Dietary Lipids and Arteriosclerosis

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ABSTRACT

A great deal of attention has been given to the question of whether dietary fats in general and certain fats in particular play an important part in such arteriosclerotic complications as heart attacks and strokes. Milk fats have been widely accepted as desirable nutritional fats. Cow milk fat, or butter, contains a wide variety of fatty acid derivatives, including the important, medium chain acids. The structural configuration of butter triglycerides facilitates absorption of the palmitate present in butter. However, there have been objections to the use of butter and other forms of milk fat because of the preoccupation of many investigators with the unproven lipid theory of arteriosclerosis, and because serum cholesterol levels are relatively high after the intake of milk fat. Re-evaluation of the lipid theory suggests that cholesterol can hardly be an atherogenic factor. Cholesterol occurs under conditions of tissue repair, and it may well be that the high serum levels in arteriosclerotic conditions are a consequence of such processes. The low serum levels occurring after the consumption of polyunsaturated vegetable oils are often associated with high tissue levels of cholesterol. Long term clinical studies and population surveys suggest that this century's changes in mortality and morbidity are much less related to dietary factors (other than overeating) than is claimed. New insights in the fields of immunology and microbiology may be vastly more important for an understanding of some etiological factors in arteriosclerosis.

INTRODUCTION

Milk and milk fat have been intimately involved in man's history and, until recent years, they have been taken for granted as a staple of man's diet. The last decades have seen a steadily increasing interest in the biological effects of dietary fat, especially in relation to arteriosclerosis—one of the major medical problems of western man.

Therefore, it seems advisable to consider whether fats are really as important as has been postulated in the lipid theory of arteriosclerosis, which implicates cholesterol in particular. There is an impressive body of evidence indicating that many observations related to the development of degenerative diseases can not be explained by the prevailing theories involving cholesterol, dietary saturated fatty acids, and, more recently, hyperlipidemias.

CHOLESTEROL METABOLISM

Because so much hinges on whether cholesterol, as such, or the lipoproteins with which it occurs in plasma, is atherogenic, it seems necessary to review briefly some of the biological functions of this material (1,2). Cholesterol is turned over in the body at the rate of 1000-2000 mg/day. The plasma turnover amounts to about 1000 mg daily, and the greater part of plasma cholesterol is esterified with fatty acids. On centrifugation, a large part appears in the fraction of low density lipoproteins which corresponds to the β-lipoproteins obtained by electrophoresis (3).

Most of the body's cholesterol is endogenous in origin and is produced mainly in the liver and intestines. The usual American diet supplies about 300-800 mg cholesterol/day, of which only about 150-300 mg are absorbed. This is true even wtih higher dietary levels (4). Under normal conditions, most tissue cholesterol is a key substance in membranes; some appears in the bile and some in lipoproteins; about 2% is used in the synthesis of steroid hormones.

Under some pathological conditions, large amounts of cholesterol are found in such tissues as scars, old fibroids, granulomas (tubercles, gummata). Thus, it appears to play an important part in many repair processes, usually in combination with calcium.

The efforts of countless investigators have been devoted to proving that cholesterol, which is an integral part of membranes and scars, is, nevertheless, the villain in the development of degenerative disease. A few undeniable facts have emerged which do show that choleserol is somehow associated with degenerative disease: (A) It is true that the atherosclerotic plaque does contain large amounts of cholesterol and its esters; (B) Persons with sufficiently elevated serum cholesterol values have a higher risk of developing such arteriosclerotic complications as heart attacks and strokes; (C) Diseases associated with high serum cholesterol levels (e.g., nephrosis) are associated with pronounced arteriosclerotic lesions; and (D) Feeding of cholesterol to some mammalian species induces deposition of cholesterol in many tissues, including arteries.

However, there are contradictions in the evidence which must be reconciled in any explanation of the disease. The earliest manifestation of the disease is seen in infants and may conceivably occur in utero (5). The typically spotty distribution of the lesions is not explained by the assumption of a metabolic disease. There is often no correlation between extensive arteriosclerotic disease at autopsy and premortal cholesterol values. In fact, one study showed that the most severe lesions at autopsy occurred in people who had had quite low serum cholesterol values (6).

Therefore, it seems worthwhile to attempt a different interpretation of the factors linking cholesterol with degenerative disease, and the role of cholesterol in repair processes may be a good place to start. It could account for the presence of large amounts of cholesterol in the atherosclerotic lesion. It would be compatible with the correlation of high serum cholesterol with more frequent arteriosclerotic complications. As in other chronic conditions, induction of the lesions by a causative agent would result in accumulation of cholesterol as part of the repair process. Thus, such diseases as nephrosis could intensify pre-existing arteriosclerotic lesions which require cholesterol for their repair. The so-called experimental arteriosclerosis induced in animals by the feeding of large amounts of cholesterol is not really relevant to the human disease. In such animals, many tissues are over-loaded with cholesterol (which is not the case in man), and among them are the arteries. Any similarity between the appearance of such arteries and those in man may be due to the limited response potential of these structures. Even less convincing are lesions induced by feeding of additional bile acids or by manipulation of the thyroid.

At this point, it may be well to discuss briefly how thinking about cholesterol has been influenced by statistical studies of the incidence of various degenerative diseases. The concept of "risk factors" has arisen from the undeniable evidence that people with hypertension, obesity, addiction to heavy smoking, or high serum cholesterol levels have, as a group, a higher incidence of arteriosclerotic disease. Denoting all of these factors as "risk factors" suggests that they all have the same relationship to the disease. It may well be that excessive smoking or obesity is a causitive factor in the disease, whereas elevated serum cholesterol

levels are symptomatic of some disease process. If this difficulty were only of semantic interest, it would not be so important. However, the insistance on cholesterol as a causative agent has led to all sorts of attempts to lower serum levels, some of which have actually been harmful (Triparanol, for example, or some of the hormones [7]). Recently, the National Heart and Lung Institute reported that, on the basis of findings of the Coronary Drug Project, such hypocholesterolemic drugs as clofibrate and niacin have no influence on the survivors of myocardial infarctions (8).

With this in mind, one may ask in what way the intake of milk fat affects cholesterol metabolism. There is ample evidence that serum cholesterol values are high after the intake of milk fat (9,10,11) and low after the intake of vegetable oils high in linoleate, especially corn oil. Essentially, this contrast is the basis for the claim that such vegetable oils are preferable to animal fats in general and milk fat in particular in the prevention of arteriosclerosis. The effect of these fats on tissue cholesterol is much less emphasized. Gran and Nicolaysen (12) have summarized the evidence, and conclude that "it thus seems to be well established that polyunsaturated fatty acids can induce redistribution of cholesterol from palsma to liver, but it does not seem to be a constant occurrence." It is probably not sufficient to assume a mere redistribution of cholesterol because Carroll (11) came to the conclusion that "in most cases, it has been found that dietary fat stimulates incorporation of acetate into liver cholesterol and unsaturated fat appears to be somewhat more effective than saturated fat." To this can be added the observation of Gerson, et al., (13) that feeding of corn oil to rats increased tissue cholesterol, even in the arterial walls.

More recently, studies have been carried out in human subjects to investigate cholesterol balance under the influence of dietary polyunsaturated fat. In studies of patients with familial hypercholesterolemia, Grundy and Ahrens (14) found no consistent alteration of the enterohepatic circulation of cholesterol, and concluded that the reduction of plasma cholesterol with the intake of corn oil is best explained by the redistribution of cholesterol in the tissues. Later, in patients with hypertriglyceridemia, Grundy (15) found increased excretion of steroids upon feeding polyunsaturated fats. In normal subjects, there were small increments in fecal steroids, but there was no close correlation between decrements of plasma cholesterol and increments of fecal steroids.

These findings make it necessary to re-interpret the significance of changes in serum cholesterol. By and large, the feeding of polyunsaturated fats does not seem to reduce total tissue cholesterol and may even elevate it. If one is convinced of the atherogenicity of cholesterol, its increased incorporation into the tissues is not an advantage. If, on the other hand, one thinks in terms of tissue repair, the elevated tissue cholesterol associated with the feeding of polyunsaturated fats could be an expression of tissue damage and repair. The evidence for this will be discussed later.

FATTY ACIDS AND TRIGLYCERIDES

Together with the word "cholesterol", the terms "saturated" and "unsaturated" have become household words during the last twenty years. The practice of thinking of fats as saturated or unsaturated has stemmed from their often opposite effects on serum cholesterol levels. The preceding discussion may have given some inkling that this classification is rather unimportant.

Emphasis on the biologically unspecific property of unsaturation obscures the great complexity of constituent fatty acids. For example, Jensen (16) has pointed out that milk fat contains over 500 different fatty acids and derivatives, and some may be of biological importance, at least for the young. Milk fat triglycerides contain about 13% of medium chain (C_{6-10}) saturated fatty acids. Such acids have been the subject of many studies in recent years. Their absorption differs completely from that of long chain acids, accounting for their wide use in the management of malabsorptive diseases. It has been found that a number of conditions (vitamin deficiencies, intake of oxidized fats, Masugi nephritis) were beneficially influenced by these acids. Their intake is associated with a reduction of serum and tissue cholesterol, and they lead to less adipose tissue formation than do long chain fats (17). The different biological properties of medium and long chain saturated fatty acids show how inadequate saturation is as the main determinant of biological activity. It has been pointed out before (18) that generalizations on the basis of saturation are useless because different saturated fatty acids have different effects on serum cholesterol levels. An early study dealing with fats of different iodine numbers emphasized that the effects may not have been due to saturation, but may just as well have been due to the unsaponifiable fraction (19).

It has also been observed that the position of fatty acids in the triglyceride molecule may be of great importance (20). Cocoa butter and mutton tallow are good examples of fats having ca. the same fatty acid composition but with different structural arrangements. Milk fat has been found to have certain characteristic structural properties (21,22,23). Although there is some disagreement as to the distribution of the shorter acids, it is generally accepted that palmitate is preferentially esterified in the β position, and this arrangement is thought to facilitate the absorption of palmitate by the young animal. Furthermore, structural arrangements of dietary triglycerides have been found to influence tissue triglycerides to some extent (24), which suggests that this aspect of dietary fats should not be ignored.

NONTRIGLYCERIDE FRACTION

The nontriglyceride fraction of natural fats makes up ca. 2-4% of their total; yet, the biological effects of this fraction may sometimes be of great importantce. This fraction contains the fat-soluble vitamins and a large number of pharmacologically active materials which vary from fat to fat. Butter contains a variety of compounds responsible for its characteristic aroma (25,26), but does not contain as many compounds as most vegetable oils (27).

Although studies of the pharmacological effects of the nontriglyceride fractions are scant, it has been reported that the elevation of serum cholesterol seen after the intake of milk fat can be induced by feeding its nontriglyceride fraction (28). Moreover, it has been reported that the seum cholesterol lowering effect of corn oil persists after hydrogenation of the oil, which suggests that the effect may not be due to its linoleic acid content, but to compounds in the nontriglyceride fraction (29). This is borne out in studies in which the cholesterol elevating effect of eggs was not altered when large amounts of linoleate were fed to hens to produce eggs with a high linoleate content. The intake of these linoleate rich eggs still induced the same elevation of serum cholesterol (30) although the same amount of cholesterol (about 200 mg/egg) gives hardly any elevation when fed to man in the absence of egg.

The possible importance of the unsaponifiable fraction was suggested in a long-term study in which rats were fed ten different fats and oils (31). Inasmuch as differences between groups could not be correlated with unsaturation or any other of the usual properties of fats, it was postulated that it was the nontriglyceride fraction which was responsible (see below). Vegetable oils can be assumed to contain active materials because of the large number of such materials in plants.

LONG-TERM ANIMAL FEEDING STUDIES

In one study (32), it was reported that feeding of a semipurified diet containing 20% of milk fat induced significantly more aortic lesions ("atherosis") in rabbits than a diet containing corn oil. From this, it was concluded that milk fat is atherogenic. However, the authors did not sufficiently appreciate the fact that rabbits have a high requirement for linoleic acid. It has been estimated that rabbits need about 4% of their calories as linoleate (33), whereas, in Moore's and Williams' experiment (34), the milk fat diet supplied only about 1% of calories as linoleate. In a later study from the same laboratory, rabbit atherosis was markedly reduced when additional maize oil was added to the milk fat diet. In surveying the literature on coconut oil (35), we concluded that many of the unfavorable results were a consequence of insufficient dietary linoleate.

In a long-term study carried out in our laboratory (31), we also fed milk fat to rats, which have a lower requirement for essential fatty acids. In this study, groups of forty male rats were fed a purified diet containing 20% of one of ten fats and were observed from weaning until they died spontaneously. Histological specimens taken at autopsy revealed a wide array of pathological findings, including infectious, neoplastic, and degenerative diseases. Among other things, most of the rats were found to have varying degrees of cardiac fibrosis. When all rats had died and all histological examinations had been completed (including evaluation of the degree of fibrosis in a blind test), statistical analysis of the data showed that the groups fed olive oil and the linoleate-rich cottonseed, soybean, and corn oils had more severe cardiac fibrosis ($P<0.01$) than did those fed lard, beef fat, chicken fat, and milk fat. Many of the rats had a marked proliferation of the bile ducts, which occasionally was so pronounced that it could be termed biliary cirrhosis. Here, too, the changes were more pronounced in the rats fed vegetable oils. In the same study, there were significant ($P<0.02$) differences in tumor incidences among the various groups; the group fed milk fat had one of the lowest incidences of tumors (36).

In a study of cynomolgus monkeys comparing the nutritional value of several filled milks, the control monkeys were fed a skim milk with added milk fat for as long as five years. The milk fat provided about 98% of their total fat intake, and these animals thrived on their diet and were in excellent condition when the experiment was terminated (37).

Although the lack of a true correlation between any of the usual chemical and physical properties of fats and their biological properties suggests that only long-term feeding studies are valid for determining the desirability of any dietary regimen, this naive approach also presents difficulties. Not only are such studies time consuming and expensive, but they may not be relevant to the human condition because of their design. In an animal experiment, it is customary to feed rats, for example, a purified diet in which one constituent is varied, the dietary fat, for instance. Such a procedure will exaggerate the effect of the fat so that one can not be sure what would happen if it were fed in combination with other constituents.

BLOOD CLOTTING

The question of what part lipids, in general, and dietary fat, in particular, play in thromboembolic phenomena has received a great deal of attention. Hellem and Stormorken (38), in reviewing the subject, came to the conclusion that elevated serum levels of "free fatty acids" (evidently nonesterified fatty acids bound to albumin) are associated with an increased incidence of thromboembolic complications. As to the influence of dietary fats themselves, investigations have centered around clotting time (39) or one or more of the various parameters of the blood clotting process, i.e., thromboplastin time, platelet adhesiveness, platelet clumping time and turnover rate (40). However, their role in actual thrombus formation is by no means clear.

Keys (39) concluded that a high dietary fat intake shortens clotting time; Mirsky and Nossel (41) found that there was no difference among dietary fats, including milk fat. On the other hand, Mustard and Murphy (40) also thought that persons fed a diet high in egg yolk and dairy fat had alterations in coagulation parameters associated with faster clotting than did persons fed a low fat diet. When subjects were fed a mixture of vegetable and animal fats, values were believed to be intermediate. The interpretation of these data is difficult, because in the measurement of whole blood clotting, two of seven patients had a somewhat prolonged clotting time, and one showed no change. When the effect of the vegetable-animal fat diet was compared to that of the low fat diet, the same subjects again had a somewhat longer clotting time. These data seem to bear out Key's results (39) as to the effect of fat in general. Whether or not the data imply that milk fat has properties different from other fats is highly speculative. Not only is there no statistically significant difference, but it is hardly possible to evaluate the effect of egg yolk lipid. This latter lipid seems to have very special properties as was shown when Adams (42), observed severe kidneys lesions in rats fed egg oil.

The interpretation of other data in which milk fat appeared to have a special effect on clotting is equally difficult. In one such study (43), rats were fed as much as 30% of milk fat, 5% of cholesterol, and 2% of bile acids. The entirely unphysiological composition of the experimental diet does not permit any conclusions as to the effect of milk fat on clotting under normal conditions.

If one summarizes the reports on the role of fat in the human diet, it is probably true that a high fat diet reduces clotting time, and milk fat is not very different from other fats, including vegetable oils. However, it remains to be seen in what way alterations in the clotting mechanism are related to the actual occurrence of thrombosis.

CLINICAL STUDIES

What is the clinical evidence, if any, that milk fat or other animals fats differ in their nutritional properties from the vegetable oils? In one study lasting five years (44), persons eating soybean oil had lower serum cholesterol levels and fewer heart attacks than did the control group having the typical fat intake of Norway. However, the control group had a daily intake of about 3000 calories, whereas the group fed soybean oil consumed 2400 calories/day, lost 4 to 5 pounds, and maintained this reduced weight. In view of the importance of weight reduction in relation to arteriosclerotic complications, it is hard to understand why the difference were ascribed to the saturation of the fats used.

In a twelve year study carried out simultaneously in two Finnish mental hospitals (45,46), the patients in one hospital were given the experimental polyunsaturated diet and those in the other hospital served as controls with their usual diet. After six years, the dietary regimens were reversed and the study was continued for another six years. It is reported that among the male patients, there was a significantly ($P<0.002$; $P<0.06$) reduced mortality from coronary heart disease while on soybean oil. There was a small, but not statistically significant, decrease in total mortality. Among the female patients, the reduction in mortality from coronary heart disease was too small for statistical significance, and there was no reduction in overall mortality. The authors emphasize the difficulties in assessing fluctuating populations and in comparing psychiatric pa-

tients with a normal population. However, the most important flaw was the absence of data on food intake and body wt. The Norwegian study showed that body wt and food intake can be strongly modified by similar diets.

In a double blind study (47) carried out in California over a period of nine years, two groups were fed "animal fat" or "vegetable oil." Death rates were identical in the two groups. When the number of all atherosclerotic events were combined, the incidence was somewhat lower in the "unsaturated" group. Chemical analyses of aortic material taken at autopsy from the two groups revealed no differences in the concentrations of various lipid fractions. In view of the fact that the same number of subjects in each group during the experiment, one cannot help but suspect that differences in dietary fat were of little importance.

Clinical studies specifically dealing with the long-term effects of eating butter were carried out by a group of workers at the "Bundesanstalt für Milchforschung, Kiel" (48,49). In these studies, butter with a linoleate content of 5% was compared with a margarine containing 12.5% of linoleate. About 1000 patients were kept on the experimental diet for one-five years, during which time many parameters were examined. The serum cholesterol values of the butter-fed group were higher than the cholesterol values of the margarine-fed group after 4-6 weeks. However, after one year the serum cholesterol values of the butter-fed group were lower. Total serum lipids and triglycerides were higher in the margarine-fed group. Examinations of eye grounds, electrocardiograms, and blood pressures revealed no differences between the two groups.

There exist a number of population surveys which have some bearing on whether the rapid increase in coronary disease in the U.S. is related to diet. In one such study (50), the kind of fatty acids and carbohydrates consumed by the general public was surveyed from the turn of the century to about ten years ago (using retail market supplies as an index). The conclusion was that the long-term change in dietary fat intake was not quantitatively or qualitatively consistent with the increase in the rate of coronary disease. However, during the last five-ten years, there has been a decline of about 15% in deaths from heart disease. The chief author of the study (51) emphasizes that it is highly unlikely that the current enthusiasm for exercise and dieting can give an adequate explanation because they have come too recently to affect the basic process responsible for most heart disease deaths.

In a study in which changes in serum cholesterol was associated with changes in the U.S. civilian diet between 1909 and 1956 (52), the conclusion was reached that serum cholesterol levels had not changed remarkably with changes in dietary fat intake. At the same time, life expectancy in industrialized countries has been increasing steadily, which is a strong argument against any radical alterations in current dietary patterns. In an exhaustive survey of the literature dealing with coronary heart disease (CHD), especially in relation to diet, a committee of the Royal Society of New Zealand concluded that "so far as the general population is concerned the present stage of knowledge does not justify advising any major changes in dietary habits aimed specifically at reducing the incidence of CHD (53)." In the United Kingdom, the Advisory Panel on Diet in Relation to Cardiovascular and Cerebrovascular Disease unanimously agreed that "they cannot recommend an increase in the intake of polyunsaturated fatty acids in the diet as a measure intended to reduce the risk of the development of ischaemic heart disease." The majority of the Panel recommended that the total amount of fat in the diet be reduced, especially saturated fat (54).

These recommendations are somewhat at variance with the "Report of the Inter-Society Commission for Heart Disease Resources," which reflects the opinion of the National Heart and Lung Institute (55). The main thrust of their recommendations is directed toward reducing dietary fat in general and saturated fat in particular, and toward reducing cholesterol intake. The recommendation to reduce total fat intake in the American diet to a level of less than 35% of calories can hardly be faulted. They further recommend limitation of saturated fats to about 10% of calories and an intake of 10% of calories for monounsaturated fats and for polyunsaturated fat. Of course, there is no proof that such a marked alteration in the composition of the dietary fat would influence arteriosclerosis. The report also recommends reduction of cholesterol intake to 300 mg/day. We have discussed above evidence that the dietary level of cholesterol does not appreciably influence serum levels of cholesterol.

At the present time, it would probably be more rewarding to examine the possibility of a specific infectious factor in the etiology of arteriosclerosis. Such a possibility was deduced from the clinical and epidemiological features of the disease some years ago (1, 2), and this somewhat vague hypothesis has since become rather attractive because of a number of new insights. First among these is the discovery of slow viruses (56, 57). Furthermore, the appearance of extra- and intracellular cholesterol crystals in cells infected with feline herpes virus (58), the important part played by the smooth muscle of the arterial wall in arteriosclerosis (59), and studies suggesting that atherotic plaques are clones of aberrant cells arising from smooth muscle cells in response to viruses or chemical mutagens (60) are also provocative findings.

Thus, it seems likely that the period may be coming to a close in which arteriosclerosis research is dominated by the controversy over dietary fats.

ACKNOWLEDGMENTS

R.E. Johnson, V. Babayan, and P.P. Noznick helped formulate the views expressed in this paper.

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[Received January 27, 1975]