavilainen, in preparation)*

Period	Hospital	Diet	CHD/1000 patients
1959–65	N	Experimental	54
	K	Normal	124
1965–71	N	Normal	91
	K	Experimental	72

In the Helsinki study (Turpeinen *et al.* 1968), men aged 35–64 years were recruited initially, and the groups have been kept approximately constant in size by new entries in the same age range. During the first 6 years, the incidence of new CHD in the experimental group was less than half of that of the controls (Table 2). After reversal of the diets, the incidence also became reversed, but now the difference has not reached statistical significance. However, when the study is examined in its entirety (Table 3), a significant difference is observed: the incidence among the experimental subjects was 61% of that in the controls (O. Turpeinen, M. Miettinen, M. J. Karvonen, P. Roine, M. Pekkarinen, R. Elosuo and E. Paavilainen, in preparation).

Table 3. *Incidence of new coronary heart disease (CHD) during pooled diet and control periods (O. Turpeinen, M. Miettinen, M. J. Karvonen, P. Roine, M. Pekkarinen, R. Elosuo and E. Paavilainen, in preparation)*

Diet period	Patients with CHD	Total no. of patients
Experimental	37	591
Normal	61	580

$\chi^2=6·37$; $P=0·012$.

Special problems

Vitamin E. In animals given a large amount of polyunsaturated fatty acids a disturbance in metabolism may ensue, which can be prevented by increasing the supply of vitamin E. In animals, this metabolic derangement may cause muscle or brain disease, but no corresponding clinical syndrome is known in man. Some vegetable oils are rich in vitamin E, but this may not always be so. Obviously it is advisable to pay attention to an adequate supply of vitamin E when the intake of polyunsaturated acids is increased (Dayton *et al.* 1969).

Total mortality and cancer. In the Los Angeles veterans study, a statistically non-significant excess of cancer incidence and of cancer mortality was reported among those on the experimental diet (Dayton *et al.* 1969; Pearce & Dayton, 1971). This, however, has not been the rule in other similar studies. And when the results of five studies (Oslo, London, Helsinki, Faribault and Los Angeles) were combined, the total mortality of those on the diet was only 85% of that of their controls. There was no significant difference in cancer incidence or mortality in the combined material (Ederer, Leren, Turpeinen & Frantz, 1971).

Fat and sugar intake. In the Helsinki study the dietary intervention was limited to fat only; the diets were not modified in other respects. The sugar intake was higher in Hospital K all the time, both before and after the reversal of the diets. Towards the end of the experiment, this difference has tended to become smaller.

The mean concentration of serum triglycerides has similarly been higher all the time in Hospital K, and the reversal of the diets produced no essential change in the triglyceride concentrations. The behaviour of the serum triglycerides is possibly attributable to the pattern of sugar intake. The reversal of the fat component of the diet was associated with a reversal of the incidence. Evidently, neither the sugar intake nor the serum triglyceride concentration were main determinants of the incidence of CHD in this study (Karvonen, Turpeinen, Miettinen, Roine, Pekkarinen, Paavilainen & Elosuo, 1970).

Conclusions

These long-term intervention studies have provided answers to several problems which awaited their solution in the late 1950s.

First, it has proved feasible to produce palatable cholesterol-lowering foods and diets which can be introduced without unduly disturbing the traditional food habits of people.

Second, lasting suppression of the mean serum cholesterol concentration by up to 50 mg/100 ml by dietary means has proved feasible in practice.

Third, the composition of human adipose tissue and cell lipids has been proved to depend on the type of dietary fat.

Fourth, the suppression of the serum cholesterol concentration by approximately 50 mg/100 ml has resulted in a decrease of the incidence of CHD to roughly one-half of that among those eating typical American or Finnish diets.

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