Lipids and Atherosclerosis

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Abstract

More than 50 years ago the observation was made that the prevalence of atherosclerosis is unusually low among some of the world's populations. Shortly thereafter came the suggestion that this circumstance is due to the low fat content of their diets and the low cholesterol concentration in their blood. Efforts to apply this thinking for the benefit of human health have taken various turns. The first approach was to recommend a low-fat diet. It was thought that the type of fat in the diet was immaterial and that the dietary cholesterol content made no difference either. Later, it was shown that excellent falls in blood cholesterol could be obtained with high-fat diets if most of the fat was polyunsaturated. Dietary cholesterol was found to play a role, but it must be held at exceptionally low levels before its importance becomes evident. Recently, we have become fearful of excessively high intakes of polyunsaturated fats because no population has consumed such a diet over a long period of time and because of suggestive experimental and epidemiological evidence that the incidence of some forms of cancer may be increased. A low-fat, low-cholesterol diet is the preferred prescription for hyperlipidemia.

In this paper, the evolution of medical thinking about the relation of lipids to atherosclerosis will be traced from its early beginnings, with special emphasis on the way in which a possible relationship to cancer has affected this thinking in recent years.

In 1857, Mettenheimer (44) first attributed the doubly refractile properties of fat droplets present in sclerotic arteries to the presence of cholesterol. Disagreements concerning the validity of this observation still occurred, however, until chemical measurements by Windaus in 1910 (62). Windaus applied his gravimetric method for quantification of cholesterol, based on precipitation with digitonin, to the analysis of normal and atheromatous aortas. He found substantial quantities of both free and esterified cholesterol in the normal vessels and several times greater amounts in those that were diseased. In the atheromatous vessels, the ratio of esterified to free cholesterol was greatly increased. Sixteen years later, Schönheimer (55) confirmed these results and found a positive correlation between the age of the patient and both the total lipid and the cholesterol ester content of the aorta.

The observation that cholesterol and other lipids are major components of the atherosclerotic plaque led to attempts to produce atheromatous lesions in experimental animals. Ignatowsky (28, 29) was the first to succeed, in 1908, by feeding eggs, meat, and milk to rabbits. Five years later, Anitschkow (4) obtained similar results by feeding pure cholesterol dissolved in oil. The rabbit normally consumes no dietary cholesterol. Its mechanisms for eliminating cholesterol from the body are poorly developed, so that raising its blood cholesterol by dietary means is easily accomplished. In species with efficient systems for the excretion of cholesterol, experimental atherosclerosis may be induced by facilitating cholesterol absorption or by interfering with its excretion. Hartroft and Thomas (27) succeeded with the rat by increasing absorption through the addition of bile salts. Steiner and Kendall (57) made dogs atherosclerotic by depressing their thyroid function during the cholesterol feeding. Cholesterol excretion was depressed, and cholesterol in the blood rose and was deposited in the arteries.

In parallel with these experiments in animals, epidemiological observations were made in various parts of the world that pointed to fat in the diet as a possible cause of atherosclerosis in man. In 1929, Donnison (18) reported an unusually low prevalence of arteriosclerosis among a group of natives in Kenya, but did not suggest diet as the cause. Five years later, Rosenthal (53), working with data assembled by himself and by Raab (50), drew the inference that a low prevalence of atherosclerosis is associated with a high-protein, low-fat diet. In subsequent years, many surveys have confirmed a relationship between fat in the diet, cholesterol in the blood, and atherosclerosis (19, 30, 31, 33, 35, 36, 38–40, 43, 51, 52, 56, 58–60, 63).

The experimental studies in animals and the epidemiological observations of man led to the hope that atherosclerosis could be prevented and treated by dietary manipulation. Regression in non-human primates of even rather advanced lesions has been clearly demonstrated (5, 6, 61). Fairly convincing evidence is beginning to accumulate that regression can be achieved also in human beings by various cholesterol-lowering techniques such as administration of drugs or the ileal by-pass (7, 9, 10, 16, 48).

Many attempts have been made to conduct clinical trials that would demonstrate experimentally the efficacy of dietary modification for the prevention of human atherosclerosis. Probably, the most believable of the attempts at secondary prevention is that of Leren (42), and at primary prevention, that of Dayton et al. (17). Most workers in the field agree, however, that a fully convincing trial has not yet been conducted. A task force appointed by the National Heart and Lung Institute to study this question concluded in 1971 that a definitive test of the lipid hypothesis in the general population is urgently needed but is not feasible because of the exorbitant cost in money and in scientific manpower (47).

Despite the lack of absolute proof of the lipid hypothesis, many physicians elect to recommend lipid-lowering diets to patients whose blood cholesterol or triglyceride is elevated. The changes that have occurred in our choice of diets for this purpose and the reasoning, sometimes erroneous, that led to these changes constitute a fascinating bit of medical history.

On the basis of the evidence then in hand, Keys (34) in 1952 states, "The ensemble points strongly to the conclusion that, other things being equal, the serum cholesterol level in adult man is independent of the cholesterol intake over the range of

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zero to at least 700 mg daily. Many hospital diet manuals of that era included a low-cholesterol, low-fat diet. Keys' conclusions from his metabolic ward experiments led to a de-emphasis of the importance of reducing dietary cholesterol. Theoretical support for this change was drawn from the demonstration by Gould et al. (25) that cholesterol synthesis is strongly suppressed in the liver of the dog by dietary cholesterol. It was argued that eating cholesterol made no difference because each additional mg consumed was offset by a mg that the liver did not synthesize. The flaw in this argument was that what holds for the dog and rat does not necessarily apply to man. Kaplan et al. (32) showed that, by feeding labeled cholesterol until the radioactivity of the blood cholesterol reached a plateau, a much smaller proportion of the blood cholesterol in man is derived from sources that are subject to suppression by cholesterol in the diet. Connor et al. (15) then carried out feeding experiments in man that established beyond doubt that the blood cholesterol is affected by the cholesterol content of the diet, although the effect is small unless the cholesterol intake is reduced to very low levels, in the range of 0 to 100 mg per day. The low-cholesterol diet returned to the hospital diet manuals where it is still firmly entrenched.

Keys (34) continued: "But the fat intake is quite another matter and appears to have great importance. However, there is not the slightest evidence for a difference between animal and vegetable fat in this regard (Abelin) (1)." In this same year, a paper by Kinsell et al. (41) appeared in which it was shown that polyunsaturated fats in the diet lower blood cholesterol, while saturated fats raise it. This observation was fully confirmed by Ahrens et al. (2). Keys et al. (37) also confirmed this and showed that addition of 2 g of polyunsaturated fat is about as effective in lowering the blood cholesterol as removal of 1 g of saturated fat. A formula for predicting dietary effects on serum cholesterol constructed on this principle came to be known as the KAG Equation. We entered an era during which a low-fat diet was prescribed only in rare patients who required it to prevent chylomicronemia. Dietitians preferred diets that provided some 40% of calories from fat, much of it polyunsaturated. Such diets were considered more palatable than those provided some 40% of calories from fat, much of it polyunsaturated. Generous amounts of meat could be included if only its cholesterol-raising effect was balanced by polyunsaturated fat. The notion of the P:S ratio gained vogue, although, as Keys et al. (37) pointed out, the actual number of g of saturated and polyunsaturated fat is a more accurate predictor of the effect on blood cholesterol. The truth of this statement becomes immediately apparent if one considers that, if the total fat content is made very small, even extreme values of the ratio can exert little influence. The P:S ratio remains a useful concept, however, for diets containing natural fats in quantities within the usual range.

Ahrens et al. (3) presented evidence that led to the conclusion that, under their experimental conditions, many, perhaps most, cases of hyperlipemia appeared to be "carbohydrate induced." This discovery provided additional incentive for abandonment of the low-fat diet. A system for sorting patients with hyperlipoproteinemia into 5 different phenotypes was devised by Fredrickson et al. (23), and 5 diets corresponding to the 5 types were recommended (22).

During the last few years the pendulum has begun to swing back towards the low-fat diet because of 2 happenings: (a) accumulation of some inconclusive evidence that polyunsaturated fats in the diet may be carcinogenic (discussed more fully below); and (b) rather convincing evidence from several groups of investigators (5, 14, 54) that the supposed adverse effects of large amounts of dietary carbohydrate have been exaggerated. It is now apparent that, when a high carbohydrate diet is fed to normal persons, to diabetics, and even to patients with type IV hyperlipoproteinemia, any rise in plasma triglycerides that may occur is transient and subsides within a few weeks. During the initial period immediately following the transition to high carbohydrates, the elevation in triglycerides is less or nonexistent if the comparison is made on averages over the 24-hr day rather than on fasting levels only.

The importance of the high-density lipoproteins as a negative risk factor for coronary heart disease has recently gained great prominence (13, 24, 45). Insufficient data are available at this time on the effect of diet on this component to justify discussion. It is clear, however, that lipid-lowering diets will require reevaluation to take into account their effect on high-density lipoproteins.

Coincident with reemergence of the low-fat, low-cholesterol diet as a reasonable approach to the management of most forms of hyperlipoproteinemia, there began to arise within the medical community a growing disenchantment with polyunsaturated fats. This uneasiness rested not so much on scientific evidence as on fear of the unknown. No one could identify populations that had subsisted for any length of time on diets with P:S ratios approaching those being recommended for treatment of hyperlipidemia or, for that matter, consumption by the general public. Physicians were haunted by the specter of drugs that had seemed safe when administered to relatively small numbers of patients over short periods of time but proved to be unacceptably toxic when distributed more widely. The viewpoint of the environmentalists that any tampering with the natural order of things is dangerous until proved otherwise had its impact.

Some experimental and epidemiological evidence suggesting that dietary fats may be involved in the causation of cancer has appeared. An example of an informative epidemiological study is a report in 1968 by Haenszel and Kurihara (26) on cancer incidence in Japanese living in Japan and in Japan and the United States and white residents of the United States. Japanese living in Japan showed a much higher age-adjusted mortality from cancer of the esophagus and stomach than did U.S. whites. Cancer of the rectum, pancreas, lung and bronchus, and cervix did not differ greatly for the 2 groups. Cancer of the intestine, breast, uterus other than cervix, ovary, and prostate were much lower in Japan, and leukemia was also lower. The most striking feature of the data for Japanese immigrants to the United States is the nearly complete transition to the rates for U.S. whites for cancer of the colon. Breast cancer incidence rose only slightly towards U.S. rates. Cancer of the stomach fell towards U.S. levels but did not nearly reach them. It is tempting to attribute some of these differences to the large difference in fat content of the Japanese and American diets in exactly the

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2 The abbreviation used is: P:S, polyunsaturated:saturated.
same way as we have been inclined to explain the difference in risk of coronary heart disease.

Seven years after publication of the paper by Haenszel and Kurihara, Carroll and Khor (12) assembled data relating mortality from cancer at various sites to dietary fat intake in many countries. Comparisons of this sort suffer from the limitation that dietary fat intake is calculated from food disappearance. Nevertheless, many of the associations were impressive. The highest correlation coefficients were female breast, +0.935; intestine (except rectum), +0.928 (men), +0.911 (women); prostate, +0.892; leukemia, +0.857 (men), +0.838 (women). Positive correlation coefficients greater than 0.5 were also calculated for rectum, ovary, lung-bronchus-trachea (men), pancreas (men), skin, and bladder (men). Smaller positive correlations were found for bladder (women), buccal cavity and pharynx (men), lung-bronchus-trachea (women), and larynx (men). Correlation was near zero for esophagus, thyroid, stomach, and uterus. For liver and biliary passages, negative correlation coefficients of −0.487 and −0.676 were noted for women and men, respectively. Smaller negative correlations were found for buccal cavity, pharynx, and larynx in women. The authors recognized that fat intake tends to correlate highly with total calories and with protein. Cancer mortality appeared to correlate more closely with fat intake, however, than with any other feature of the diet.

Burrill (11) reviewed the evidence for an association between cancer of the colon and rectum and dietary components. He pointed out the negative correlation usually observed between dietary fat and fiber and reached the conclusion that low fiber was probably a more likely cause of intestinal cancer than high fat.

Enig et al. (21) have reviewed the epidemiological evidence for a relationship between cancer and dietary fat. After examining trends over a 60-year period, they reached the conclusion that vegetable fat is more to be implicated as a causative agent than animal fat. Their calculations suggest that the content of trans-fatty acids in partially hydrogenated vegetable fats may be responsible for much of the postulated carcinogenic effect of vegetable fats. Consumption of trans-fatty acids is said to have increased in the United States from 4.4 g/capita/day in 1910 to 12.1 g in 1972.

Carroll and Khor (12) also reviewed evidence from animal experimentation that dietary fat can contribute to carcinogenesis, presumably acting as promoter rather than initiator. These authors fed various fats to female rats following a single p.o. dose of the carcinogen 7,12-dimethylbenz(a)anthracene. More mammary tumors appeared in the rats fed unsaturated fats than in those fed saturated fats. Trials designed to test the hypothesis that clinical manifestations of atherosclerosis can be reduced by dietary means have usually used treatment diets that were low in cholesterol and saturated fat but high in polyunsaturated fat. Although they can tell us nothing about the relation of total fat in the diet to cancer, they can provide information on the extent of unsaturation. In the trial conducted by Pearce and Dayton (49) in a Los Angeles veterans domiciliary, 31 deaths due to cancer occurred in the treatment group and 17 in the control group (p = 0.06). Ederer et al. (20) compiled the data from this trial and from 4 others and concluded that, when all available data were combined, no significant differences could be discerned. It should be noted, however, that the Los Angeles trial involved men only, with the mean age of the subjects greater than for the other trials; that it contributed more cases than all of the other trials combined; and that its period of observation was the longest. Unpublished data from the Minnesota Coronary Survey showed a trend, somewhat lesser in magnitude and even further from statistical significance, in the same direction as in the Los Angeles trial. Thirteen deaths due to cancer occurred in the treatment group and 10 in the control. The clinical trials have been too small in size and duration to yield significant results concerning the effect of polyunsaturated fats on carcinogenesis.

It is fortunate that we are no longer entirely dependent on diets high in polyunsaturated fat for the management of hyperlipoproteinemia. Recognition of the importance of weight reduction and cholesterol restriction and of the transient nature of the increase in triglycerides when fat in the diet is replaced by carbohydrate has relieved us of this dependence. More work is needed to establish with certainty if fats, either saturated or unsaturated, with or without trans-double bonds, play a role in human carcinogenesis. In the meantime, the low-cholesterol, low-fat diet is effective and probably safe.

References

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