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The Mediterranean diet: fish and olives, oil on troubled waters

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Dietary recommendations have been made over the past two decades which have little regard for the pleasure people derive from eating. The prohibitive nature of this dietary advice may be one reason why such a small portion of the population meet the Committee on Medical Aspects of Food Policy (COMA) (Department of Health and Social Security, 1984) recommendations on healthy eating (Gregory *et al.* 1990). The Mediterranean diet is characterized by the use of olive oil as the major culinary fat. It is also characterized by the inclusion of oily fish such as sardines and anchovies. Olive oil, unlike the more contemporary vegetable oils, has a long history of use. It is stable to heat and its use is associated with a low incidence of coronary heart disease.

The Seven Countries Study clearly showed that the type of fat, rather than the level of fat, in the diet was related to risk of coronary heart disease. Mediterranean countries with relatively high intakes of total fats, in the order of 35% energy, had lower rates of coronary heart disease and this was strongly correlated with a low intake of the saturated fatty acids (Keys, 1970). However, not all Mediterranean countries have low rates of coronary heart disease. Malta, where there has been a strong British culinary influence, has a coronary heart disease incidence equivalent to that of the United Kingdom (Pisa & Uemura, 1989). Differences in saturated fat intake explain two-thirds of the differences in the median plasma cholesterol concentration between countries. Experimental studies have shown that saturated fatty acids C_{12}–C_{16} increase plasma cholesterol levels. High intakes of saturated fats can also induce atherosclerosis in primates and in susceptible rodent species. More recently, it has been shown that a high intake of saturated fats increases thrombotic tendency (Hornstra & Lussenburg, 1975; Renaud *et al.* 1986; Miller *et al.* 1989).

The intra-country comparisons only show a weak relationship between the intake of saturated fats and plasma cholesterol levels (Shekelle *et al.* 1985). The variability between individuals is more probably related to genetic differences rather than environmental influences. However, when differences in saturated fat intakes are large, for example between vegans and the general population, then differences in plasma cholesterol due to diet are seen (Roshanai & Sanders, 1984). Despite the dissenting views there has been a general consensus amongst expert committees (European

Atherosclerosis Society, 1987; National Research Council, 1989). The consensus has been that it is desirable to decrease the intake of saturated fatty acids to below 10% of the energy intake. What is disputed is what should replace the energy currently provided by saturated fats.

There are four alternatives to saturated fats in the diet. The first is to increase alcohol intake, but this option is generally regarded as unacceptable in view of the known social and clinical consequences of excess intake. However, moderate alcohol consumption (2–3 units/d) is associated with a decreased risk of coronary heart disease and all cause mortality (Burr, 1988). An alcohol intake of 2 units/d would provide approximately 6–8% of the energy intake.

Low-fat, high-carbohydrate diets are less palatable and may be less effective in lowering plasma lipids than diets with a modified fat composition (Ginsberg *et al.* 1990). A reduction in total fat intake is accompanied by a decrease in high-density lipoprotein (HDL)-cholesterol levels (Grundy, 1986; Mensink *et al.* 1989). Increasing the intake of carbohydrate also increases post-prandial insulin output and hyperglycaemia (Van Amelsvoort *et al.* 1989). It seems likely that the decrease in HDL-cholesterol with high-carbohydrate diets is related to the increased insulin secretion.

Polyunsaturated oils, rich in linoleic acids, such as sunflower, maize and soya-bean oils, have traditionally been advocated for the replacement of saturated fat in the diet. However, this dietary recommendation has never been supported by epidemiological evidence. For each 1% of the energy from saturated fat replaced by linoleic acid, there is approximately a 0·13 mmol/l reduction in plasma cholesterol. Intakes of linoleic acid up to 12% of the energy intake do not lower HDL-cholesterol concentrations (Mensink & Katan, 1989), but higher intakes do (Mattson & Grundy, 1986). Small amounts of polyunsaturated fats are needed in the diet and both the *n*-6 and *n*-3 series need to be balanced with respect to one another. The long-term effects of high intakes of linoleic acid-rich vegetable oil are unknown. Some studies suggest that high intakes of linoleic acid increase the incidence of gallstones (Grundy, 1989). Furthermore, oils high in polyunsaturated fats are less stable to heat than other oils. A number of adverse effects of high intakes of linoleic acid have been noted in animals, in particular diets rich in linoleic acid are immunosuppressive (Sanders, 1988). Several studies have shown that monounsaturated (Grundy, 1989; Mensink & Katan, 1989) fatty acids are just as effective as polyunsaturated fatty acids when they replace saturated fat in the diet for cholesterol lowering. Besides olive oil, low-erucic rapeseed oil, which is the main constituent of vegetable oils in the UK, also has effects on plasma lipid levels (McDonald *et al.* 1989). Studies where olive oil has been fed to volunteers as a supplement to the diet show neither an influence of the additional olive oil on blood lipids nor blood pressure nor platelet function (Rogers *et al.* 1987; Sanders, 1991). These studies suggest that olive oil is neutral with regard to its effects on cardiovascular disease.

Recent studies have shown that the low-density lipoprotein (LDL) particle needs to be modified before it becomes atherogenic. Cholesterol-containing LDL particles which are not taken up by the LDL receptor are taken up by tissue macrophages (Steinberg *et al.* 1989). These tissue macrophages become engorged with lipids to form foam cells which are the earliest atheromatous lesions. Macrophages do not recognize native LDL and only take up modified LDL. Endothelial cells are believed to play a major role in modifying LDL. The LDL particle undergoes oxidative modification and this involves the oxidation of cholesteryl linoleate. LDL particles containing cholesteryl oleate are

less prone to oxidation. However, there is no evidence that high intakes of linoleic acid induce modification of LDL or are atherogenic, as claimed in the popular Press. The observation that the drug, probucol, which itself is an antioxidant, has an anti-atherosclerotic effect led to the view that antioxidants may inhibit the modification of LDL. It has subsequently been suggested that antioxidant nutrients such as carotene and vitamins E and C, may inhibit the modification of LDL (Steinberg *et al.* 1989; Carpenter *et al.* 1990; Jilial *et al.* 1990). Indeed case–control studies have found lower levels of vitamin E, ascorbic acid and β-carotene in the plasma from patients with angina compared with controls (Riemersma *et al.* 1991). However, it needs to be recognized that cigarette smokers have lower levels of these vitamins due to an increased rate of breakdown of these vitamins due to activation of drug-metabolizing enzymes (National Research Council, 1989). High intakes of vitamin E have even been found to exacerbate atherosclerosis in the rabbit, rather than inhibit it (Godfried *et al.* 1989). Fish oil containing eicosapentaenoic acid (EPA; 20:5*n*–3) and docosahexaenoic acid (DHA; 22:6*n*-3) are extremely prone to lipid peroxidation, yet they inhibit the development of atherosclerosis in dogs, primates and pigs (Sanders, 1988). These observations tend to challenge the simplistic hypothesis that atherosclerosis is caused by lipid perodixation.

Eskimos on their traditional diet have a low incidence of coronary heart disease. Their traditional diet consists mainly of caribou and marine mammals, with smaller amounts of fish (Sinclair, 1953). The Eskimos have a prolonged bleeding time and markedly different blood lipid levels from Western populations (Bang & Dyerberg, 1980). Experimental studies where volunteers have been fed the equivalent amounts of marine lipids as in the Eskimo diet have noticed a number of changes in platelet function, plasma lipid and in the inflammatory response (Leaf & Weber, 1988; Sanders, 1991). Oily fish also contains similar marine lipids to those found in marine mammals. However, the concentrations in white fish are very much lower. A prospective study in the Dutch town of Zutphen found that fish consumption was associated with protection of coronary heart disease. However, the amounts of fish required to give protection was extremely small, equivalent to eating fish one or two times weekly (Kromhout *et al.* 1985). This would provide a quantity of fish oil very much lower than the amounts used in experimental studies. It could be argued that fish intake was acting as a marker for other aspects of lifestyle, rather than actually having a direct effect. For example, it is well known that Christianity is associated with regular fish consumption and that religious adherence is associated with a decreased risk of cardiovascular disease. The association between moderate fish consumption and decreased risk of coronary heart disease has been confirmed in some, but not in all, studies (Shekelle *et al.* 1985; Norell *et al.* 1986). The association with protection from cardiovascular disease appears to be with the consumption of oily fish rather than white fish. For example, in the Orkneys the consumption of fish is very much higher than in the mainland, yet coronary heart disease rates are similar (Barber *et al.* 1986). Comparisons between farming and fishing communities in Norway have also failed to show differences in coronary heart disease rates (Simonsen *et al.* 1987). However, the fishing communities were consuming white fish, mainly cod, rather than oily fish. It has been proposed that there may be a threshold effect where oily fish consumption is protective beyond which further increases in fish consumption yield no further benefits until extremely high intakes, equivalent to that found in Eskimos, are achieved. The strongest evidence for the protective effect of moderate oily fish consumption comes from a secondary prevention trial in coronary heart disease (Burr *et al.* 1989).

The patients given advice to consume two portions of oily fish weekly showed a 29% reduction in all causes of mortality over the following 2 years. There is abundant evidence that the consumption of either fish oil supplements or oily fish prolongs bleeding time in man (Sanders, 1988). This appears to be due to a change in the relative balance between thromboxane and prostacyclin production. Studies in animals have shown that high intakes of fish oil inhibit atherosclerosis, probably by inhibiting the production of factors that stimulate cellular proliferation. Other studies have shown that *n*-3 polyunsaturated fatty acids prevent ventricular fibrillation in experimental animals following myocardial ischaemia (McLennan *et al.* 1990). The high intake of *n*-3 fatty acids in Eskimos, and other populations that consume large amounts of fish, is the likely explanation for their low rates of cardiovascular disease. However, a plausible hypothesis still needs to be advanced to explain why moderate fish consumption offers protection from coronary heart disease.

In conclusion, with regard to the Mediterranean diet, monounsaturates are neutral with regard to risk factors for coronary heart disease. The partial replacement of saturated fatty acids with monounsaturated fatty acids gives flexibility in planning diets to lower plasma cholesterol concentrations. Modest oily fish consumption is associated with protection from coronary heart disease, yet the precise mechanism by which protection is afforded still remains to be elucidated.

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