Diet and Coronary Artery Disease

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ATHEROSCLEROSIS of the coronary artery is currently the leading cause of death in the United States and in many western countries. It is remarkable that a disease that was not recognized clinically before 1912 could have in half a century come from this relative obscurity to the commonest cause of death in middle-aged and elderly persons. Although its exact etiology is far from settled, intensive study over the past three decades has pointed increasingly to nutritional factors as playing a prominent role.

The concept of any disease arising from a single cause is obsolete and misleading. On the contrary, as Gordon pointed out, "To recognize a disease as the resultant of ecologic forces within the dynamic system made up of agent, host, and environment may often clarify our concepts of that disease." Atherosclerosis is undoubtedly a disease of multiple causation, which appears to have so many determinants that they tend to defy orderly classification under titles of agent, host, and environment. It is certain that atheroma arises within the host as the result of a complex interaction between host and environment. Instead of arising in the environment and constituting an independent variable such as the agents of infection, allergy, poisoning, addiction, or vitamin deficiency disease, the agent of atherosclerosis is an endogenous and dependent variable. Since this agent arises within the host, it obscures the usual distinction that is made between agent and host response.

Nevertheless, it seems to me that it is important to postulate an agent, if possible, for this disease, in order to formulate concepts useful for further research on pathogenesis as well as prevention and control. Groups of host factors definitely involved in the pathogenesis of atherosclerosis may be grouped into (a) humoral and (b) local factors. The humoral factors include the lipoproteins of plasma, the heparinoid substances involved in clearing of lipid from the blood, and possibly other plasma proteins concerned with coagulation. The last group of proteins may have more to do with the pathogenesis of thrombosis than with atheroma itself. Under local factors, i.e., those promoting atherogenesis as a result of influencing the condition and function of the artery itself, one can identify (a) hemodynamic factors relating to blood flow, turbulence, and pressure; (b) metabolic factors intrinsic in the arterial tissue; (c) structural factors relating to differentiation of intima, internal elastic membrane, and other components of the arterial wall; and (d) traumatic factors relating to injury, ulceration, and repair. Environmental factors known to influence one or more of these conditions within the host include such variables as diet, drugs, exercise, occupation, culture, and climate. Factors intrinsic to the host that may also modify the humoral and local factors leading to atherogenesis include genetic constitution, age, sex, endocrine balance, and psychic state. The problem centers about the sorting of this welter of factors into more conventional packages labeled agent, host, and environment.

Do we have sufficient evidence to name the agent of atherosclerosis? If we do, it seems useless to continue to visualize the pathogenesis of this illness as being the random com-
ombination of a large variety of endogenous and exogenous factors. In a system of multiple etiology, the agent is only one cause. It must, however, be an essential cause. It would be impossible, for example, to visualize the occurrence of tuberculosisis in the absence of the tubercle bacillus, although easy to visualize its nonoccurrence in the presence of the bacillus. Thus, the agent must be an essential, though not necessarily a sufficient cause. The agent for atherosclerosis is unique only in the sense that it arises within the host and becomes a threat to the host as a part of his internal instead of external environment. In my opinion the evidence is at hand to name the β-lipoproteins as the agent for atherosclerosis, and this view may be defended according to Koch’s postulates.4

The dose of an agent may or may not be the determining factor for disease causation. In man on an abundant diet the β-lipoprotein concentration may be a less important variable in causing overt disease in given individuals than hypertension, tortuosity of vessels, or hereditary predisposition to the degeneration of vascular connective tissue.

If one accepts this evidence in favor of the view that the plasma β-lipoproteins can be considered the agent for atherosclerosis, all other factors known to be involved may be viewed to determine whether they influence the concentration of the agent in the plasma or whether they influence the reactivity of the arterial wall to the agent. Host and environmental factors may then be grouped according to the following epidemiologic triangle (fig. 1).

Since the β-lipoproteins are known to be synthesized in the liver, this organ can be regarded as the source of the agent.

An understanding of the pathogenesis of a given disease is essential to its successful prevention. An ecologic view is important in determining a strategy of attack upon the causes. In coronary artery disease there is little doubt that hypercholesteremia (as a sign of hyper-β-lipoproteinemia) and hypertension are contributory factors. There is a considerable controversy about the role of obesity.8-11 Since both hypercholesteremia and obesity may result from overnutrition, the possibility of a dietary approach to prevention of atherosclerosis must be carefully evaluated.

The evidence supporting a relationship between diet and coronary artery disease rests upon 3 pillars. These are (1) epidemiologic studies of populations differing widely in disease prevalence and correspondingly in nutritional, socioeconomic, cultural, and other environmental status; (2) clinical investigations of small groups of subjects fed carefully controlled diets under the conditions of the metabolic ward; and (3) laboratory investigations of the effect of various purified diets upon serum cholesterol, β-lipoproteins, and atheromatosis in a variety of experimental animals. This evidence is summarized below under these headings:

Epidemiologic Studies
Many studies of diet in relation to mortality for degenerative heart disease12,13 have shown that populations that have high rates of coronary artery disease have high mean serum cholesterol and β-lipoprotein concentrations and eat diets rich in animal protein, fat, and calories. This seems to be a real asso-

![Figure 1](http://circ.ahajournals.org/)

Agent (β-lipoproteins)

Host
- Age
- Liver function
- Arterial reactivity
- Hemodynamic status
- Endocrine status
- Psychic state

Environment
- Diet
- Drugs
- Exercise
- Occupation
- Culture
- Stress

Figure 1
sion despite differences in diagnoses and reporting in various parts of the world. Yerushalmy and Hilleboe and Yudkin have presented data suggesting a stronger association between dietary animal protein intake and mortality from coronary heart disease than between dietary fat intake and that mortality. The association between animal protein intake and mortality for coronary disease may in part reflect the association of relatively saturated fat with most animal protein as well as a possible "protective" effect of animal protein-lack at the low end of the scale.

A relative lack of association of dietary fat intake with coronary morbidity and mortality appears at high levels of fat intake. Bronte-Stewart has shown, however, that if one plots the hard fat:liquid fat ratio (as a crude index of relative saturation) against coronary mortality in men 55 to 59 years of age for countries consuming between 100 and 140 Gm. of fat per capita per day, a remarkable parallelism emerges.

Study of populations living with contrasting dietary patterns in the same community has shown that dietary pattern correlates closer with serum cholesterol level and incidence of coronary artery disease than any other environmental variable. The study of Bronte-Stewart, Keys, and Brock of the Bantu, Cape colored, and Europeans living in Capetown, South Africa, is now well known. Toor et al. have made similar observations on the mixed population of Israel. Gupta, Iyer, and Nath have found that patients with coronary artery disease in New Delhi have significantly higher serum cholesterol levels than healthy urban Indians matched for age and occupation. Groen has noted that Trappist monks, who are strict vegetarians, have lower serum cholesterol than Benedictine monks, who eat a more varied diet. Keys and associates have shown that Japanese living in Japan, Hawaii, and Los Angeles have serum β-lipoprotein cholesterol values and coronary mortality in proportion to their intake of fat calories, which were respectively, 13, 32, and 40 per cent. Studies in Finland have revealed a high mortality and morbidity rate from coronary artery disease in that country, a high mean serum cholesterol (260 mg. per cent), and a diet with 35 per cent of calories from fat, most of which is saturated.

Coronary artery disease appears to correlate better with serum β-lipoprotein concentrations and dietary fat intake than other forms of atherosclerosis, suggesting that the coronary vessels are particularly prone to atherogenesis under conditions favored by overnutrition and possibly other factors.

Clinical Investigation

No hypothesis supported solely by associations developed in epidemiologic studies is on firm ground. Confirmatory evidence developed in small groups of intensively studied human subjects is essential for the support of such hypotheses. In addition, such clinical investigations enable the investigator to control with better precision a variety of variables and emerge with more specific knowledge of etiologic factors, control of which is impossible in the field. The general hypothesis developed from field studies is:

\[ \text{Diet} \rightarrow \text{serum } \beta\text{-lipoproteins (serum cholesterol)} \rightarrow \text{coronary disease rate} \]

The first part of this hypothesis, developed in the field, has been subjected to study on the metabolic ward. In more specific form, this hypothesis is:

\[ \Delta \text{Diet} \rightarrow (1) \rightarrow \Delta \text{serum } \beta\text{-lipoproteins} \]

\[ \Delta \text{serum } \beta\text{-lipoproteins} \]

\[ (2) \rightarrow \Delta \text{coronary disease rate} \]

\[ \text{Metabolic ward studies} \]

\[ \text{Controlled population study} \]

Examination of the second part of this relationship will require additional study of part one, particularly a study of the practicality of achieving dietary control away from the metabolic ward. Then, a specially designed field study involving relatively large numbers of middle-aged men will have to be carried out to determine if any change in clinical morbidity follows alteration in serum cholesterol and β-lipoproteins by dietary means.

Studies of Diet

Effects of diet on serum cholesterol and β-lipoproteins are discussed under (a) calories, (b) fat, (c) protein, (d) other factors. In a
consideration of the effects of variation of the major constituents of the diet (calories, fat, protein, and carbohydrate) upon the concentration of plasma β-lipoprotein, it is important to remember that variation of one of these variables causes a change in at least one other. In view of the extent to which given foods vary in their total nutrient content, variation in diet sufficient to cause a variation in the intake of a major constituent will usually cause a change of several dietary variables. Further, in epidemiologic studies in which comparisons of dietaries are made it is virtually impossible to obtain "paired" populations subsisting on diets differing in only two of the many possible dietary variables. Hence attempts to interpret the effect of changes in dietary composition upon the concentration of plasma lipoproteins in man must be reserved for well-controlled laboratory studies.

In the ensuing section the effect of variation of calories, fat, protein, and other dietary factors upon postabsorptive plasma cholesterol, and β-lipoprotein levels are discussed. In any discussion of dietary variation (Δdiet), a statement regarding the baseline from which the variation is to be measured is essential. Although arbitrary, the baseline from which the changes will be computed on this paper is the "average American diet" containing calories to maintain weight (regardless of the weight of the individual) and a distribution of nutrients as per cent of calories as follows: (protein 15 per cent; fat 40 per cent; and carbohydrate 45 per cent; summarized P 15, F 40, C 45). This method of expressing nutrient intake of course is not complete. The specific amino acid pattern of the protein, the specific fatty acid pattern of the fat, and the specific combination of sugars and polysaccharides must also be defined for complete information.

A. Calories

In starvation the body depends mainly upon fatty acids as the source of energy. Triglyceride stored in the adipose depots provides these fatty acids, since lipogenesis in adipose tissue and liver ceases under these conditions. Fatty acids are transported from the depots to various organs in the form of nonesterified fatty acids,26 and this flow of substrate can account for the total energy expenditure by the fasting man. Most observers agree that there is a small but an undramatic increase in β-lipoprotein concentration in human subjects fasted for periods in excess of 2 days, of the order of 20 per cent with a lesser increase in serum cholesterol, since about half the increase is in the very low density protein.

The feeding of insufficient calories for maintenance of body weight (reducing diets) in man appears to have somewhat different effects upon the level of plasma lipoproteins than in complete starvation even though mobilization of depot fat also occurs in this situation. In Keys' study of semistarved normal young men, it was found that subsistence on diets containing half the caloric requirement resulted in slight but significant fall in average total serum cholesterol from 169 to 151 mg. per cent.29 Walker et al.30 found a slight decrease, 14 mg. per cent of serum cholesterol in middle-aged obese subjects offered a 1,000-calorie diet containing 50 Gm. of fat over a 4-month period. Olson31 noted no permanent change in the serum cholesterol concentration of 61 obese men and women losing an average of 20 pounds over a 1-year period after these individuals had attained caloric equilibrium at a new and lower weight. Most of these patients did have transitory decreases during the period of rapid weight loss but these were not sustained. It would appear that weight reduction per se and hypocaloric diets approaching the original ad libitum fare in the distribution of major nutrients causes little or no change in β-lipoprotein configuration of serum after attainment of the new and lower weight. More marked changes can occur during the early phases of negative caloric balance. These decreases are primarily in the triglyceride-rich low-density fractions of the β-lipoprotein spectrum.

B. Dietary Fat

The simplest variation in dietary fat is a variation of fatty acid composition of the fat.
without a change in the total fat intake. In 1952, Groen and associates\textsuperscript{32} observed that vegetarians had considerably lower serum cholesterol values than nonvegetarians. This effect was independent of the level of total fat ingested. Independently in the same year, Kinsell et al.\textsuperscript{33} observed that the isoecaloric substitution of vegetable oil for animal fat in the diet of patients on measured dietary intakes dramatically reduced the serum cholesterol and phospholipids concentrations. These observations were further extended and confirmed by the elegant studies of Ahrens and his collaborators,\textsuperscript{34, 35} employing a formula by which a variety of fats at a constant level (P 15, F 40, C 45) were fed to subjects on a metabolic unit for periods up to 3 years. These and other studies\textsuperscript{36–40} established beyond question that isoecaloric substitution of unsaturated vegetable oils for animal fats and saturated vegetable fats in the diet of man resulted in the fall of serum cholesterol and other lipids of the order of 20 per cent.

It is now clear that the terms “animal” and “vegetable” do not distinguish between fats that raise and lower serum lipids. Both butter and coconut oil raise serum cholesterol, whereas both corn oil and whale oil lower it.\textsuperscript{18} Furthermore, the terms “saturated” and “unsaturated” are not suitably descriptive of opposites, since neither all saturated fatty acids nor all unsaturated fatty acids are identical in their effects upon serum cholesterol in man.\textsuperscript{18, 41, 42} The dietary fats containing saturated fatty acids in the range of C\textsubscript{6} to C\textsubscript{14} appear to cause more hypercholesteremia than saturated fatty acids in the range C\textsubscript{16} to C\textsubscript{20}.\textsuperscript{36, 43} On the other hand, monoenoid fatty acids such as oleic are not so potent in inducing hypercholesteremia as linoleic, linolenic, arachidonic, and the highly unsaturated fatty acids of fish oils.\textsuperscript{39, 44, 45} Finally, the terms “nonessential” and “essential” do not distinguish the serum cholesterol-altering capacities of the various polyunsaturated fatty acids. Both linoleic acid,\textsuperscript{44} which is essential for preventing dermal signs and preserving efficiency of food utilization in rats\textsuperscript{46} and infants,\textsuperscript{47} and linolenic acid,\textsuperscript{40} which is nonessential, have potent hypocholesteremic properties. Furthermore, the fish oils contain a large variety of polyunsaturated fatty acids that are nonessential and share the 3, 6, 9 triene moiety (counting from the methyl end) with linolenic acid, and are potent in lowering serum cholesterol in men.\textsuperscript{36, 48}

The precise mechanism by which polyunsaturated dietary fat lowers \( \beta \)-lipoprotein and cholesterol concentrations in the serum is not completely elucidated at this time although a variety of studies suggest that the polyunsaturated fatty acids promote the elimination of free cholesterol (which is in equilibrium with plasma free and ester cholesterol) from the liver as neutral sterol and bile acids.\textsuperscript{49–51}

A reduction in the level of relatively saturated fat in the diet from 40 to 10 per cent of total calories without changing its fatty acid composition at a constant protein intake results in a decrease in the total serum cholesterol, phospholipid, and \( S_{0-12} \) lipoproteins and an increase in total triglycerides and \( S_{12-400} \) lipoproteins. In normal cholesterolemic men the decrease in serum cholesterol and phospholipid is about 15 per cent and the increase in triglycerides is about 50 per cent. The net change in total \( \beta \)-lipoproteins is nil although there is a change in the distribution of lipoproteins of various densities as indicated. In epidemiologic studies of various populations,\textsuperscript{23} the plot of mean plasma cholesterol content versus per cent of total calories from a dietary fat, gives a slope that is twice as great as a plot slope of the same line obtained in the study of well-controlled patients in the United States.\textsuperscript{52} It seems likely that factors other than the dietary fat level are operating in the populations studied epidemiologically. Low-fat diets reduce the fecal neutral sterol excretion.\textsuperscript{53} Varying the content of saturated dietary fat has no effect upon the bile acid output, and it appears that reduced hepatic synthesis of cholesterol may be the primary cause of the reduction of \( S_{0-12} \) lipoproteins and serum cholesterol in human subjects on low-fat diets.

\textbf{C. Protein}

Description of diets in terms of protein content alone is inadequate and should include
a statement of the distribution of the essential
and nonessential amino acids in that protein.
Of the 20 amino acids in the common dietary
proteins, 8—methionine, valine, tryptophane,
leucine, isoleucine, lysine, phenylalanine, and
threonine—are required by adult human be-
ings in specified amounts, and, in addition,
histidine is required by infants. In general,
animal proteins contain amino acids in pro-
portions resembling those found in the tissues
of man, and hence have a higher biologic value
for man than vegetable proteins, which may
not resemble animal tissues in amino acid
composition. Some vegetable proteins are ac-
tually deficient in certain essential amino
acids such as methionine, isoleucine, lysine,
tryptophane, and threonine. For these reasons
populations living on an exclusively vegetable
protein diet are more likely to be marginal
in amino acid nutrition than populations sub-
sisting mainly on animal proteins. The re-
quirement for protein of high biologic value
by adult humans has been estimated to be
from 0.4 to 0.5 Gm. per Kg. of body weight.51
At energy expenditures associated with seden-
tary activity this represents about 5 per cent
of the calories. No population studied thus far
has been found to subsist on such a meager
intake although populations living exclusively
on vegetable protein have developed protein
deficiencies on intakes representing twice this
or 10 per cent of calories. The generous rec-
ommendation of the National Research Coun-
cil of 1 Gm. per Kg. per day of good quality
protein for adults represents only 11 per cent
of calories at a sedentary level of activity.

Our understanding of the effects of a re-
duced level of dietary protein from 15 to 4
per cent of calories is considerably less specific
and complete than the effects of alteration of
dietary fat over the same proportional range
in man. Kempner and others35, 56 observed
marked hypocholesteremia in patients fed the
rice diet, which is low in protein (25 Gm.) and
fat (5 Gm.). Since this effect upon serum cho-
lesterol was out of proportion to the effects
observed in subjects fed diets low in fat but
replete with protein, Olson et al.17 undertook
a series of studies to determine the effect of
low-protein diets upon the serum cholesterol
and β-lipoproteins in man. Middle-aged human
subjects were fed a control ration containing
100 Gm. of protein, 80 Gm. of relatively sat-
urated fat, and 320 Gm. of carbohydrate (P
16, F 30, C 54) for periods of 1 to 4 weeks.
Isoenergetic substitution of carbohydrate for 75
Gm. of protein yielding a diet containing 25
Gm. of protein (P 4, F 30, C 66) resulted in
an average fall in serum cholesterol 44 ± 4
mg. per cent (15 per cent) over a 1- to 4-week
period. The fall was sustained as long as 10
weeks. All of the essential amino acids except
methionine were supplied by the 25 Gm. of
vegetable protein in amounts meeting Rose’s
tentative minimum requirements57 although
these may be low when several amino acids
are at borderline levels. The fatty acid pat-
tern was kept constant, and fiber was kept in
the range of 5 to 7 Gm. per day in both diets.
Serum β-lipoproteins of the S 40-12 class de-
creased about 25 per cent, with lesser changes
in the lower density groups S 40-12-400.

Furman, Howard, and Norcia58 have also
recently reported that isocaloric substitution
carbohydrate for all the protein in formula
diets fed to adult men caused a marked de-
crease in serum cholesterol and β-lipoproteins.
These workers noted further that this effect
was in addition to the effect of polyunsatu-
rated fats, since the basal formula employed
used corn oil furnishing 40 per cent of cal-
ories.

Severe protein malnutrition in infants char-
erized by weakness, weight loss, wast-
ing, edema, hypoalbuminemia, hepatomegaly,
gastrointestinal mucosal atrophy, and nega-
tive nitrogen balance is known as kwashiorkor.
This appears to be a multiple amino acid de-
iciency, a disease in which one or more amino
acids may be limiting. In this disease the
serum lipids are low (cholesterol - 80 mg.
per hundred ml. or less and both α- and β-
lipoproteins are decreased).59-61 The hypo-
cholesteremia of the child with kwashiorkor
responds promptly to the feeding of fat-free
milk proteins and suggests strongly that di-
tary fat is not the critical nutrient related to
this hypocholesteremia. In fact, it supports
the view that serum lipoproteins are not elaborated by the human at normal rates in the presence of protein deficiency.

Sebrell and co-workers have found in a nutritional survey in Haiti that marked hypercholesteremia was seen in a population subsisting on a diet deficient in protein but moderate in fat (P 9, P 21, C 70).

It appears from both these field and clinical investigations that animal protein intake may become limiting for formation of β-lipoprotein and that in conditions of protein deficiency the serum cholesterol may be depressed on this basis alone.

D. Other Dietary Factors

Dietary carbohydrate appears to exert an influence upon lipoprotein concentrations in two ways. The first is by providing glucose for absorption and metabolism by tissues concerned with lipid storage and transport. The second is by modifying the bacterial flora of the gastrointestinal tract, thereby altering the bacterial metabolism of sterols and bile acids. The first effect varies reciprocally with the level of dietary fat or protein or both, and has been discussed in relationship to the variations of these nutrients in previous sections. In general, low-carbohydrate intakes are associated with the reduction of serum triglycerides and low-density \( S_{\text{tri2-400}} \) lipoproteins and high-carbohydrate intakes are associated with an elevation of triglycerides and low-density β-lipoproteins. The second effect relates to the diversion of metabolites of cholesterol from the enterohepatic circulation by oxidations carried on by intestinal microorganisms. This subject has recently been reviewed by Portman and Stare.

Evidence that the intake of vitamins and minerals within the ranges encountered in populations influences the concentration of serum lipoproteins is not impressive. Two surveys by the Interdepartmental Committee on Nutrition of National Defense failed to show any relationship between specific vitamin deficiency and serum cholesterol. Certain pharmacologic effects of niacin have been reported that are not in this province of discussion. Niacin in doses of 1 to 6 Gm. causes a significant hypocholesteremic effect in man and the corresponding large excretion of nicotinic acid. It has been suggested that the mechanism of this effect might be via the diversion of coenzyme-A from cholesterol biosynthesis to the CoA-dependent glyce conjugation of nicotinic acid to yield nicotinic acid. Further evidence is needed to support this interesting hypothesis.

Laboratory Investigation

The study of atherosclerosis in experimental animals has both aided and hindered the development of accurate concepts regarding the role of various etiologic factors in human atherosclerosis. Species variation in responses of animals to a variety of experimental procedures has become evident to most investigators. The evaluation of the enormous bulk of experimental data and particularly its relevance to the human problem can be simplified, in my opinion, by looking at the problem of pathogenesis in animals in the light of a 2-step reaction as in the case of man, viz.

1. effect of variations in diet and metabolic status upon serum cholesterol and β-lipoprotein concentration, and
2. the effect of increased β-lipoprotein concentrations upon the condition of arterial vessels.

In 1913 Anitschkow observed that the feeding of a diet rich in cholesterol to rabbits resulted in experimental atheromatosis. Since that time innumerable experimental animals have been used to study the problem. It has been discovered, however, that not all animals react with hypercholesteremia to cholesterol feeding. In fact most common laboratory animals (rat, mouse, dog, cat) unlike rabbit and chick but, like man, resist hypercholesteremia when simply fed cholesterol; other measures must be employed to alter metabolism in order to obtain elevated serum cholesterol and β-lipoprotein values. Thyroid ablation (chemical or surgical) or cholic acid feeding (which increases cholesterol absorption and retards the conversion of cholesterol to cholic acid) must be added to the cholesterol feeding regimen in order to obtain appreciable hypocho-
lesteremia. Once hypercholesteremia of sizable magnitude is obtained, however, de novo atheromatosis occurs in all species examined. The problem, therefore, is overcoming the control mechanisms that guard the serum cholesterol concentration. Once this is done the problem may be studied in the experimental animal. Even myocardial infarction has been produced in the rat with massive hypercholesteremia.71

The role of specific dietary fats in the control of hypercholesteremia in animals is also somewhat different from that in man. In rat, dog, chick, and rabbit the feeding of large amounts of polyunsaturated fat in the absence of dietary cholesterol exerts no appreciable effect upon the serum cholesterol level; in the presence of cholesterol the effects are not identical to those observed in man.72

In general, animal experimentation supports the basic hypothesis previously alluded to. First, diet can influence the serum cholesterol and β-lipoprotein concentration in experimental animals. Second, when the β-lipoprotein is high enough, atherosclerosis will develop in a previously normal artery.

From the total of epidemiologic, clinical, and experimental data, it appears that one must accept the fact that diet plays a role in human atherosclerosis. It is certainly not the only factor, and in many cases it may be a minor factor. Furthermore, it must be remembered that clinical disease associated with atherosclerosis is a complication of the basic process in which other factors that may precipitate thrombosis play an important part. The problem of studying this disease in man, therefore, is made difficult by the multiple etiology of atherogenesis plus the multiple etiology of thrombosis. These difficulties, however, should not obscure our vision to the facts that have emerged regarding the role of diet in atherogenesis.

With this information about dietary factors in mind, is it possible to elaborate a practical program of preventive medicine against atherosclerosis at this time? Although our knowledge of all the factors operating in the process of atherogenesis is incomplete, our understanding of some of the factors is advancing in an encouraging way. Although it is not possible to eradicate the agent (plasma β-lipoproteins) of this disease, it is possible through appropriate diet therapy to modify the concentration. It remains to be shown, as indicated above, that when β-lipoprotein concentrations of a large number of persons living under conditions of western culture are lowered through appropriate diet therapy, this change will modify their morbidity and mortality from clinical coronary disease. Nevertheless, the evidence is convincing enough at this time, in my opinion, to advise patients with coronary proneness as evidenced by a positive family history and elevated concentration of cholesterol or a disease such as diabetes or hypertension, to follow appropriate diet therapy in the hope that lower serum cholesterol values will improve the prognosis.

The probability of materially influencing the course of coronary artery disease after the occurrence of myocardial infarction is, in my opinion, somewhat less. Nevertheless, clinical judgment must be utilized in recommending diet therapy to such patients in the hope of reducing the rate of recurrence. The studies of Morrison78 are suggestive although not conclusive that indeed this might be the case.

**Summario in Interlingua**

Es postulato que un factor particular pote esser designate como le agente de un morbo si il es possibile demonstrar que illo representa un causa essential (ben que non necessarimente sufficiente) del morbo in question. Le autor presenta su conviccion que in iste senso le lipoproteinas beta pote esser considerate como le agente de atherosclerosis. Sub iste assertion ille trova possibile classificar le componentes del sistema dynamic del multiple causation de atherosclerosis in duo columnas. In le columna de elementos associate con le hospite (i.e. le patiente) ille lista le etate, le function del hepat, le reactivitate arterial, le stato hemodynamic, le stato endocrin, e le stato psychic. In le columna de elementos ambiental, dieta, drogas, exercerio, occupation, cultura, e stress es listate.

Le evidentia supportante un relation inter dieta e morbo de arteria coronari es revistate in tres partes. Istos es: (1) Un discussion de studios epidemiologie de populationes a marcate differentias in le preva-
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lentia del morbo e correspondentemente in lor stato
nutritional, socio-economique, cultural, e alteremente
ambiental. (2) Un discussion de investigations clinic
de micr grupos de subieto recipiente cautamente
regulate dietas sub le condition de sala metabolic
de un hospital. E (3) le discussion de investigations
laboratorial relative al effect de vari purificate
dietas super le cholesterol soral, le lipoproteinas beta,
e le genese de atheromatosis in diverse experimentales
experimentales.

Super le base de iste revista le autor conclude que
il es possible modifie le concentration de lipoproteinas beta, reguardate como le agente de athero-
sclerosis, per le prescripion de un appropriate the-
rapia dietari—isto in despecto del facto que le mul-
tiple aspectes de linteresate campo causal es certo
non complemente clarificite. Le prove practic de
iste prediction remane a obtenet e etiam le prove
que le reduction del lipoproteinas beta in un considerabile
segmento del population resulta in un correspondente
reduction del mortalitate per morbos del arteria coro-
nari.

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