Atherosclerosis and the Fat Content of the Diet

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A report to the American Heart Association and to the American Society for the Study of Arteriosclerosis the Nutrition Committee of the Council on Community Service and Education of the American Heart Association and others.

The aim of this discussion is to summarize and evaluate evidence for and against the concept that the fat content of the average present-day North American or north European diet is a significant factor in the genesis of cerebral, myocardial, renal, or peripheral atherosclerosis. To date there is no incontrovertible evidence for such a relationship; nevertheless, a strong case is developing to suggest that the nutritional status of an individual is an important environmental factor in the etiology of this disorder. The total fat and the type of fat in the diet are among the nutritional factors particularly involved.

General Principles

A review of this kind may provide nutritionists and physicians with a guide when health recommendations are made to groups or to individuals. In formulating these recommendations, however, one must always bear in mind that the results of clinical studies on patients and experimental studies on animals are not necessarily applicable to healthy individuals.

It is hoped that industries concerned with the manufacture, processing, and distribution of foods and the insurance industry, will take responsibility for performing and promoting effective basic as well as applied research on the problem of the relationship between diet and atherosclerosis. Industry is usually generous in the support of research for product development. It has given very limited support to basic research in this vital field, even though the results of such investigative work would enable management to plan more intelligently for the future. The need for reliable information and appropriate action is urgent.

One of the first things that occur to lay individuals in thinking about chronic diseases is a possible change in diet. Frequently this reasoning is applied to situations in which diet is of little or no importance. The result is a flood of diet fads and quackery. In the case of atherosclerosis, there is some evidence that diet may be of considerable importance. It is now the responsibility of research workers to determine more exactly this possible role of diet in the etiology of atherosclerosis.

Atherosclerosis in all probability has no single cause. It results most likely from a combination of factors, or is, as Page suggests, a "multifaceted disease." Among those facets presently implicated are heredity, diet, morphologic and chemical anatomy of the blood vessel wall, arterial blood pressure, lipid content of the blood, and sex. Atherosclerosis is a focal lesion. Because its consequences are widely variable, there is no practical means of clinical diagnosis of the uncomplicated, potentially reversible lesions. A large plaque may be so located as to cause little injury and a small one may be placed so strategically in a coronary vessel as to cause death by direct occlusion. Atherosclerosis is believed by some investigators to be episodic, with the plaques building up rapidly in days or weeks and remaining quiescent for months or years thereafter. Many workers believe this process to be reversible, at least in its early stages.

The approach to the problem by animal experiments has shown that atherosclerosis, similar to but not identical with that of the human type, can be produced in a variety of experimental animals by dietary variations. Many kinds of diets have been used; some are deficient in one or more nutrients, others contain excessive amounts of certain constituents or combine excess of one with deficiency of another. The results of such experiments have influenced significantly the opinions of clinicians about diet.

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Various types of dietary surveys have been conducted in the United States and in other countries to determine if a relationship exists between diet and atherosclerotic coronary artery disease. The importance of the evidence derived from these epidemiologic approaches and its seemingly obvious implications justifies a critical evaluation of this phase of the problem.

The opinions of clinicians vary greatly. Some hold in high favor the view that atherosclerosis and the lipid or cholesterol content of the blood are related directly. There is evidence both for and against this view. The most cogent evidence presented in favor of the serum lipid theory is that hyperlipemia over a sufficient length of time is associated with premature atherosclerosis. The first question raised concerns the concentration of plasma lipids that constitutes an abnormal elevation. Are the present normal standards and ranges biologically optimal? Or are they normal only for the North American population, a large proportion of which has premature or latent atherosclerosis? If the relationship between hyperlipemia and atherosclerosis is one of cause and effect, it follows that any regime that will reduce even “normal” blood lipid concentrations should also decrease the incidence of atherosclerosis. Is reduction of dietary fat or change in its type the only practical means of accomplishing this? And will it be effective?

More recently, evidence has been presented that the degree of unsaturation of fat in the diet and, in particular, the essential fatty acid content of the diet in proportion to total dietary fat may be of critical importance in determining the level of cholesterol and associate lipids in blood.

Another important aspect of the problem of coronary occlusion and its relationship to atherosclerosis of the coronary vessels is the possibility that the thrombosis is due more to a defect in the clotting mechanism than to an “incidental” coronary atherosclerosis. Defects of clotting mechanisms have been related by some workers to the fat content of the diet. Even the atherosclerotic plaques themselves have been related to abnormal clotting rather than to primary deposition of lipids. These alternatives are mentioned to illustrate the danger in taking too narrow a view of the problem in our concern with dietary fat and the mechanisms that may relate it to atherogenesis.

Most of the investigation of atherosclerosis must be done of necessity with animals. No clinical, objective method of antemortem diagnosis of uncomplicated atherosclerosis is available. This fact must be kept in mind when reading the clinical literature.

This is a time when great pressure is being put on physicians to do something about the reported increased death rate from heart attacks in relatively young people. People want to know whether they are eating themselves into premature heart disease. They are entitled to an unprejudiced answer. On the one hand, some scientists have taken uncompromising stands based on evidence that does not stand up under critical examination; on the other, certain industrial groups appear to believe they can suppress the problem by advertising campaigns. The current spate of articles in the lay press often does not present a balanced account of current opinion.

In the opinion of the authors of this review, there is not enough evidence available to permit a rigid stand on what the relationship is between nutrition, particularly the fat content of the diet, and atherosclerosis and coronary heart disease. We are certain of one thing: the evidence now in existence justifies the most thorough investigation. This should be done soon, thoroughly, and uncompromisingly.

Many nutrients, either in excessive, or in insufficient amounts, have been implicated in the pathogenesis of atherosclerosis. Fats, alone or in association with cholesterol, have been given most attention, but intakes of protein, carbohydrate, choline, pyridoxine, and organic sulfur also have been implicated in atherogenesis, although largely from the aspect of their relationships to fat and cholesterol metabolism. Fat is certainly the central issue of both basic and clinical investigation and, now, also of lay speculation. This association
of fat with atherosclerosis has been pursued in nearly every part of the world and at various levels, epidemiologic, clinical, and experimental. No attempt will be made to document all of the evidence but rather to point out some of the seemingly significant directions it has taken, with the aim of formulating some interim conclusions.

**Epidemiologic Approach**

The starting point of this approach is the assumption that data are available that can convincingly show the association, or lack of association, between diet and especially coronary and cerebral artery disease. Some of the difficulties of determining the prevalence and severity of coronary atherosclerosis are indicated above and have been summarized elsewhere. The clinical diagnosis of coronary arterial heart disease dates substantially from the first decade of this century. No one questions the remarkable increase in the reported number of cases of this condition. Undoubtedly the wide use of the electrocardiogram in confirming clinical diagnosis and the inclusion in 1949 of Arteriosclerotic Heart Disease in the International List of Causes of Death play a role in what is often believed to be an actual increased “prevalence” of this disease. Further, in one year, 1948 to 1949, the effect of this revision was to raise coronary disease death rates by about 20 per cent for white males and about 35 per cent for white females. Lew states:

In fact 30 per cent of the increase in the crude death rate from coronary artery disease since 1940 is due merely to the aging of the population. Another 40 per cent of the increase in the crude death rate can be ascribed directly to the changes in procedures and classification adopted with the sixth revision of the International Causes of Death. In my judgment, a major part of the remaining 30 per cent represents merely the acceptance of a broader concept of coronary artery disease, better diagnosis and increasing usage of the certifying causes of death. In other words, probably less than 15 per cent of the increase in death rate can be attributed to a real increase in the mortality from this disease.

Nearly a third of the reported cases of arteriosclerotic heart disease show a disparity between clinical and autopsy diagnosis, in part attributable to the wide range of subclinical coronary atherosclerosis. Hence, some statisticians do not accept the proposition that, in this country at least, there is an increasing incidence of this condition; others believe that such may be the case, particularly in younger age groups.

These difficulties in interpretation of the vital statistics occur even when the area under study is a single community. They become magnified as the area of study widens. Thus, a comparison of the 1950 vital statistics of the United States and Italy for the age group 50 to 54 shows wide differences. In the United States cerebrovascular lesions would seem to be 10 (females) to 16 (males) per cent less common than in Italy, while in the United States degenerative heart disease (coronary, angina pectoris, myocardial infarction) is 3 times more common in males and 1.5 times more common in females. Ill-defined causes of death are more common in Italy than in the United States. Clearly, differences in diagnosis and certification between 2 countries account for some of these differences.

The unexpected finding is that like differences also arise between different parts of the United States, and even between neighboring states. For example, the age-adjusted cardiovascular disease rate for 35- to 64-year-old white males indicates a spread from 348 (South Dakota) to 734 (District of Columbia) and from 550 (Virginia) to 608 (Maryland) and from 395 (Arkansas) to 524 (Alabama). In the specific case of coronary artery disease, the distribution of deaths in the United States assumes a geographic pattern with maxima in the Middle Atlantic States and California and minima in the East South Central States. The highest rate occurs in New York and the lowest in New Mexico. The meaning of these differences is obscure. The data show that the vital statistics of an area can serve only as a crude index for comparison with other areas and that the value of such an index decreases greatly when the areas studied have different cultures or when one suffers the disorganization imposed by hard times, by famine, or by war.

These difficulties on the diagnostic side occur also on the nutritional side. Comparative
nutritional surveys range from estimates based on the food balance sheets of 2 nations to carefully measured intakes of individuals. A national balance sheet includes estimated domestic production, plus imports, less exports, and allowances for carry-overs of food stocks. Estimates must then be made of grain used for seed or animal feed, of edible crops used industrially (potatoes or grain for alcohol, fats and oils for paint, soap, etc.) and of wastage and spoilage. Finally, the food consumption can be estimated by distributing net residual food through the population by age groups, making allowance, if possible, for differences in food customs between different parts of the country, such as the home use of corn in the southern and of wheat in the northern United States. It is obvious that such estimates may indicate trends in single countries or demonstrate wide differences in the adequacy of the diets available, but that they have little application to small groups, especially if the differences are small.

The problem is exemplified in a study of individual food balance carried out by the Medical Nutrition Laboratory in U. S. Army messes. The master menu called for the purchase of 3,900 calories daily per man, but the food offered in the mess hall measured from 3,068 to 3,326 calories daily per man. The cooking of bacon was one reason for the disappearance in calories; it involved a loss of 39 per cent of the original weight as drippings with a loss of 1,600 calories per pound of bacon used. Of the 182 Gm. of potentially edible fat available daily to each man only 134 Gm. were actually consumed. Thus not only national balance sheets can be deceiving but even estimates made under closely supervised conditions as in the U. S. Army messes. Evidently purchase and inventory records do not accurately indicate the true value of the food consumed.

Keys and Anderson have attempted to circumvent these difficulties by personal estimates of diet consumption and of the incidence of coronary atherosclerosis in many parts of the world, supplemented in some studies by autopsy data. Reference will be made to some of these studies below. They concluded that, in general, there is indeed an association between total fat intake and the incidence of deaths attributed to arteriosclerotic heart disease. In Minnesota, Sweden, and Denmark, and high-income groups in Spain and Italy, they reported a high fat intake and a high incidence of coronary vascular disease. In the poor of these 2 countries, and in Japan, where the fat intake was low, they reported low incidence of coronary vascular disease. If the data can be confirmed, the trend of the findings is unquestionably significant. That the dietary factor, i.e., fat intake, rather than the genetic factor is possibly the more significant variable is indicated by comparisons of southern Japanese in Kyushu with their relatives in Hawaii and of southern Italians living in Boston with those living in Naples. It must be borne in mind that there is a difference in the collection of the vital statistics in the areas under comparison that may vitiate these conclusions. The validation of vital statistics in these studies by inspection of hospital records and examination of groups of patients may not be as cogent as it would seem at first glance because standards for seeking hospital admission vary widely with cultural and social levels.

That the genetic factor may influence results of such studies is indicated by a recent cooperative study made by the life insurance companies in the United States. They investigated 18,000 insured lives for periods of up to 15 years and showed conclusively that persons who had reported 2 or more cases of early cardiovascular renal disease in their families were subject to death rates from cardiovascular disease that were from \(1\frac{3}{4}\) to \(2\frac{1}{2}\) times those prevailing among all persons insured at standard premium rates.* More recently, Epstein et al. have reported a study among garment workers which indicated that serum cholesterol and body weight, as well as blood pressure, were determinants in the incidence of coronary heart disease in men of Italian but not in those of Jewish origin.

Thomas has reported recently on the incidence of acute fatal myocardial infarction in about 17,000 autopsies that were performed between 1910 and 1954. A change has occurred

in the relative incidence of the disease in white individuals of the 2 sexes from 2:1 (males: females) before 1940 to 1:1 since 1940. This is thought to be due primarily to the greater increase of fatal infarction in elderly females. They also reported that the over-all incidence of fatal infarction was 5 times as high among the whites as among Negroes. This difference was greater in the period 1940 to 1954 than in the period 1910 to 1939 because the incidence among white individuals had risen greatly but that among Negroes had risen only slightly.

**CLINICAL APPROACH**

This approach depends primarily upon the association of increased incidence of atherosclerosis and of coronary arterial disease with certain diseases such as diabetes, myxedema, nephrosis, and xanthomatosis, when associated with hyperlipemia and hypercholesterolemia. This experience indicates that the equation of atherosclerosis with hypercholesterolemia is presumably valid, but does not establish the association between fat intake and hypercholesterolemia. Thus, Page and Farr found no effect of high or moderately low-fat diets on plasma lipids of nephrotic children in short time experiments, and Mann found no significant increases in serum cholesterol or \( \beta \)-lipoprotein in 2 normal young men fed high fat diets. On the other hand, some hypertensive patients exhibit large increase in both, while others show little or none. The wide variation in individual response deserves much more attention. Turning to normal populations, the evidence is not concordant. Women in Iowa and Nebraska eat high-fat diets, but have a mean serum cholesterol of only 209 mg. per 100 ml. On the other hand, Mayer et al. found that high-fat animal or vegetable diets increased and low-fat diets decreased serum cholesterol of normal subjects, confirming earlier data of Keys.

**Cholesterol**

Many years ago the clinical association between hypercholesterolemia and atherosclerosis was correlated with the finding that rabbits fed cholesterol in oil developed atherosclerosis. Cholesterol, once regarded as a non-metabolizable building block in animal tissues and then as the mother of hormones, became to many the villain underlying arterial catastrophe. A large factor in this association—but biologically the least significant—was that the Liebermann-Burchard reaction made measurement of serum cholesterol easier than measurement of other lipids. In fact, the reaction may have dragged a blue-green herring across the trail of investigation by concentrating too much attention on cholesterol at the expense of substances of equal or greater potential interest.

The concentrations of plasma lipids usually tend to vary simultaneously in the same direction and any one of them might be as significant as cholesterol. In man, it seems likely that serum cholesterol concentration is virtually independent of the intake. But this cannot be stated firmly as a generalization. Thus “pure” vegetarians with low-cholesterol intakes tend to have lower serum cholesterol concentrations than nonvegetarians. A problem of absorption also may be involved, since egg yolks added to the normal diet increase serum cholesterol concentration more effectively than pure cholesterol in a majority of normal subjects.

Apart from the possibility that cholesterol may not play a dominant or specific role in atherosclerosis, determinations of serum cholesterol began to go out of fashion after the first of a series of reports by Gofman and his associates. They found a close association between coronary atherosclerosis as manifested by myocardial infarction and subsequent serum concentrations of certain low-density lipoproteins; the association with over-all serum cholesterol content was not so close. These observations initiated a vast study, the results of which recently have been reported. Unfortunately, the interpretations of the data are to some extent contradictory. The majority opinion holds that as an index the total serum cholesterol is as good as, if not better than, the low-density lipoproteins. The Gofman group continues to emphasize the clinical significance of the low-density, in their view atherogenic, lipoprotein molecules as compared to serum cholesterol. There are wide areas of agreement. Both serum cholesterol and low-density lipoproteins were found to have a statistical correla-
tion with each other, based primarily on the fact that the \( \beta \)-lipoproteins of lower \( S_1 \) value are cholesterol-rich. Both also correlated with the incidence of myocardial infarction. It was concluded further that neither the analysis of one or both has specific predictive application for any one individual. It seems that comparative cost and complexity make it likely that serum cholesterol will remain the most used clinical guide to hyperlipoproteinemia and that chemical, ultracentrifugal, or electrophoretic determinations of serum lipoproteins will be used primarily in research. The need for both determinations is exemplified by the occasional dissociations between the 2 measurements.

Such were found in rural Central Americans\(^3\) and in Nigerians\(^3\), both groups having low levels of cholesterol but definitely elevated levels of low-density serum lipoproteins.

Analytic methods for cholesterol must be rigidly standardized before data from different laboratories can be compared accurately. Due regard must be paid to such factors as day-to-day variability and variations between individuals in any “therapeutic” trials. It must be decided soon whether the North American “normal” mean is biologically a useful value. Lastly, before assuming that cholesterol intake is of no significance, it can be pointed out that in animals it is the feeding of fat and cholesterol together that provokes atherosclerosis. Feeding fat alone is comparatively, but not absolutely, ineffective. The significance of serum cholesterol concentrations in excess of the normal American range is illustrated in the Framingham study. In that study hypercholesterolemia, not necessarily from the diet, was associated with a 3-fold increased incidence of coronary artery disease.\(^3\)

**Fat**

*Total Fat Intake.* Perhaps total fat consumption is more relevant to clinical atherogenesis than the intake of cholesterol. Keys, in particular, has placed emphasis on the proportion of total dietary calories contributed by the common food fats. His thesis is that changes in this proportion “result in corresponding changes in serum cholesterol concentration, even when the intake of calories, cholesterol, protein, and vitamins is constant.”\(^3\)

Certainly there is an abundance of data, both clinical and experimental, that tends to relate excess fat intake to atherosclerosis. Unfortunately, other significant parameters, such as total caloric intake, relative rate of caloric expenditure, and true obesity and exercise, are not easily disentangled from the problem of excess fat intake, so that this attractive hypothesis finds opposition in some quarters. With regard to the often-cited Norwegian experience, Morris\(^5\) notes that mortality from cardiovascular disease is not easily estimated from the Norwegian vital statistics. Apparent mortality from this cause tended to decrease *before* the food shortages of World War II became severe, and this decrease was associated with declines in rates for dental caries, tonsillar hypertrophy, maternal mortality, suicide, and schizophrenia. He notes that in Britain, cardiovascular mortality decreased at the beginning of the war in 1939 (fat rationing began in 1940) but resumed a climbing trend in 1943, in spite of the fact that fat restriction continued and even intensified in 1947. He goes on to suggest that there may be “several causes and mechanism . . . involved in the human disease, some of them not related in simple fashion to serum cholesterol . . . but [that] it is a fallacy to consider that this automatically renders them unimportant.”

There has indeed been a tendency to gloss over data that would run counter to the proposition that high-fat intake, plus hypercholesterolemia, results in atherosclerosis. Thus, Wilkinson, Blecha, and Reiner\(^7\) found no relationship between diet and blood cholesterol and Shaffer\(^8\) could not detect an increased incidence of coronary atherosclerosis among men on “ulcer” diets of milk and cream. In contrast is the association between fat intake andcholesterolemia demonstrated in normal subjects.\(^9\) This last study was applied quickly by Morrison\(^10\) to patients who had had myocardial infarcts. From the results of an 8-year survey, Morrison claimed increased survival (28 of 50 patients) among patients on a low-fat diet as compared with controls (12 of 50 patients) on a normal diet.
The Kempner rice diet is a good example of the effect of fat restriction. During the first months when there is usually a marked loss in weight, patients consuming this diet show considerable decreases in concentration of serum cholesterol. This is most evident when the initial cholesterol level is high.\textsuperscript{41} Watkins et al.\textsuperscript{43} found that this dietary regimen brought about an average decrease of 40 mg. per 100 ml. of total cholesterol, involving 5 mg. of free and 35 mg. of ester cholesterol. The disproportionately large decrease in ester cholesterol confirmed Starke's observations\textsuperscript{49} and was associated with decreased cholesterol-to-phospholipid ratio and with decreased serum neutral fats. This raised the question of possible hepatic dysfunction, perhaps imposed by the low-protein character of the diet. That the decisive factor was not protein lack was suggested by the fact that addition of small amounts of a vegetable oil to the diet of 5 patients and the feeding of 10 Gm. of oleic acid daily to 2 others restored the proportion of free-ester cholesterol and the other serum lipid abnormalities to normal without increasing serum cholesterol.

Mann et al.\textsuperscript{44} have shown a rather striking effect of severe exercise in regulating levels of serum lipoproteins and cholesterol in young adult males who consumed a diet high in fat, both in total (153–174 Gm.) and in animal fats, with a daily caloric intake of approximately 6,000. The serum lipids were not increased as long as their caloric expenditure was great enough to prevent any appreciable weight gain. As soon as forced exercise was stopped, there was a gain in weight and an increase in level of serum lipids. In contrast to these findings, Keys et al.\textsuperscript{45} as part of their epidemiologic studies, have estimated the physical activity of the groups of men they have studied in the several countries and have concluded that "differences in physical activity do not explain the large differences in serum cholesterol which are found when groups with different dietary habits are compared."

The problem of total fat intake, of the effect of moderate restriction of ordinary fats, and of the effect of exercise on the level of serum cholesterol must all be considered unresolved.

\textit{Animal vs. Vegetable Fat}. The possibility that the kind rather than the amount of fat in the diet is responsible for atherogenesis has been raised. The first area of such studies has been a comparison of effects of animal fats with those of vegetable fats.

Some of the relevant data come from studies of vegetarians. In one study, serum cholesterol levels were higher in nonvegetarians than in lacto-ovo-vegetarians and "pure" vegetarians. The lowest concentrations of cholesterol were found in the "pure" vegetarians, in spite of the fact that 35 per cent of their total calories came from fat.\textsuperscript{29} Somewhat comparable are the data that compare male adult mean serum cholesterol concentrations among Peruvian Indians, Navaho Indians, American Trappist monks, and Cleveland Americans.\textsuperscript{46} The respective levels were 186 ± 11.8, 175 ± 6.2, 184 ± 14.9, and 229.7 ± 4.4. In all 3 special groups there were lower serum cholesterol concentrations than in the Cleveland group although the Navaho Indians may be somewhat low partly because they were in the hospital.\textsuperscript{47} The Peruvian diet was largely vegetarian. The diet of the Trappist monks was lacto-ovo-vegetarian and relatively low in calories, 1,600 daily, (protein 51, fat 34, carbohydrate 275). Reports on the Navaho diets show that they consume a not inconsiderable amount of fat and cholesterol, but that there is uncertainty as to the exact composition of the diet, particularly in places well removed from the hospitals.\textsuperscript{48}

The possible association between vegetarianism and low levels of serum cholesterol is also tested by the data from a study of Eskimos, who eat a high-meat, high-fat diet. With a procedure that yielded a mean value of 177 mg. per 100 ml. total serum cholesterol for the control group of Canadians, the mean in 27 Eskimos was found to be 141 (range 93–222) and in 6 Devon Island Eskimos—presumably consuming less than the others of cereal fare—132 mg. (range 116–158). The fats consumed were largely of marine origin, and, like vegetable fat, relatively unsaturated. However, tuberculosis is common among Eskimos and may account for the relative lipopemia.\textsuperscript{49}

\textit{ Unsaturated Fats}. The reported effects of
vegetable fats may be a function of their degree of unsaturation or of their content of "essential fatty acids." The parameter of saturation of fat as a significant factor in cholesterolemia and, by extension, in atherosclerosis, recently has been explored in human beings by Kinsell, Ahrens, Beveridge, and Bronte-Stewart. These experiments showed that relatively unsaturated fats of vegetable or marine origin tend to lower while, per contra, the particular hydrogenated vegetable fats usually, and saturated animal fat rather regularly, tended to increase serum cholesterol.

It is important to keep in mind that the "test conditions" (variously, formula diets, tube feeding, grossly distorted diets, hospitalized patients, medical students, poor Bantus) do not necessarily bear directly on the possible effects of addition of reasonable amounts of unsaturated fat to a North American "meat and potatoes" diet, and, at present, cannot be extrapolated to the normal diets of large groups of people free of cardiovascular disease. It is, of course, only possible to obtain the evidence on which to base a way of dietary life where such strictly controlled investigative conditions can be imposed. This is still an area of clinical investigation. It is reasonable to assume that none of the dietary regimens studied will be of practical value, as such, to people who are in good health. Some of the diets contained as much as 40 to 60 per cent oil or fat by weight. The bizarre character of some of these diets is exemplified by one that included 100 Gm. of pilchard oil daily (iodine number 180). This was found to counter the hypercholesterolemic effect of concurrently consuming 10 eggs daily. This observation was made with 2 cooperative Bantu subjects and for periods of only a few days. Nonetheless, this preliminary evidence has provided an important investigative area that is now under intensive study.

The mechanism by which unsaturated fats might counter lipemia and hypercholesterolemia is not understood. Beveridge, Connell, and Mayer are less concerned with the degree of saturation than with as yet unidentified cholesterol-increasing and cholesterol-depressing factors found respectively in animal and vegetable fat.

Speculative hypotheses, like those of Sinclair and Schroeder have been formulated. The starting point of this type of hypothesis is that cholesterol is normally esterified with unsaturated fatty acids. When these are unavailable, cholesterol esterifies with saturated fatty acids provided by the dietary fats or synthesized in the body from carbohydrates. The hypothesis states that it is these saturated cholesterol esters which tend to be deposited in the arterial intima. Inability to form arachidonic from linoleic acid (2 essential fatty acids) may be involved, and this latter synthesis may depend on pyridoxine. Therefore, pyridoxine deficiency might have the same effect as a deficiency of unsaturated fatty acid. It is also suggested that cholesterol excess might have similar effect. On this basis, hypercholesterolemia and atherosclerosis would be attributable to absolute or relative deficiency of unsaturated fatty acids. Sinclair's estimates of the composition of western European diets led him to conclude that they are indeed marginally deficient in unsaturated fatty acids, but more recent evidence does not support this estimate. Lack of essential fatty acids now seems an unlikely factor in atherogenesis. Schroeder's speculation is that trace metals contaminating prepared foods might poison the pyridoxal enzyme systems and lead to atherosclerosis in people whose diets are rich in saturated fat and cholesterol. Again, there is no substantial evidence in favor of this view.

Both series of propositions are highly speculative. It would be premature to act on these assumptions without good evidence for their validity. The fact is that the basic problem is not only lipemia, hypercholesterolemia, or the loading of the liver with lipid, but it is atheromatosis, and, in particular, myocardial infarction or cerebral thrombosis. Atheromata have not been described or associated clinically or experimentally with fatty acid deficiency. Further, myocardial infarction is not generally precipitated in animals by excessive intake of any particular fat or of cholesterol, or by a deficiency of pyridoxine or any unsaturated fatty acid. Incompletely reported experiments of Hartroft, however, suggest that in rats on special diets this may be possible.
Other observations of interest include those of Curran,\textsuperscript{57} who has evidence that cholesterol esters of rabbits fed saturated fats hydrolyze less rapidly \textit{in vitro} than the cholesterol esters of animals given unsaturated fats. This suggests that the latter esters may be less stable and perhaps more easily metabolized \textit{in vivo}. This view could easily be tested on the large series of cholesterol esters synthesized by Page and Rudy.\textsuperscript{58} Very low fat diets increase hepatic and decrease plasma cholesterol in rats.\textsuperscript{57} Absence of essential fatty acids may be the result of failure of cholesterol esters containing other than polyunsaturated acids to be available for proper metabolism. In monkeys\textsuperscript{8} increasing amounts of corn oil caused serum cholesterol to rise progressively; hydrogenated cottonseed oil at low, medium, or high levels, caused even greater rises in serum cholesterol, while native cottonseed oil gave responses similar to corn oil; the responses to lard resembled those obtained with the hydrogenated cottonseed oil. That the changes in serum lipid may not reflect the tissue fat pool is shown by measuring hepatic, as well as serum cholesterol in rats fed an unsaturated oil (soya bean oil) and one more saturated (coconut oil): on these rations, hepatic cholesterol was more than doubled in rats receiving the unsaturated oil as compared with their controls fed saturated fats. There was a tendency to low serum cholesterol concentration in the rats with the high levels of hepatic cholesterol.\textsuperscript{60} Saturation, as such, is not the only factor. Thus, rats were given a variety of fats with added cholesterol and cholic acid.\textsuperscript{61} They were sacrificed at 8 and 12 weeks and the serum cholesterol mean values were averaged. Those rats given coconut oil and butter respectively showed mean serum cholesterol levels of 553 and 453 mg. per 100 ml.; those given cottonseed and corn oils had lower cholesterol levels, namely 308 and 392 mg. per 100 ml.; hydrogenated cottonseed oil with two thirds the iodine number of the raw oil yielded a mean of 461 mg. per 100 ml. Tung oil, which is highly unsaturated, yielded the highest mean serum cholesterol, namely 1130 mg. per 100 ml. The fact that tung oil is rich in eleostearic acid, an octadecatrienoic acid and an isomer of linolenic acid, which is un-characteristic of animal tissue, may bear on this unanticipated result. The amount of sudanophilic material under the endothelium of the valvular endocardium and aorta was estimated and with all oils was found to be proportional to the level of serum cholesterol. Thus, if this sudanophilic material is indicative of early \textquotedblleft atherogenic activity,\textquotedblright{} it would appear to be mirrored by the level of serum cholesterol.

It has been suggested that the spacing of fat meals is important. Certainly, in hyperlipemia and many of the secondary lipemias, blood lipids can be maintained at \textquotedblleft normal\textquotedblright{} level by properly spacing fat without reducing the total daily intake.\textsuperscript{63}

\textit{Fat and Clotting}. The hypothetical sequence in vogue since the time of Virchow from hypercholesterolemia to increased intimal lipid deposition ending in atheroma has been questioned. Duguid has restated the Rokitansky concept that atheroma begins in deposition of fibrin and extends by incorporation and organization of these deposits.\textsuperscript{61, 64} The bridge between this view and that which associates atherogenesis with lipemia is provided by experiments showing that lipemic blood may hasten coagulation \textit{in vitro}\textsuperscript{65-67} or shorten plasma clotting time induced by an incomplete thromboplastin.\textsuperscript{68} Increase in coagulability of lipemic plasma does not seem to be found by all observers.\textsuperscript{69} The effect of fat ingestion on coagulation is possibly associated with changes in circulating phosphatidyl-ethanolamine,\textsuperscript{66, 70} which may act as a thromboplastin. Fibrinolysis appears to be inhibited by alimentary lipemia, among other things.\textsuperscript{71} These associations are of considerable interest, since they tend to link atheroma and lipemia with thrombosis. They are preliminary. In particular, the concept of atherogenesis on the basis of fibrin deposition has little, if any, direct or sequential demonstration.

\textit{Carbohydrate}

The conversion of carbohydrate to saturated and mono-unsaturated fatty acid is implicit in the \textquotedblleft corn-hog ratio,\textquotedblright{} which dictates a portion of the farm economy. Further, ingestion of a high carbohydrate diet usually implies a low-fat ration and vice versa. But there may
be still subtler influences of carbohydrate feeding. Thus, in rats, the kind of carbohydrate fed seems to affect the catabolism of cholesterol to bile acid.72 Chow-fed rats excreted more bile acid than rats fed sucrose as the primary carbohydrate source. When a variety of purified carbohydrates was studied, it was shown that starch elicits a larger bile acid output than the simple sugars. When cholesterol was added to the diet, rats given starch had lower levels of serum cholesterol than rats fed simple sugars. In man it has been shown that the total blood lipids of Chinese, who consume only 10 per cent of their calories as fat and 90 per cent from carbohydrate and protein, are higher than comparable groups of Americans, who consume 43 per cent of their calories from fat.87

Proteins

Dietary proteins also may be involved in experimental atherosclerosis. The production of atherosclerosis in the monkey was accomplished by means of diets containing a protein prepared from soybeans and commonly referred to as "alpha protein" and prevented when casein was the dietary protein.7 This effect of alpha protein is presumable due to its low sulfur acid content, but this supposition has not been rigorously proved. Similar results have been obtained in rats. Other studies with rats34 showed that the hypercholesteremic response varied according to the protein level. The lowest response was observed among those animals receiving the highest level of dietary protein. Since atherosclerosis in man is associated with an abundant diet, it is difficult to believe that diets low in protein or low in essential amino acids can be a causative factor. Possible interrelations between fat and protein intakes are unexplored. In any event, these are indications that cannot be completely ignored.

American Diet

Has there been a marked change in the American diet during the past one or two generations—a period in which the incidence of coronary heart disease and atherosclerosis may have increased? What are the principal changes, and do they involve the amount and type of fat?

Katz et al.75 stated unequivocally that the fat content of the American diet has increased. To prove his point, he cited data from the Department of Agriculture going back to 1910. But these data are of food estimated to be available at the retail level and are really no true measure of the actual food consumed. Stare78 was not nearly so certain that there has been any marked increase in the fat content of American diets. He pointed out that data on food consumption for estimates of dietary changes are generally obtained by 2 methods: the official tables of food availability prepared by the Department of Agriculture, and survey data of families or particular groups. The first method, that of food availability, erroneously called food-consumption data, consists of estimates of food stuffs available for civilian consumption based on foods at the retail level. The data have not been adjusted for waste in homes or wastes in institutions. Data on waste are usually not very reliable; however, quantity of waste is probably very important. For example, how much fat is discarded after the cooking of meats, bacon, or fat frying? Have not the cooking methods changed in this country so that more food is broiled and excess fat discarded? Since in periods of prosperity waste may be greater than in periods of austerity, food-availability tables may not present a true picture of changes in the dietary. The tremendous fat collection from kitchen waste during the war years is an indication of the degree of the loss.

From the data of the Department of Agriculture77 it is found that from 1935 to 1955, the average caloric consumption per capita per day has decreased slightly, approximately 70 calories. Protein has increased from 90 to 97 Gm., fat from 134 to 148 Gm., and carbohydrates have decreased from 440 to 384 Gm. per day. The decreased use of potatoes and cereals, and an increase in milk, meat, and eggs seem to have been responsible for these changes. Since consumption of cereals and potatoes has decreased, as well as total calories, the percentage of fat in the diet would show an increase even if the total fat consumed has not changed.
The second method of estimating food consumption is the dietary survey. Many studies, ranging from approximately 1900 to the present day, show a considerable variation in dietary intake, depending on the group and area under scrutiny. However, variations with time are not very striking. For example, a dietary survey of college men in a “boarding club” in 1891 showed 44 per cent of the calories coming from fat, and a survey of women eating at college clubs in 1894 reported 36 per cent of the calories came from fat. And even the Harvard Crew in 1898 consumed a diet providing 39 per cent of the calories as fat. A study in 1953 of adult women showed the percentage of calories derived from fat ranged from 36 to 46 per cent of the total. Thus, there may not have been an increase in fat consumption by Americans over the past 50 years as claimed by some. A study of the U. S. Army rations in the western outpost in the late 1880’s showed a fat content almost identical with current U. S. Army rations. This lack of change in American dietary can be correlated with the stand taken by the few that there has been no real increase in coronary heart disease, but only an increasing awareness.

It is true that the use of hydrogenated fats has increased in the past 50 years, but since the 1920’s there has been no major increase until after the war (about 1945), when the use of margarine went up sharply. Hydrogenation is a controllable process and within limits the relative amounts of mono-unsaturated and poly-unsaturated fatty acids can be varied. As hydrogenation is practiced commercially, it is not carried to complete saturation. On the contrary, considerable amounts of unsaturated fatty acids remain, including essential fatty acids.

Actually, the proportion of animal and vegetable fats in the diet has remained relatively constant. Again, from Department of Agriculture tables, of 132 Gm. of fat available for human consumption in 1935 to 1939, 73 per cent was from animal sources and 27 per cent from vegetable fats. In the 1955 preliminary report of 158 Gm. of fat were available, 70 per cent animal, and 30 per cent vegetable fat—very little change.

It may be of interest to mention that early margarines in this country were made partly from beef fat, though for many years hydrogenated vegetable fats have been used almost exclusively. Margarine in other countries is made from various types of fats, whale oil being used extensively in the United Kingdom. Interestingly, per capita availability of lard is about the same now as it was in 1910 but lard processing now includes decolorization, and often the addition of some amounts of hydrogenated fat (also, in some cases, addition of gum guaiac and various anti-oxidants).

It might be pointed out that an increase in the consumption of hydrogenated fats during the past 25 to 30 years does not necessarily mean a decrease in the intake of the essential fatty acids. This follows from a number of reasons.

1. While the use of hydrogenated vegetable oils has increased over the past several years, these fats are substitutes for lard and butter and hence their use has increased slightly the amounts of essential fatty acids in the diet. While it is true that hydrogenation gives rise to a variable mixture of isomers, there is no evidence that those isomers act as anti-linoleic compounds, particularly with regard to cholesterol. In fact, there is evidence that the linoleic acid in fats treated by selective hydrogenation has biologic activity and is at a level as high as 13 per cent and usually not less than 10 per cent. In addition the use of these same oils in their natural state has increased and has led to a substantial contribution of essential unsaturated fatty acids.

2. Gross measurements of changes of saturation induced by hydrogenation and frequently evaluated by determination of iodine number do not necessarily indicate the degree of change in the content of biologically active polyunsaturated acids. During hydrogenation, the content of normal linoleate of an oil, while reduced, is not abolished.

McCann and Trulson have recently estimated the intake of essential fatty acids in current and past American diets. They comment as follows: “However, there has been no marked change in the total amount of essential unsaturated fatty acids in the American diet
over the past half century. The increased saturation of fats induced by the hydrogenation of shortenings and margarines has been balanced by an increased consumption of ‘other fats and oils,’ fats which are mostly unsaturated and have a high content of essential fatty acids.” The increased consumption of other fats and oils has not increased the total fat intake because of decrease of butter, lard, bacon, and trimming off the fats of meats.

**General Comment**

One can summarize the hypotheses presented as follows: (1) that diet may play an important role in the pathogenesis of atherosclerosis, (2) that the fat content and the total calories in the diet are probably important factors, (3) that it may be more the type of fat than the total fat, or the ratio or balance between the saturated and certain unsaturated fats that is the basic determinant, and (4) that the proposition that the character of the American diet has so changed during the past 50 years as to increase the incidence of coronary vascular disease cannot be supported. It was indicated that (5) other aspects of fat metabolism may be determinants, and (6) that a wide variety of other factors, dietary and nondietary, may be of equal or greater importance, and (7) that infarction, the real nub of the problem, is not generally produced experimentally, despite the extensive and severe atherosclerosis that has been produced. Possibly this objection has been very recently overcome.

It should be realized that these conclusions are subject to some very basic criticism. One is that most of the studies have focused attention on the concentrations of serum cholesterol, serum lipid, or serum lipoprotein without proper emphasis on the focus of the problem, which is atheroma and infarction, whether myocardial or cerebral. Is there compelling evidence that, if we treat the hypercholesterolemia by dietary means, we are doing anything to lessen the chances of myocardial infarction? Perhaps the best that can be said is that there is an association that has statistical value, but that is not an obligatory association either in small groups or, and much less so, in an individual.

Even if one accepts the equation hypercholesterolemia = atherosclerosis (or some variant thereof) the fact that serum lipid concentrations, perhaps more in some people than in others, show considerable “spontaneous” fluctuations makes its application difficult. Variations of serum lipid concentrations among individuals of the same sex and age, consuming similar diets, are also great. Consequently, data based on single determinations are potentially highly inaccurate, and control data, by repeated observation on standard regimes, should be secured over several weeks.

Vital statistics, particularly from countries with different methods of reporting, under-staffed health departments, and low autopsy rates, are very likely to be misleading. The diagnostic accuracy of all physicians is not equal, standards vary from place to place. The taking of diet histories is time consuming and, at best, yields data of only moderate accuracy. When obtained through interpreters, under the press of time and when good rapport has not been possible, diet histories lose even this limited value. A national diet low in fat is usually also low in sucrose and animal protein; it is usually high in fiber and starch, and the vitamin and mineral content may differ from American diets.

Lastly, there are other common factors in human life that are atherogenic, but not related to lipemia. Of these, the most common and best documented is arterial hypertension. This association is well recognized. The greatest frequency of complications of atherosclerosis, fatal and nonfatal, was found in the group of patients whose severe hypertensive disease had been brought under some control with antihypertensive drugs. Among these, such complications occurred 3 times as often in those with high (greater than 110 mm. Hg) diastolic pressures than in those with lower average pressure. In these patients, there was no demonstrable association between the incidence of these complications and the level of serum cholesterol or of the light or dense lipoprotein fractions.

**Conclusion**

Atherosclerosis, cerebral thrombosis, and myocardial infarction are diseases in which
numerous factors are involved. Diet and nutrition are important factors in experimental atherosclerosis and, very probably, in the human disease. Thrombosis and infarction of the cerebral, cardiac, and renal vessels occur in severely sclerosed arteries, but so far neither has been clearly produced experimentally.

Evidence is presented to suggest a possible general association with high fat consumption, but it is difficult to disentangle this from caloric balance, exercise, changes in body weight, and other metabolic and dietary factors that may be involved. Thus, the evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral artery disease. On the other hand, the fact that obesity is a nutritional failure, that it is caused by consuming more energy than one expends, that dietary fats are the most concentrated source of energy, providing some 40 to 45 per cent of the daily caloric intake, suggests that many should consume less calories. For most, this will mean eating less fat.

Prudence, as well as habit and taste, will dictate the selection of a diet with some fat. Diets providing 25 to 30 per cent of the calories from fat, rather than the current 40 to 45 per cent in the American diet, can still provide palatable meals for our accustomed tastes.

The key points of nutritional common sense for better health generally, and most likely in regard to atherosclerosis specifically, consist of a balanced, varied diet that adjusts total calories to reach or maintain a desirable weight. Such a diet should provide more protein from lean meat, fish, poultry, and animal products, cereal and grain products, and a reasonable selection of fruits and vegetables. The fat content should be sufficient only to meet caloric and essential fatty acid demands.

These conclusions obviously apply to the general population, and not to patients or to individuals with a strong family history of early deaths from cardiovascular disease, who are being observed with some regularity by their physician. Here, the newer concepts of nutrition readily suggest various types of diet therapy that may prove useful to certain patients. Investigative procedures of this type, together with continued basic research, will, in time, provide the facts upon which sound dietary recommendations may be made to the public at large and which may help in lessening the prevalence of cerebral and coronary disease with consequent stroke and myocardial infarction.

**Summario in Interlingua**

Aterosclerosis, thrombosis cerebral, e infarcimento myocardial es morbos in que un grande numero de factores es implicate. Dieta e nutrition es factores de alte importancia in aterosclerosis experimental e probabilissimamente etiam in le occurrentia del morbo in humanos. Thrombosis e infarcimento del vasos cerebral, cardiac, e renal occurre in arterias que es severmente sclerotic, sed usque al tempore presente ni le un ni le altere ha essite reproducite claramente per medios experimental.

Es presentate datos que supporta le vista que il existe un association general con alte grados de consumption de grassia, sed il es dificile isolar iste factor ab le balancia caloric, le intensitate de exercitios, alterationes del peso corporee, e altere factores metabolic e dietari que es possibilemente interessate in le problema. Assi, le datos nune disponibile non justifica le recommendation de drastic modificationes dietari—specificamente con respecto al quantitate o al typo de grassia in le dieta del population general—con le expectation que tal modificationes va definitemente reducer le incidentia de morbo de arteria cerebral o coronari. Del altere latere, le facto que obesitate es un dysfunction nutritional, que illo resulta del consumption de un exceso de energia in comparation con le expension de energia, e que grassias dietari (que provide 40 a 45 pro cento del diurno ingestion caloric) es le plus concentrate fonte de energia supporta le recommendation que multe personas debere reducir lor consumption de calorias. In le majoritate del casos isto significa un reduccion del consumption de grassia.

Prudentia insimul con habitudo e preferentia personal va determinar le selection de un dieta
con un certe portion de grassia. Dietas que deriva 25 a 30 pro cento de lor contento calorie ab grassias (in loco del 40 a 45 pro cento in le dieta american currente) es certo capace a provide repastos appetibile secundo nostre gustos habitual.

Le punctos cardinal in un programma dietari de senso commun—tanto in le interesse de un meliorate stato de sanitate physic in general como etiam con respecto a atherosclerosis in particular—es recommendationes visante a un balanciate e variate dieta que subordina le total caloric al objectivo de attinger o manteni un peso desirabile. Un dieta de iste genere providea plus proteina ab carne magre, pisces, volatiles, cereales, e produtos animal e cereal insimul in un selection adequate de fructos e vegetales. Le contento de grassia debe suffer solmente a satisfacer le requirementes caloric e le requirementes de acido grasse essential.

Il es obvie que iste conclusiones vale pro le population general e non pro patientes o pro individuos con pronunciate historias familial de morte prematur ab morbo cardiovascular, le cuales es sub le observation plus o minus regular de lor medicos. Pro tal personas, le plus recente conceptos nutritional suggere varie typos de therapia dietari che va possibilemente provar se benefic in casos specific. Investigationes del presente typo, insimul con continue recercas fundamental, va establish in le curso del tempore le factos super le base del cuales salubre recommendationes dietari pote esser facite al publico in general e ab le cuales on pote expectar que illos va servir a reduce le prevalencia de morbo cerebral e coronari con consequente apoplexia e infarceimento myocardial.

REFERENCES

19 —: Personal communication, 1956.
22 Page, I. H., and Farr, L. E.: The influence of high and low fat diets and thyroid substance on


58 Bronte-Stewart, B., Antonis, A., Eales, L.,


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