Sufficient to reveal this paper's flavor is one quotation from it: "There are good enough reasons to suspect that our present high-fat diet in the United States is scarcely favorable to the health of adult men, even though it is premature to blame it as the whole cause of our excessive mortality from heart disease."

Prediction and Possible Prevention of Coronary Disease*

ANCEL KEYS, PH.D., F.A.P.H.A.

Director, Laboratory of Physiological Hygiene, and Professor, School of Public Health, University of Minnesota, Minneapolis, Minn.

THE problems of diagnosis and of management of coronary heart disease are so numerous and important that great efforts should be made toward their solution, but several limitations must be recognized. From all the available evidence there is no reason to hope that coronary heart disease can ever actually be cured in the sense that a cancer may be "cured" by surgical excision, or even that tuberculosis may be permanently arrested. Moreover, there is some reason to doubt whether, at present, early diagnosis of coronary heart disease will greatly change the eventual prognosis.

The basic lesion in almost all cases of coronary heart disease is the deposit of lipid materials in the walls of the coronary arteries. Once thoroughly established, these atherosclerotic deposits are nearly, or perhaps totally, irreversible. The real focus of attention for the control of coronary heart disease must be the problem of preventing these deposits from developing further. An essential part of this problem is the question of predicting the threat of coronary disease, which is pretty much the same thing as recognizing the tendency of atherosclerosis to progress.

Not so long ago it was widely held that arteriosclerosis, and the particular variety called atherosclerosis, was an essential part of aging. The result was a defeatist attitude and a regrettable lack of research interest. Now, however, it is clear that age alone does not bring with it the cholesterol deposits in the arteries that currently constitute the basic cause of more deaths in the United States than any other disease category.

Atherosclerosis is a progressive development and it seems highly probable that the eventual appearance of clinical coronary disease usually represents the cumulative effect of a factor, or factors, operating over a period of years. Age, per se, is certainly not the cause, as is evident from the great variations between individuals of the same age in spite of a general *average* progression with age.[1, 2] Many factors are probably involved in the atherosclerotic development and in the clinical appearance of coronary heart disease, but there is no longer any doubt that one central item is the concentration, over time,

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of cholesterol and related lipids and lipoproteins in the blood serum.[3-7] No other etiological influence of comparable importance is as yet identified.

At this point, however, controversy begins about the particular substances in the blood that are most significant in this regard. Detailed arguments about the relative merits of different blood analyses for the recognition or prediction of coronary disease are not essential to the present discussion.[8-12] It is clear enough that total cholesterol, free cholesterol, phospholipids, beta lipoproteins, and the lipoproteins of various sizes and densities as they can be separated in the ultracentrifuge are all intimately interrelated and that none, by itself, affords a safe basis for prediction about the disease process in the individual. There is no doubt that of the several different analytical methods for recognizing these substances each may yield averages that differentiate, statistically, between *groups* of patients with clinical coronary disease and *groups* of clinically healthy persons who are otherwise comparable. From the evidence so far available, it is not possible to accept the claim of Gofman and his colleagues in California for the remarkable virtue of the ultracentrifuge in this regard. At this point a word of caution is appropriate to guard against the overinterpretation of any of these laboratory data for particular patients.

The argument for giving a prime place to the total blood serum cholesterol in any consideration of the public health aspects of these problems is simple. As a discriminator between coronary patients and their healthy counterparts, the total cholesterol measurement seems to have much the same value as some other measurements (e.g., lipoprotein fractionation, ultracentrifugation); it is not claimed to be appreciably better. It has, however, a considerable practical advantage because the relatively simple cholesterol method is far more suitable for large-scale application and there is much more knowledge about it. Moreover, it should not be forgotten that cholesterol itself is the main intruder in the actual lesions of the coronary arteries. This cholesterol comes from the blood.

As will be seen, the cholesterol level in the blood (and the level of the related lipoproteins) can be influenced by the diet, both in man and in some animal species. However, the situation has been greatly confused by too much reliance on experiments with animal species differing from man in cholesterol metabolism. Adding equal amounts of cholesterol itself to the diet produces widely different results in the several species studied so far, the rabbit and the chicken being at one extreme, while man, the dog, and probably the monkey are at another and opposite extreme.[12] Atherosclerosis may be readily produced in the rabbit and in the chicken by feeding a diet containing large amounts of added cholesterol.[13] There is no doubt that the resulting arterial deposits of cholesterol are directly related to the concentration of cholesterol in the blood which rises to great heights in these species, while feeding cholesterol to man, or to the monkey, has very little effect on the blood even when enormous doses of cholesterol are given.[12-15]

The cholesterol-fortified diet commonly used to produce hypercholesterolemia and subsequent atherosclerosis in the rabbit contains 1–5 per cent of added cholesterol. A 2 per cent cholesterol diet for the rabbit, which is most commonly used, corresponds to about 15 gm. of cholesterol in a 3,000-calorie diet for a man. Such an amount of cholesterol is fantastically far above anything that occurs in any natural human diet, the upper limit of the latter being of the order of 1 gm. in 3,000 calories. Even when concentrating on foods of naturally very high cholesterol content, it is

difficult to devise a regular diet to provide, experimentally, as much as 2 gm. of cholesterol in the daily diet.[16-18]

That dietary cholesterol is not important for man would be predicted from the fact that the biliary output of cholesterol from the human liver is from 10 to 20 times as much as the daily amount of cholesterol in any diet of natural foods. Repeated careful dietary surveys on large numbers of persons in whom blood cholesterol was measured consistently fail to disclose a relationship between the cholesterol in the diet and in the serum.[19-21] Infants and children, as well as adults, show this lack of dependence of serum content upon the exogenous supply of cholesterol,[22] but this does not mean that the diet is unimportant in regard to the blood cholesterol. Controlled experiments on men clearly show that serum cholesterol changes in direct relation to a change in the total amount of fat in the diet.[7, 23-25] Both animal and vegetable fats show this effect and the addition or removal of cholesterol in the diet does not change the result. The blood cholesterol may fall, however, if the diet is almost exclusively pure fat and is free of carbohydrate;[26] this highly artificial experiment would seem to have no relevance to natural situations.

Now this being the case in controlled experiments limited to a few months' duration, it is important to discover what may be the situation where there are lifelong differences in the amount of fat in the diet. Moreover, the controlled experiments so far have been limited to individuals who have previously always subsisted on a relatively high-fat diet.

The fact of the matter is that practically all Americans in modern times eat a relatively high-fat diet. Forty years ago the fat calories averaged slightly over 30 per cent of the total and at present, on the average, fats provide over 40 per cent of the total calories in the foods sold at the retail level in the United States.[27, 28]

No other country appears to match this level of fat consumption, the next highest values, with fats providing from 38 to 39 per cent of the calories, being in Australia, New Zealand, and Canada. From 30 to 35 per cent of the total calories come from fats in the United Kingdom, the Netherlands, and the Scandinavian countries. Far lower fat consumption is characteristic of Italy, Portugal, and Spain where, on the average, the total fats cover only some 19–23 per cent of the total calories. Even lower values are found in parts of Latin America, while the smallest percentage of fat calories in the total, 10 per cent or less, is found in Asia and Africa.

Before examining blood cholesterol data obtained in other countries, it is essential to consider the situation in the United States. Normative data for the urban "white collar" class have been provided by several thousand clinically healthy men in Minnesota,[29] and the findings are in good agreement with other smaller series studied elsewhere in American cities.[8, 30-32] The main features of these data are a marked curvilinear age trend and a considerable variation between individuals at any given age. The mean value for men aged 20 is about 180 mg. of total cholesterol per 100 ml. of serum and this tends to rise more or less linearly with age until around 50 years, the means from 50 to 60 years of age are about 260 mg.; in very old persons low values predominate. This age trend in serum cholesterol is very similar to the findings on the incidence of marked atherosclerosis at autopsy.[1, 33]

These characteristics of clinically healthy men in American cities are to be compared with recent findings in Italy, England, and Spain.[12, 33-35] The first of these comparative studies was begun in Naples in 1952, where the gen-

TABLE 1

Mean Serum Total Cholesterol Concentration, in mg. per 100 ml., in Clinically Healthy Men in Naples, London, and Two Classes of Spaniards. All Values Here Pertain to the Nonbasal State and Therefore Are Not Precisely Comparable to the Basal Norms for Minnesota.

Age	*Naples*	*London*	*Spaniards*	
			Poor	*Rich*
20	135	187	181	202
30	216	205	215	217
40	231	248	223	243
50	229	255	210	264

eral average of the diets, both of the whole population and of the particular men studied, was about 20 per cent of calories from all fats.

The serum cholesterol values showed that the Minnesota and Neapolitan trends are not significantly different in youth but around age 30 they begin to diverge. In the fifties the Minnesota men averaged 40–50 mg. per cent higher than the Neapolitans. In this respect, the Italian men are not aging like the Americans who have been studied. It might be asked whether this difference is related to relative obesity in the two countries. Actual measurements, however, showed that our Italian subjects were just about as fat as our Minnesotans as gauged both by relative body weights and by measurements of the thickness of subcutaneous fat.

This finding has extraordinarily interesting connotations and it is important to check it with other populations. Opportunity to do this was found in Spain. Our main series of Madrid subjects, in 105 poor families, was found to be characterized by subsistence on a diet low in both fats and total calories. These men were, on the average, much thinner than either the Minnesotans or the Italians, but in serum cholesterol they closely resembled the latter. Again, when comparison was made with the United States, the correspondence in youth and the divergence after age 30 was striking. In the fifties these Madrid men averaged over 50 mg. lower than the Minnesotans.

In Spain the great majority of the population is poor and subsists on a low-fat, low-calorie diet. The small wealthy and professional class, racially identical, lives on a diet at least as luxurious, and as high in fats and in calories, as in the United States. Study of a sample of clinically healthy men of this class in Madrid showed them to be very similar to the Minnesota men in regard both to body fatness and to serum cholesterol concentration. There was, then, a striking difference between the poor and the relatively rich Spaniards, as indicated in Tables 1 and 2.

Finally, it was possible to study a sample of clinically healthy men in the

TABLE 2

Mean Serum Total Cholesterol Concentrations at Ages 30–55 in the Several Populations of Clinically Healthy Men, Expressed for Each Population as a Percentage of the Mean Value at Age 30.

Age	*Minnesota*	*Naples*	*London*	*Madrid*	
				Poor	*Rich*
30	100	100	100	100	100
40	112	107	121	103	112
50	127	106	124	98	122
55	131	109	127	100	127

London area of England. These men were found to be, on the average, considerably thinner than the Minnesotans, the Neapolitans, or the rich Spaniards. Their diets, studied individually in a careful survey, averaged 35 per cent of all calories in the form of fats—that is to say much more like the diets of the Minnesotans and rich Spaniards than the diets of the Neapolitans or poor Spaniards. The mean serum cholesterol values for these Englishmen are given in Table 1. The relative trends from age 30, given in Table 2, most precisely indicate the differences in the populations. Clearly, the whole series of data suggests that the serum cholesterol concentration and its age trend is primarily related to the fat content of the diet but not to the body fatness. So far, then, the picture is that the serum cholesterol is more or less independent of the diet in youth but that progressively after about 30 years of age the serum level is directly related to the total fats in the diet. The effect of obesity itself is apparently not so important, although in each population we found a small correlation between obesity and serum cholesterol. The next question is whether all this is related to the incidence and mortality from coronary and related heart disease.

For Spain we can only say that coronary heart disease is strikingly uncommon in the general population as surveyed in the hospitals and public clinics. There were, however, many cases among the wealthy patients of our friends, the fashionable practitioners. Unfortunately, Spanish vital statistics are either practically nonexistent or are relatively unreliable, so that it is impossible to cite valid figures for mortality specific for age and sex. For some other countries, however, comparable statistics are available, both for death rates and for national diets, and these prove to be extremely interesting.

Table 3 summarizes the death rates for men aged 40–44 and 50–54 ascribed to all circulatory diseases and to what may be termed "degenerative heart disease," predominately coronary heart disease, as computed from official statistics for 1948–1949 in several countries. Taken at face value, there is indicated a tremendous range from the figures for white men in the United States to Japanese men. For the age range 50 through 54 years, these data indicate that the death rate from coronary heart disease and allied myocardial disorder in the United States is more than four times that of Italian men and over 10 times that of Japanese men of the same age.

Broadly speaking, death rates as-

TABLE 3

Deaths of Men in 1948–1949, Rates per 1,000 of Given Age, Ascribed to All Circulatory Diseases (International Category VII) and to Degenerative Heart Diseases (Myocardial Diseases and Coronary Heart Disease, Categories 93 and 94 in the International List of 1938).

Category	All Circulatory Diseases		Degenerative Heart	
	40–44	50–54	40–44	50–54
U. S. Whites	1.66	5.65	1.19	4.44
Canada	1.10	4.03	0.89	3.43
" , % U. S.	66%	71%	75%	77%
England and Wales	0.70	2.73	0.27	2.04
" " " , % U. S.	42%	48%	22%	46%
Italy	0.63	1.86	0.25	1.02
" , % U. S.	38%	33%	21%	23%
Japan	0.55	1.25	0.14	0.37
" , % U. S.	33%	22%	12%	8%

TABLE 4

Death Rates, from All Causes, in 17 Countries with a Total Population of About 310 Millions. All Values Are for the Period 1947–1949 and Are Expressed as Percentages of the Corresponding Rates in the United States in 1949.

Age	*40–44*		*50–54*		*60–64*	
Sex	*M*	*F*	*M*	*F*	*M*	*F*
Australia	75	91	87	96	94	94
Belgium	96	89	91	96	97	101
Canada	78	91	76	92	84	96
Denmark	59	83	63	88	70	100
England and Wales	68	78	76	83	93	88
France	96	100	91	91	93	91
Ireland	80	78	57	86	69	88
Italy	91	100	77	88	75	97
Japan	156	216	111	153	113	207
Netherlands	52	69	56	76	63	89
New Zealand	55	72	66	81	85	88
Norway	64	78	53	65	54	68
Portugal	139	125	99	96	99	103
Scotland	93	97	93	100	97	107
South Africa	93	108	102	115	94	104
Sweden	61	86	63	85	68	92
Switzerland	78	97	78	97	88	108
Mean	84.3	97.5	78.8	93.4	84.5	101.1

cribed to specific causes are not very reliable under the best of circumstances. Certainly it would be difficult to insist that the values in Table 3 for "degenerative heart disease" in the different countries are strictly comparable nor would it be reasonable to suggest that the values listed for all circulatory diseases are actually precise. Yet we are not dealing here with the minutiae of differential diagnosis of relatively rare diseases. Can it be suggested seriously that in Canada a third of the deaths from circulatory diseases are missed? Or, conversely, that in the United States many thousands of death certificates for relatively young men are each year falsely or erroneously labeled with one or another variety of circulatory disorder when the proper label should have been pneumonia or tuberculosis or some other cause in a completely unrelated category? It should be observed that in 1949 over one-third of all deaths of white men from 40 through 44 years of age were ascribed to circulatory diseases. To bring the rate down to the Italian or Japanese level would require either the assumption that the great majority of circulatory disease deaths reported in the United States actually were due to other causes or that in Italy and Japan only one-fourth to one-tenth of the true circulatory disease deaths were recognized as such.

It is useful to shift the focus to the total death rate from all causes, retaining, of course, the essential specification of age and sex. Table 4 assembles such information for 17 countries for the period 1947–1949, expressed as percentages of the corresponding death rates in the United States in 1949. For the countries listed, these rates for deaths from all causes are, presumably, not subject to large errors.

The outstanding feature of Table 4 is that it shows the mortality from all causes to be surprisingly high in the United States, in comparison with other countries, for adults in this range of from 40 to 65 years of age. The relative inferiority of "health," as indicated by the death rate of the American male

is particularly marked. Only Japan and Portugal have poorer records, and in these countries the high incidence of infective and parasitic diseases explains the high total mortality. The explanation of the high mortality among adult American males is, of course, ready at hand—excessive mortality from heart disease.

The improvement of vital statistics recording, and the accuracy of the death certificates on which they are based, has now reached the point in many countries where detailed analysis is rewarding. Such work is in progress in the Laboratory of Physiological Hygiene and the results are of much interest. For example, we find that when we compare the data for men of equal ages in the United States and in Italy we find substantially the same values in the two countries for the ages 40–60 for all neoplasms, for cirrhosis of the liver, for nephritis and nephrosis, and for intracranial lesions of vascular origin. Among major causes of death, in fact, only the death rates ascribed to heart diseases are grossly dissimilar. Why? Further analysis of the death rates from all circulatory disorders shows that when the degenerative group of coronary disease, angina pectoris and myocardial disease are excluded, the death rates from the total of all *other* circulatory diseases are much alike in the two countries. Why? From every viewpoint the analysis brings us back to the conclusion that there is a major difference between these countries for the incidence and mortality of coronary heart disease. This problem is greatest among American men and tends to become progressively less as we pass to countries where fats contribute less and less to the total diet. As far as data have been made available, the blood cholesterol picture in the clinically healthy members of the populations are entirely in keeping with the dietary and the mortality data.

It should be recognized that, in addition to the character of the diet, another factor may possibly be involved. Differences in habitual physical activity cannot be ruled out of the picture since, in general, the population groups on the lower fat diets are also characterized by a higher level of physical activity. Special studies on this point are already in progress.

Let us now return to the diet. There are enough good reasons to suspect that our present high-fat diet in the United States is scarcely favorable to the health of adult men, even though it is premature to blame it as the whole cause of our excessive mortality from heart disease. The changes in mortality in countries forced to alter their diets during the late World War cannot be ignored. These changes conform to the concept that the proportion of fat in the diet is closely related to the development of arteriosclerotic heart disease.[36-38] Changes in diabetes mortality among patients over 45 years of age, notoriously related to atherosclerosis, were equally marked during the war and the parallel with the dietary change is equally striking.[39, 40]

From the start of acceptable systematic records of the U. S. Department of Agriculture in 1909, the proportion of fats in the national food supply has steadily risen from roughly 30 per cent of total calories to over 40 per cent in 1950–1952. The same data indicate that the protein contribution to the total calories has remained substantially constant at around 12 per cent, or a trifle less. Because of the uncertainties in regard to kitchen and plate waste, the actual intake of the several major nutrients cannot be specified with great precision; but there is no doubt that the per capita consumption of total fats in the United States is higher than anywhere else and it has been, and still is, steadily rising. In view of the facts and concepts expressed above, this consti-

tutes a real problem for the public health.

Among other immediate questions that arise is that of the several sources of the fats in the present national dietary. In the classification of the U. S. Department of Agriculture, by far the largest proportion of the total fats, from 45 to 50 per cent in recent years, is "fats and oils as such, excluding butter." This means cooking and salad fats and oils—lard, corn oil, cottonseed oil, hydrogenated vegetable oil shortening, margarine, mayonnaise, etc. Butter contributes about 5 per cent of the total fat calories. It is evident that a large reduction in our present high-fat consumption could be achieved without affecting the fats associated with the more nutritionally valuable foodstuffs. In other words, it should not be difficult to reduce the total fat intake and still have a diet excellent in all other respects.

In this discussion I have attempted to present some salient features of a large and complex problem. The evidence is drawn from many fields but the whole provides, I believe, a consistent and important basis for further studies and perhaps major public health attention. The focus is on men from age 30 to age 70. About women we know much less, but the coronary heart disease problem is apparently less important for them until later in life. Women, too, are eventually less than immortal, and their death rate from degenerative heart disease is high in the United States, the chief peculiarity being a later age of onset than that for men. From a study of vital statistics it appears that women are less prone to suffer from angina pectoris and sudden fatal coronary occlusion, a less spectacular, chronic development, leading to a diagnosis of chronic myocarditis or myocardial degeneration, being the rule. Finally, the effect of habitual differences in the level of physical activity has scarcely received any research attention. These and many other questions can and should be clarified by extensive and critical epidemiological studies.

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National Science Foundation Announces Fellowships

The National Science Foundation has announced its fellowships for the academic year 1954–1955. It will award about 750 graduate and postdoctoral fellowships to persons planning to undertake study during the coming academic year in the biological, engineering, mathematical, medical, or physical sciences. Depending on the academic status of candidates, stipends range from $1,400 to $3,400 annually, plus dependency and travel allowance, tuition, and laboratory fees.

Postdoctoral applications must be received in the Fellowship Office by December 15, 1953; graduate applications by January 4, 1954. Applications should be accompanied by copies of college transcripts and a plan of study for advanced training. The official announcement, application blanks, and further information from The Fellowship Office, National Research Council, 2101 Constitution Ave., N. W., Washington 25, D. C.