Appraisal of dietary fat as a causative factor in atherogenesis

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This document attempts to evaluate the strengths of the associations between dietary fat and the genesis of atherosclerosis; the kinds of evidence on which these associations are based; and the risks and benefits caused by changing the quantity and quality of dietary fat in the American diet. The role of dietary fat will be evaluated herein as a factor independent of such other putative dietary factors as *1*) total caloric intake, *2*) quality and quantity of dietary carbohydrate, *3*) intake of alcohol, and *4*) intake of salt.

The section on "Cholesterol" points out the difficulties inherent in evaluating cholesterol independently of dietary fat. However, saturated fat foods (the putative factor to be discussed in this section) are characteristically rich in cholesterol; therefore, this section will consider fat and cholesterol as conjoint factors when this is appropriate.

Kinds of evidence

Epidemiological evidence

During World War II, food rationing in Northern Europe led to lowered total caloric intakes, a higher proportion of carbohydrate calories, and a reduced proportion of all dietary fats as well as of cholesterol. Although the statistical data frequently cited have many shortcomings in regard to disease prevalence and food intakes, it is generally conceded that mortality from atherosclerotic disease decreased abruptly in the early years of the War and rose again after cessation of hostilities. Indeed, the abruptness of the changes in disease rates has led to the question whether the decline in disease was due to regression of atherosclerosis, or whether it was due to entirely separate mechanisms(s). Although these observations stimulated interest in the role of diet in the genesis of cardiovascular disease, they did not permit evaluation of the role of dietary fat intake independently of the other associated variables.

Retrospective cross-sectional surveys have produced data that are consistent with the concept that low-fat, low-cholesterol diets are characteristic of populations suffering low rates of atherosclerotic disease. However, in some populations the incidence of atherosclerotic disease is found to be very low even though the diet is rich in saturated fat and cholesterol (the Masai tribesmen of East Africa, for instance). In all such studies, it is difficult to assess the interaction of such confounding variables as total caloric intake, habitual energy outputs, and coincident disease causing malnutrition.

In dietary surveys conducted in highly developed areas no significant dietary differences in saturated and polyunsaturated fat intake have been detected among those suffering higher versus lower rates of atherosclerotic disease. Exceptions are the studies of vegetarians, which also are retrospective and cross-sectional, and which have shown a positive correlation between atherosclerotic disease incidence (low) and saturated fat and cholesterol intakes (very low). However, there are important differences in life-style, cigarette smoking, and alcohol intake that confound the interpretation of these data, as well as the fact that the individuals choosing such diets may be different in other ways from the general population. Similar interpretative difficulties exist in considering the raised incidence of atherosclerotic disease in persons migrating from areas with low disease rates (where the diet is lower in fat and cholesterol) to areas in which the indigenous population suffers high disease rates (where the diet is higher in saturated fat and cholesterol).

Animal experimentation

The experiments in animals that provide information on the independent effect of di-

etary fat are limited in number. Most animal species respond to the combination of dietary cholesterol with either saturated or polyunsaturated fat with an increase in serum cholesterol concentration and the development of arterial lesions. Regression of lesions also has been shown in some species (including nonhuman primates) by simple removal of cholesterol from the diet or by removal of dietary cholesterol coupled with replacement of saturated fat either by carbohydrate or polyunsaturated fat.

Assessment of the independent role of dietary fat is made difficult, since in most animal studies there have been coincident changes in dietary cholesterol. Moreover, there are differences among various animal species (and between animals and man) in their responses to dietary fat (quality and/or quantity). The variability among animal species in susceptibility to dietary cholesterol and to quality of dietary fat does not permit any conclusive assessment of their separate roles in human atherosclerotic disease.

Human experimentation

There is no evidence, either observational or experimental, that conclusively demonstrates a causative relationship between dietary fat per se and human atherosclerotic disease.

There is, however, abundant evidence from a number of large prospective studies here and abroad that the incidence of new events of atherosclerotic disease is directly correlated with plasma cholesterol levels and with levels of low-density lipoproteins, but inversely with high-density lipoproteins. Although it has been claimed that an elevated plasma triglyceride level is an independent risk factor, multivariate analyses that consider such risk factors as plasma total cholesterol, plasma high- and low-density cholesterol, plasma triglycerides, age, sex, smoking, hypertension, and glucose intolerance indicate that the predictability of atherosclerotic disease is not significantly improved by adding plasma triglycerides to the list of risks. This is not to say that the metabolism of triglycerides is unrelated to the process of atherogenesis, for it may well be that the factors leading to high triglycerides are the same as those leading to high levels of low-density lipoproteins and low levels of high-density lipoproteins. There has been no prospective study of diet in prevention of atherosclerotic disease in populations selected specifically for hypertriglyceridemia.

Thus, the linkage between disease causation and dietary fat intake in man is an indirect one: many experiments have shown in young and middle-aged men, "normolipidemic" by American standards, that plasma cholesterol concentrations are predictably increased by a diet high in saturated fat, and these changes are largely independent of dietary cholesterol. The same effects have also been demonstrated in men and women who are hyperlipidemic.

In the few studies that have tested strictly the interaction of dietary cholesterol and degree of saturation of dietary fat, the addition of cholesterol to a saturated fat diet of healthy normolipidemic adults has led to a slightly larger increase in plasma cholesterol level than when cholesterol was added to a polyunsaturated fat diet.

In large prospective population studies it has not been possible to predict which individuals will suffer a new event of atherosclerotic disease on the basis of survey information concerning dietary fat intake. However, a number of prospective studies have been carried out to test whether alterations in dietary fat and cholesterol that lead to lower levels of plasma cholesterol can be shown to reduce the incidence of new events of coronary heart disease. Both secondary and primary diet-heart trials have been reported; while in no case have the trials shown unequivocal reductions in disease incidence or reduction in total mortality, the results have been supportive of the premise under test. Because of problems inherent in their design, execution, and analysis, these diet-heart trials have not unequivocally proved or disproved the underlying hypothesis that cholesterol-lowering leads to reduced incidence of atherosclerotic disease.

Quality and strength of the evidence

Consistency among various population groups

Dietary surveys in many parts of the world have shown that populations eating diets rich in saturated fats and cholesterol have higher

plasma cholesterol concentrations and a higher prevalence of atherosclerotic disease than those found in populations on low-cholesterol, low-fat diets. Conversely, vegetarians (ovo-lacto-vegetarians as well as strict vegans), whose diets are low in cholesterol and saturated fats but relatively high in polyunsaturated fats and plant sterols, have lower plasma cholesterol levels and a lower prevalence of coronary heart disease; they also fail to show the increase in plasma cholesterol levels with age that is regularly seen in the nonvegetarians of highly developed societies. Moreover, migrants from areas in which plasma cholesterol levels, saturated fat intake, and atherosclerotic disease are low have shown progressive increases in vascular disease after adaptation to diets rich in cholesterol and saturated fats. There are a few exceptional population groups in which a high-cholesterol, high-saturated fat intake is claimed not to be attended by a high prevalence of atherosclerotic disease; these conclusions are based on general observations, however, and not on detailed studies of dietary intakes or on adequate pathological data.

Thus, in most comparisons of large population groups there is a strong association between saturated fat and cholesterol intake, plasma cholesterol concentrations, and mortality rates from atherosclerotic disease. However, these groups differ in many ways, both genetic and environmental (including diet), and it has not been possible to show what part of this association is due to an *independent* effect of dietary fat quality and/or quantity.

Consistency among individuals within a given population

In a large number of short-term rigorously controlled experiments carried out in young to middle-aged males who were normolipidemic by United States standards and who were free of signs or symptoms of atherosclerosis, it has been clearly shown that plasma cholesterol levels rise in proportion to increasing intakes of saturated fat, and conversely, fall on diets rich in polyunsaturated fats, where cholesterol intake has been held constant. The same effects have also been reported in hyperlipidemic adults.

In contrast to studies of different populations, studies of dietary fat intakes *within* population groups have usually failed to show a correlation between intake levels, plasma cholesterol levels, and incidence of atherosclerotic disease. However, there are large methodological errors in measurements of the quality and quantity of dietary fat intake and cholesterol intake in free-living persons; there is large intrasubject variability in plasma cholesterol concentration and susceptibility to atherosclerosis; and the intrinsic variability among individuals in regulation of plasma cholesterol concentrations on any given diet is large.

Autopsy data in man

The few published autopsy studies show no relationship between atherosclerosis and fat intake on an individual basis. Although autopsy studies in large population groups have shown such an association, this association has not been shown to be independent of other dietary and/or societal factors.

Strength of the association

Among large population groups (national or regional), and among smaller population subgroups (e.g., vegetarians), the association of dietary intake of saturated fat with plasma cholesterol concentration and with atherosclerotic disease incidence is strong. However, associations between two variables based on group means do not permit inferences to be drawn about the corresponding associations among individuals within a single group.

When individuals are examined at only one time, as in most cross-sectional studies of a single population thus far reported, there is no association between the quality and/or quantity of dietary fat and either plasma cholesterol or risk of atherosclerotic disease. When individuals are examined before and after exposure to diets with different intakes of saturated dietary fats and cholesterol under rigorously controlled conditions; however, a large proportion shows a significant diet-related change in plasma cholesterol. However, in no such groups have unequivocal changes in disease rates been demonstrated. These failures could have been due to the short duration of the studies, the age of subjects at inception of the studies, or to the inadequacy of the changes in plasma lipids

so produced. Alternatively, the underlying hypothesis may not be correct.

Independence of the association

In all observational studies of either large or small population groups, and in observational studies of individuals within any population, an independent effect of the quality and/or quantity of dietary fat on risk of disease has not been demonstrated.

In studies of individuals under strict dietary control the effect of the saturation of dietary fat on plasma cholesterol levels has been found to be largely independent of cholesterol intake. However, there are no observations of this sort in relation to risk of disease.

Temporal association

The migration of peoples from low- to high-atherosclerosis areas of the world has provided evidence that a change in dietary fat intake precedes a rise in plasma cholesterol level as well as a rise in prevalence of atherosclerotic disease in the migrants. However, the independence of the association is weak, since in no known case has a change in fat intake occurred independently of other dietary and societal changes. The recent downward trend in mortality from coronary heart disease in this country has been accompanied by many changes, including a reduction in intake of saturated fat and cholesterol and an increased intake of polyunsaturated fat, together with some decrease in mean plasma cholesterol levels. The role of any one of these factors in this decline cannot be clearly defined.

Effect of new exposure

No prospective studies have related an increase in incidence of atherosclerotic disease to an increase in saturation of dietary fat unrelated to other dietary and societal changes. However, the effect of fat saturation on plasma cholesterol levels is highly predictive for groups as well as for individuals.

Preventive effect of removal

Saturated fat intakes have been markedly decreased and polyunsaturated fat intakes increased in all of the primary intervention studies undertaken since the late 1950's; these trials have been carried out almost exclusively in middle-aged and older men. The evidence for reduction in rates of incidence of new events of atherosclerotic disease in these studies is not strong. If indeed the removal of saturated fat from the diet could truly reduce the incidence of new events of atherosclerotic disease, then the failure to reach conclusive results in those studies may have been due to the small changes achieved in plasma cholesterol lowering, to the short duration of the trials, and to the fact that the trials were not undertaken in groups that were intentionally selected for the existence of the important risk factor of hyperlipidemia.

Improvement effect of removal

In persons already known to have atherosclerotic disease, the substitution of polyunsaturated for saturated fats, together with reduction in cholesterol intake, has provided suggestive but not conclusive evidence that the incidence of new events of coronary heart disease can be reduced. Such trials suffer many of the same weaknesses as the primary trials discussed in the previous paragraph. The only prospective trial of a low-fat low-cholesterol diet reported to date was also a secondary trial; it showed no effect on the recurrence rate of atherosclerotic disease.

Animal models

The induction of experimental atherosclerosis by feeding diets rich in fat and cholesterol has been successful in several species. However, there are marked variations in susceptibility between species and to a lesser degree among individuals in any given species. Although these models are similar to the human disease, many of them have involved dietary levels of cholesterol far in excess of human intakes. Thus, in all models used, dietary cholesterol has been a contributory factor, and in regression experiments both the quality of fat and the intake of cholesterol have usually been modified. The marked species variations indicate that the effects of dietary fat exchanges cannot be transferred directly to man; indeed, we do not know which species most accurately reflects the human response.

Biological explanation

Recent advances in understanding the role of cellular receptors for low-density lipopro-

teins in genetic hypercholesterolemia in man have provided a possible biochemical explanation at the cellular level for the accumulation of cholesterol esters in arterial wall cells in the presence of elevated low-density lipoprotein concentrations, and have accounted for elevated plasma cholesterol concentrations in a small proportion of individuals. While genetic factors most certainly modulate the response to environmental factors, the latter play a more important role in explaining the high prevalence of atherosclerotic disease in the more highly developed parts of the world. The rising intake of saturated fats in the first half of the 20th century correlates with a rising prevalence of atherosclerotic disease (and in the last decade a falling prevalence of coronary heart disease correlates in time with an increased substitution of polyunsaturated fats for saturated fats), but whether these changes in environmental factors are causal or coincidental remains uncertain.

What is clear, however, is that plasma cholesterol levels can be altered by changes in dietary fat saturation. Metabolic ward studies in small numbers of individuals have shown that the isocaloric substitution of polyunsaturated fat for saturated fat causes no sustained change in excretion and/or daily synthesis rates of cholesterol in patients who are normolipidemic or hypercholesteremic. However, in many patients with hypertriglyceridemia the excretion of cholesterol and its major end-products (the bile acids) is increased. However, none of these observations has been carried out for longer than a few months, so that the long-term effects of dietary fat exchanges on the absorption, synthesis, storage, and excretion of cholesterol are not known. It is accepted that skin xanthomata soften and/or disappear when plasma cholesterol is held at lower levels, but the mechanism of this efflux of cholesterol is not understood.

The fatty acid composition of all plasma lipids is strikingly affected by the saturation of the fat in the diet, as is the composition of red blood cell lipids, adipose tissue, and presumably all cell membranes. Thus, the more unsaturated the diet fat, the more unsaturated the body fat. Conversely, diets low in fat (regardless of type) and high in carbohydrate lead to increased saturation of plasma and tissue lipids, since in man the enzymatic mechanisms for biosynthesis of polyunsaturated fatty acids are absent. Thus, in the former case the body fats become more polyunsaturated, and in the latter case more saturated. The functional effects of these differences on such key processes as membrane transport, immune mechanisms, carcinogenicity, and aging have not been defined, leaving open the question of the relative desirability of one body composition over the other, both being controllable by the quantity and quality of dietary fat.

Observations on low- and high-density lipoproteins and chylomicron-cholesterol metabolism as pathogenetic factors in atherosclerosis add a new dimension to the issues under discussion. Studies are currently being carried out with dietary fat quality and/or quantity as independent variables, but these studies are still in an early stage.

Risks and benefits caused by reduction in saturated fat and cholesterol and/or increase in polyunsaturated fat

Low-fat, low-cholesterol diets are characteristic of the nutrition of large parts of the world in which the prevalence of atherosclerotic disease is low. Also characteristic of these areas is a generally low total energy intake that is likely contributory to the small stature and leanness of these populations. Most such areas also are characterized by a high degree of physical fitness, and by a considerable proportion of caloric expenditure in physical work and in adaptations to environmental stresses such as temperature extremes. While many of these areas also are distinguished by parasitic and chronic infectious diseases as well as by nutritional deficiencies and a short life-span, there is no evidence that a low-fat diet is harmful, per se.

Proponents of such diet patterns for the general American population allude to the centuries-long use of such diets without known harm, and, indeed, a few technologically modern populations that consume low-saturated fat, low-cholesterol diets with high caloric intakes are characterized by life-spans similar to those of most Western populations. In judging such data, attention must be paid

to the different work habits of previous generations, to their energy expenditures and life-styles, very different from those of the present day, and to the large burden of diseases other than degenerative in previous generations. As pointed out in the "Cholesterol" section of this symposium, there is no known risk attached to diets low in or devoid of cholesterol: this essential body constituent can be synthesized at rates adequate to meet all known body needs for it as a precursor of steroid hormones and surfactant bile acids, and as an essential component of the central nervous system and of all plasma membranes.

However, there are few historical precedents for widespread use of diets rich in polyunsaturated fats. Modern vegetarians appear to perform well on diets low in animal products; while it is reported that atherosclerotic disease is less common in these groups, other dietary and societal factors may play important roles in this end-result. It is a fact of separate interest that there is evidence of a reduced incidence of certain cancers in these groups.

In general, then, there are few precedents for use of diets high in polyunsaturated fats. This has led scientists to question the advisability of widespread application of such diets, leaving the burden of proof of such diets' harmlessness and utility to those who promote them. The concerns have been of three sorts: *1*) the hazards of peroxides that can arise from polyunsaturated fats when insufficient anti-oxidants such as vitamin E are ingested, *2*) the hazards of unsaturated fats (or the products of their metabolism) as carcinogens or cocarcinogens, and *3*) the tendency to cholesterol gallstone formation due to changes in biliary lipid composition. The available evidence in human beings is limited to the findings of the long-term diet-heart studies in Los Angeles and in Helsinki reported in 1969 and 1972, respectively, in which total mortality was not different in the large groups fed saturated-fat, cholesterol-rich diets on the one hand, or polyunsaturated-fat, low-cholesterol diets on the other. Since the deaths due to new events of atherosclerotic disease were somewhat lower in the second group (though not convincingly so), it was concluded that the polyunsaturated fat diets had led to increased deaths from other causes. Indeed, the incidence of various malignant neoplasms was said to be increased, and in the Los Angeles study an increased incidence of cholesterol gallstones was reported. These claims have been carefully reexamined and extensively debated; it is the current consensus that, though neither claim has been judged to be valid in terms of cause and effect, the possibility of such developments should be directly tested in future experimentation. The peroxide hazard seems to have been countered by the finding of high levels of vitamin E in patients eating diets rich in polyunsaturated fats, and by the absence of any clinical or laboratory evidence of vitamin E deficiency except in newborns fed formulas rich in polyunsaturates (this has been corrected by supplementation with vitamin E). The high gallstone incidence reported in the Los Angeles study has not been confirmed by others. While lithogenic bile has been noted in some but not all hypertriglyceridemic patients when polyunsaturated fats replace saturated fats in their diets, this has not been found in hypercholesteremic individuals. In any case these questions have not been addressed in long-term fat exchange studies.

The benefits that might accrue from the ingestion of a low-fat, low-saturated fat, low-cholesterol diet have never been adequately tested except in terms of reductions in plasma lipid levels. Even then, inadequate attention has been paid to the confounding biases introduced by lowered total caloric intakes and lowered body weights. However, several studies have addressed the question whether a high-polyunsaturated, low-saturated fat, low-cholesterol diet causes a reduction in rates of new events of atherosclerotic disease. These studies, as a group, support the proposition that new events were lowered in the groups eating the highly unsaturated fat diet but that mortality was not affected.

Recent studies have reemphasized the "protective" effect of high-density lipoprotein cholesterol that appears to counterbalance the postulated "harmful" effect of low-density lipoprotein cholesterol. Studies on the effects of dietary fat exchanges per se on high-density/low-density lipoprotein ratios in normolipidemic or hyperlipidemic individuals are now at an early stage, and no conclusions can be reached as yet.

Finally, it is not known whether the possi-

ble benefits of a low-fat, low-cholesterol diet outweigh those of a moderate fat diet with a high ratio of polyunsaturates to saturates and low in cholesterol. While there is some, but not conclusive, evidence for benefit from the latter, there is none reported that bears on the advantages and disadvantages of the former.

The caveat must be repeated that the implementation of *any* dietary change in large populations carries with it some degree of risk, however small, due to changes in food processing or food purchases, or to unforeseeable hazards for individuals with marginally adequate diets.