ATHEROSCLEROSIS: A PROBLEM IN NEWER PUBLIC HEALTH*†

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The first part of the title of this paper may be a misnomer. There is no guarantee that the main points of this discussion are actually about arteriosclerosis or the particular variety labelled atherosclerosis. Since the pathological condition cannot be precisely evaluated in life, and is all too seldom verified at death, it is proper to leave the pathologist in command of his own field and to stay within the limits of the facts on which this discussion actually depends; these are the facts seen, recorded, and measured by the clinician, the biochemist and the vital statistician.

The facts to be discussed here concern three sets of items: 1) The first is the broad category of heart disease, or diseases, diagnosed by the clinician as angina pectoris, coronary heart disease, myocardial infarction, chronic myocarditis, and myocardial degeneration. In hospital and vital statistics it is rarely possible to differentiate these clearly so it is convenient to group them, for the present purpose, as "degenerative heart disease." Moreover, there is more than a suspicion that they all, in fact, share some common factors in basic etiology, but details would be out of place here. 2) The second set of items concerns serum cholesterol and allied substances which are currently considered to be importantly related to the development of some, at least, of these conditions in man. The relationship is presumably through the atherosclerotic process but this assumption is not central for my argument. 3) Finally, there is the relationship of the diet to the concentration of cholesterol and allied substances in the serum and to the death rate of the adult population.

Why these have anything to do with public health, even a "newer public health," requires a little consideration. For many decades the official as well as the general view of the subject of "public health" has been that it should be concentrated on a few major questions obviously requiring organized attention beyond the scope of the individual practice of medicine—public sanitation, control of epidemics and infective diseases, record-keeping of mortality and communities health status, and the correction of health hazards where many people congregate, as in schools and factories. These limited horizons are now being extended in two ways. First, there is general public insistence that efforts on a broad front should be made to prevent or decrease the incidence of *all* forms of illness and disability, not merely those that are infective or occupational in origin. Second,

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there is the realization that progress in both prevention and medical care demands increased knowledge which can only come from research. This means research workers and facilities whose contribution is to the common good and whose financial support must come, somehow, from the community. This justifies the fact that a large part of all our medical research is now being supported by the U. S. Public Health Service.

Now on purely financial grounds public health activities, including research, cannot be expanded indefinitely, particularly when we have such a staggering cost for military defense. But the need for major public health attention is clear whenever two conditions exist: First, when there are large numbers of the population suffering disability and death from diseases against which private medical practice is making little headway. And, second, when there is any reason to hope that the incidence of these diseases may be altered by measures applicable to the general population, even if these measures are not yet known.

Degenerative heart disease fulfills these conditions. It is unnecessary to cite the mournful facts about the great numbers of persons, and by no means merely the aged, who are affected. And everyone must admit that the present practice and progress of diagnostic and therapeutic medicine is not solving the problem; the proof is only too clear in our vital statistics. It is possible to argue about the detailed accuracy of death certification and to point out the changing age structure of the population, but no matter what qualifications and refinements of analysis are applied, the general fact remains the same. In the past thirty years, which is as far as acceptable records extend, the age-specific death rate from degenerative heart disease is certainly not decreasing. For males under 70 years, in fact, it is difficult to deny that there has been a steady upward trend. This is particularly striking in view of the fact that the total age-specific death rate, from all other causes, is steadily falling.

The mere existence of an undesirable state of affairs is not, in itself, enough reason to demand a major effort to correct it. There must also be some reason to believe that improvement is possible. In the past, a defeatist attitude about heart disease, particularly degenerative heart disease, has been a major hindrance to effort and even to careful consideration. But it is now abundantly clear that degenerative heart disease is not an inevitable consequence of ageing, beginning in youth and progressing with the years, indifferent alike to medical efforts and improvements in living conditions.

VITAL STATISTICS

The fact that the present high death rate from degenerative heart disease in the United States is not inevitable is easily shown by comparison with some other countries. The objection may be raised that certification of specific causes of death is not very reliable and that different criteria may be applied in different countries. The fact that official vital statistics indicate for Italy, for example, only a small fraction of our death rate from coronary disease conceivably may be explained in this way. But this objection loses much force if death rates for the total of all diseases of the circulatory system are compared. Physicians

may differ in the designation of kinds of heart disease but there is much less doubt when it comes to deciding whether they have to do with heart disease in general.

The data in Table 1 cover the age range from 40 through 64 years, probably the most significant 25 years of life in regard to degenerative heart disease. They show higher death rates from the total of all causes in the United States than in Italy and this disadvantage is more marked when deaths from infective and parasitic diseases and from all forms of violence are excluded. The high death rate from violence in the United States is more than offset by the high death rate from tuberculosis in Italy. When comparison is limited to deaths from all forms of cardiovascular disease, the U. S. rates are far worse than those for Italy. Finally, if only degenerative heart disease is considered, the difference is tremendous. It will be noticed, also, that the U. S. males fare much worse than the U. S. females in these comparisons. This is significant in view of the fact that the incidence of degenerative heart disease in American men is much higher than in American women, particularly before old age.

TABLE 1

Death rates in Italy (1948) as percentages of corresponding rates in the U.S.A. (1949) for men (M) and women (F) in three age groups for:

1) all causes, 2) all causes less infective and parasitic diseases and violence, 3) diseases of the circulatory system (Category VII in the International list), 4) degenerative heart disease (1).

AGE	40–44		50–54		60–64	
Sex	M	F	M	F	M	F
1. All causes	91	100	77	88	75	97
2. Excl. infective, violence	79	87	70	83	73	95
3. Circulatory system	35	79	31	59	28	67
4. Degenerative heart	20	56	23	48	25	56

The example of Italy is cited because other evidence from Italy, to be presented later in this paper, is particularly relevant to the problem. But Italy is not a peculiar exception. Many other countries appear to have much less degenerative heart disease than in the United States. They certainly have lower total death rates, as shown in Table 2. It may come as a shock to realize that, actually, the mortality record of adults in the United States is poorer than in other comparable countries in the Western World. Most of our inferiority shown in Table 2 is explicable as a result of an excessive amount of degenerative heart disease in this country.

The list in Table 2 includes the countries with good vital statistics which are reasonably comparable in race, climate, culture, medical services and vital statistics. The omissions are Western Germany and Finland, because of major population shifts and other effects from the war, and Iceland, Luxembourg and some colonies and semi-independent states with very small populations. Only poverty-stricken Portugal seems to be an exception to the rule that men in other Western countries have lower mortality rates than in the United States. But

Portugal's bad record is mainly explained by tuberculosis and Table 3 shows a different picture when deaths from infective diseases and violence are excluded.

Detailed study of the vital statistics of all these countries indicates that the differences compared to the U. S., in total age-specific death rates could be largely

TABLE 2

Death rates, from all causes, in 16 countries with a total population of about 220 millions

All values are for the period 1947–1949 and are expressed as percentages of the 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 & 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
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	79.9	90.1	76.8	89.7	82.7	94.6

TABLE 3

Death rates, per 1000, among men of three age groups in Portugal (1950) and in the United States (1949)

Lines 1 and 2 give the rates from all causes of death except infective and parasitic diseases and violence. Lines 3 and 4 give the death rates from all diseases of the circulatory system (Category VII in the International Long List or items 24 and 25 in the Abridged List).

AGES	40–44	50–54	60–64
1. Portugal	4.2	9.0	23.3
2. U. S. A.	3.8	11.0	26.0
3. Portugal	0.9	1.8	5.2
4. U. S. A.	1.8	5.9	13.9

or wholly explained by differences in the death rates from degenerative heart disease—coronary heart disease, angina pectoris, chronic myocarditis, and myocardial degeneration.

What is possible for the Italians, and the Norwegians, and the Canadians, and so on, should be possible for Americans. The data in Table 2 are a challenge.

SOME BASIC FACTS

But now let us review a few outstanding facts that bear on the question of the incidence of degenerative heart disease. These will point the way to one promising line of attack on a series of problems ranging from the question of the recognition of the tendency to degenerative heart disease in populations to the development of a physiological hygiene aimed at prevention:

1) It is a fact that, compared with healthy persons of the same age, patients with definite angina pectoris or who have survived a myocardial infarction tend to have blood serum characterized by high cholesterol and certain lipoprotein concentrations, a high cholesterol-phospholipid ratio, and a larger proportion of the total cholesterol in the beta lipoprotein fraction.

2) It is a fact that, on the average, persons afflicted with diabetes, myxedema and nephrosis tend to have high cholesterol and the other serum peculiarities mentioned above. Among these patients there is a high incidence of atherosclerosis and degenerative heart disease.

3) It is a fact that in animal experiments those measures, such as high cholesterol diets and thyroid suppression, which produce high levels of cholesterol and allied substances in the serum, are also productive of atherosclerosis.

4) It is a fact that a major characteristic of the atherosclerotic artery is the presence of abnormal amounts of cholesterol in that artery. The atherosclerotic plaque consists of 40 to 70 per cent cholesterol. It is extremely probable that most or all of this cholesterol is derived from the blood. The cholesterol in the blood does not exist as a simple solution of free and ester cholesterol; it is carried in lipo-protein complexes.

DIAGNOSIS AND PROGNOSIS FROM BLOOD ANALYSIS

All of this indicates that measurement of cholesterol and allied substances in the blood serum affords an indication of the tendency towards the development of atherosclerosis and degenerative heart disease. But two questions arise at once. How reliable is the indication derived from such measurements? And is one or the other of the various measurements much superior to the others for the recognition or prediction of degenerative heart disease in man?

In one sense the reliability is high. Whenever *groups* of individuals are compared, all of these measurements invariably seem to show statistically significant correlations between the measurements and the presence or absence of the tendency towards degenerative heart disease. But the correlations are far from perfect and the reliability is low for single individuals. These statements about the high reliability with groups and low reliability for individuals apply to all of the measurements so far studied: total cholesterol, cholesterol/phospholipid ratio, "giant molecules" of the S_f 10–20 and S_f 12–20 varieties, beta lipoproteins, the fraction of cholesterol in the beta lipoproteins, and so on. Two of the items—total cholesterol and "giant molecules"—have been studied most and merit more detailed consideration. With regard to coronary disease in man these two measurements tend to show parallel tendencies. Experiments with animals can be devised in which this parallelism is disturbed but it is questionable whether

the bizarre situation of the alloxan diabetic rabbit fed enormous amounts of cholesterol (2) has any counterpart in man.

Two years ago, total cholesterol and the S_f 10–20 fraction in the serum were compared (3, 4). It was concluded, from suitable mathematical analysis, that there was then no evidence for an important difference between S_f 10–20 and cholesterol measurements as devices to differentiate between clinically healthy people and patients with definite coronary disease and that neither measure was acceptably reliable in dealing with individuals. More recent evidence tends to confirm the propriety of these conclusions.

Jones and co-workers (2) have presented new data, this time on the S_f 12–20 fraction, and have argued for its superiority to total cholesterol measurement from comparisons made on 550 men, including 156 men who had survived myocardial infarction. The analysis of the data shows, actually, that there was no statistically significant difference between the S_f 12–20 and the cholesterol measurements in the discrimination between "normals" and "infarcts" in the 331 men from 41 to 50 years of age, though, if we accept certain assumptions, in the 219 men from 51 to 60 years of age the S_f 12–20 measurement may have achieved somewhat better discrimination.

The computation made by Jones *et al* (2) assumes that the relationship is rectilinear, that is when the S_f 12–20 or the cholesterol level is doubled the degree of association with infarction also tends to be doubled and so on up and down the scale. There is no evidence that this assmuption is proper and the computations of biserial correlation coefficients may, therefore, be invalid.

But, for the moment, let us accept the assumption and ask how good is the computed discrimination. The most favorable results obtained with the S_f 12–20 measurement were with the younger men where a biserial correlation coefficient of $r = 0.62 \pm 0.07$ obtained between the presence of infarction and the concentration of S_f 12–20 in the serum. Jones *et al* (2) argue that the relationship would be even closer with ideally perfect methods and that the correlation they found is "attenuated" by errors in measurement. However, we are concerned about what to expect with the actual methods at hand and this is indicated from the actual correlation coefficient of 0.62. What does this mean in terms of predicting which bloods come from clinically healthy men? This is readily answered in terms of the index of forecasting efficiency. Table 4 summarizes data on the forecasting efficiency in this regard.

The index of forecasting efficiency shows the percentage by which it is possible to reduce the error that would prevail if we tried to predict in the absence of any corrrelation. The correlation coefficient of 0.62 means an index of forecasting efficiency of about 21 per cent. Consider 1000 men, half of whom are clinically healthy, the others being victims of myocardial infarction. Merely given a list of 1000 code names and the information that half of these pertain to men with infarcts, the effort to classify them would be purely random guesswork and the result would be 500 correct diagnoses and 500 errors. But if S_f 12–20 measurements were made the result could be improved by making 21 per cent fewer errors; one could hope for only 395 errors instead of 500.

It is illuminating to apply this to a more realistic situation as in the last column of Table 4. Take the problem of diagnosing the trend toward infarction before the infarction occurs or the likelihood that a given individual is specifically threatened. If one out of 10 persons presenting themselves for test is actually so threatened and if such threatened persons are really identical in regard to blood chemistry with the men who have had infarcts, the likelihood of deciding which is which, and therefore of being able to give the right advice, would be one chance in ten by sheer random guesswork. With the aid of the S_f 12–20 measurement with men aged 41 to 50 years, the diagnostician's judgement would be improved by 21 per cent; he would make 21 per cent less than 9 errors out of 10. This is almost exactly the same result as would be expected with total cholesterol measurements from the data of Gertler *et al* (5, 6) in men under 50, but Jones *et al* (2) are a little less successful with cholesterol. It should be observed that Jones *et al* (2) report far better results with the S_f 12–20 measurement than were obtained by Gofman *et al* (7) with the S_f 10–20 measurement (3, 4).

TABLE 4

Discrimination between healthy men and patients with coronary disease (infarcts) by ultracentrifugal and total cholesterol measurements

"r" = biserial correlation coefficient; "Index" = index of forecasting efficiency; relative value (Rel. Val.) indicates the chance of assigning a correct diagnosis to a man with coronary disease in a population in which it is known that 10 per cent of the men have coronary disease. Data in lines 2 and 7 from Keys (3, 4) after Gertler et al. (5, 6) and Gofman et al. (7); lines 3–6 from Jones et al. (2).

ITEM	r	INDEX	REL. VAL.
1. No test or measurement	0	0	0.10
2. S_f 10–20, 31–50 yrs	0.41	9	0.18
3. S_f 12–20, 41–50 yrs	0.62	21	0.29
4. S_f 12–20, 51–60 yrs	0.61	21	0.29
5. Cholesterol, 41–50 yrs	0.46	12	0.21
6. Cholesterol, 51–60 yrs	0.30	5	0.15
7. Cholesterol, 31–50 yrs	0.61	21	0.29
8. Ideal test	1.00	100	1.00

It seems probable that something like this disappointing situation will continue to be the case with all of the items of blood analysis now proposed or which may be proposed to indicate the development of atherosclerosis and the danger of coronary disease and infarction. How could it be otherwise? A single sample of blood represents only a particular moment but the pathological process is the resultant of the operations of the blood factor (or factors) over many months, years or decades, plus all the other factors which may be concerned—the individual's peculiarities of blood flow, arterial wall and other factors yet unknown.

But this great limitation for individual clinical application should not prevent recognition of the fact that statistically, dealing with groups of people, the measurement of any and all of the items—total cholesterol, giant molecules, etc. —*is* of great significance. Correlation coefficients of the order of 0.6 do not justify

attempts at individual diagnosis or prognosis but they have high predictive significance for groups, even quite small groups. In about 95 out of 100 samples of only 10 coronary patients the average measurement would be higher than the average for clinically healthy men (Table 4, lines 3, 4, 7). Other things being equal, there seems to be no doubt that high serum levels of cholesterol, etc., are undesirable and the higher the values the more undesirable they are. Hence there is every justification for devoting great effort to discovering what determines the level in man and how that level may be controlled.

CHOLESTEROL IN THE DIET AND IN THE BLOOD

Because of the limitations of both space and data the remainder of this discussion is restricted to the total cholesterol concentration in the blood serum. The serum cholesterol level is the resultant of several factors. All animals, including man, synthesize cholesterol, mainly in the liver, and eliminate it in the bile and by chemical degradation. If there is cholesterol in the food it may be absorbed and so enter the balance picture. But when exogenous cholesterol is supplied the synthesis in the liver is suppressed (8, 9, 10). Some animals, such as the rabbit and the chicken, have little or no dietary experience with cholesterol after weaning or hatching and have little capacity to destroy or otherwise eliminate it when they are fed large amounts. Others, like the rat, the dog and man, have much greater ability to handle cholesterol and are relatively unaffected by dietary administration.

The attempt to extrapolate to man the findings from cholesterol experiments with rabbits and chickens can lead to absurdities. The typical rabbit experiment involves a diet containing 2 per cent added cholesterol, or some 5 mg. of cholesterol per Calorie. This means 15 grams of cholesterol in a human diet of 3000 Calories, an amount about ten times higher than it is *possible* to attain in any habitual diet of ordinary human foods and fifteen or twenty times what is considered a high-cholesterol diet for man (11). And it must be emphasized again that man is very different from the rabbit and the chicken in his metabolism of cholesterol.

In man and animals only a portion of orally ingested cholesterol is absorbed. From experiments with C^{14} labelled cholesterol in the rat (12) and H^3 labelled cholesterol in man (13) it seems probable that something like 20 to 50 per cent of cholesterol ingested in a fat vehicle is absorbed from the gut. But such absorbed cholesterol does not simply add to the cholesterol already present in the blood and the total concentration in the blood rises very little, even with massive doses.

From 20 experiments with young men ingesting 5 to 12 grams of cholesterol in a fat-rich meal it was found the maximum rise in the blood concentration occurred from 3 to 10 hours later but the value at 4 hours was at or near the peak. In Table 5 are the summarized data from experiments on 73 clinically healthy men who were given a breakfast of toast and butter and coffee with cream and scrambled eggs in which 10 grams of pure cholesterol were emulsified. The mean rise of 3.95 mg. per 100 ml. of serum corresponds to an increase of about 250

mg. in the total circulating blood or less than 3 per cent of the ingested cholesterol. Moreover, in 18 to 30 hours the serum level no longer shows any trace of such a single massive dose.

Continued feeding of man with diets containing 20 or more grams of added cholesterol daily eventually produces a rise in the serum level of elderly men (14), but this is trivial compared with the change in rabbits or chickens fed an equivalent amount. The data summarized in Table 6 show how greatly man differs from other animal species, particularly the rabbit and the chicken. It will also be observed that man on an ordinary diet has a higher concentration of cholesterol in the serum than the other animals listed as well as other animals studied on normal diets; these include the cat, cow, goat, guinea pig, horse, and mouse.

Horlick and Havel (19) observed that the maximum effect of dietary cholesterol in the rat is achieved by diets containing around 3 mg. of cholesterol per Calorie and that further increasing this massive dose to heroic proportions has no effect on the blood. The data suggest this may be true of man also. In any case, the

TABLE 5

Means and standard deviations for serum total cholesterol concentrations, in mg. per 100 ml., in 73 healthy young men before and 4 hours after ingestion of 10.7 grams of cholesterol in a fat-rich breakfast

	MEAN	S.D.
Before ingestion	216.35	±36.22
Change after ingestion	+3.95	±11.09

problem is not what may be the result of tremendous doses over limited time so much as the effect of prolonged ingestion of far more moderate amounts.

In the United States different persons have greatly different habits in regard to dietary cholesterol. Some persons never drink milk, eat eggs or consume more than minute amounts of butter, ice cream, cheese or fat meat. Others, however, regularly consume several eggs a day and use large amounts of meat and dairy products. The range encountered in a population sample may be from less than 100 mg. to as much as 1 gm. of cholesterol in the daily diet. But extensive surveys of the serum cholesterol concentration in inividuals of differing cholesterol intake consistently fail to show a relation between these variables.

Our surveys on clinically healthy men of the upper economic bracket in the Twin Cities have covered several hundred men in each of five successive years. Each year we have obtained negative results similar to those reported for the first year (25) and confirmed by others (6, 26). Perhaps the most significant findings are those obtained on men persistently extreme in their dietary cholesterol habits and on men who changed their dietary cholesterol intakes. Table 7 gives a summary of the data on 63 middle-aged men who were persistently extreme in their dietary cholesterol habits when studied over a period of two years. It is clear that the men who were always above the 80th percentile in dietary choles-

terol did not, at any time, have higher serum values than the men who were always below the 20th percentile of intake.

Table 7 also gives a summary of the data on 40 men who made marked changes in their dietary cholesterol intakes, in some cases because of altered domestic status, in others in a conscious effort to change the cholesterol intake. Primarily, these men changed their dietary habits with regard to eggs and changed from

TABLE 6

Mean serum cholesterol responses to cholesterol feeding in different species

The dietary cholesterol values are rough approximations to enable them all to be expressed on the same scale of mg. of cholesterol per dietary Calorie. References (referring to line numbers) are: 1, 10, 11—Cook and Thomson (15); 2, 3—Kesten and Silbowitz (16); 4, 5—Rodbard, Bolene and Katz (17); 6—Stamler and Katz (18); 7, 8—Horlick and Harvel (19); 9—Sperry and Stoyanoff (20); 12—Greenberg and Rinehart (21); 13—Moses (22); 14—Steiner (23); 15, 16, 17—Messinger, Porowsawska and Steele (14); 18—Okey and Stewart (24).

SPECIES	DIET MG./CAL.	DURATION, WEEKS	MG. PER 10 ML.		% CHANGE
			Control	Final	
1. Rabbit	5.0	8	149	1720	+1050
2. Rabbit	0.6	16	(145)*	430*	+200
3. Rabbit	1.5	5–8	141*	959*	+580
4. Chick	0.8	25	(100)	130	+30
5. Chick	6.0	15	(100)	550	+450
6. Chick	0.8	5–15	116	169	+46
7. Rat	15.0	22	(59)*	113*	+108
8. Rat	30.0	22	(54)*	129*	+139
9. Rat	3.0	?	59	163	+176
10. Rat	5.0	4	70	222	+217
11. Guinea Pig	5.0	5	96	271	+182
12. Monkey	3.0	29	175	213	+22
13. Man	1.0	16	222	223	0
14. Man	1.5	6	—	—	"slight"
15. Man	1.3†	7	235	272	+16
16. Man	1.3†	6	253	287	+13
17. Man	12.0	9+	238	276	+16
18. Man	1.4	4	154	167	+8

* Whole blood.

† Cholesterol in dried egg yolk, powder fed. This powder also provided about 20 gm. of lecithin.

butter and lard to vegetable fats, or vice versa. The result was large change in cholesterol intake with little or no change in calories, in total proteins or in total fats and the body weights were practically constant. Here again, as in the surveys of men on constant diets, there was no trace of an effect on the serum concentration of total cholesterol.

In the course of this work it was possible to study 17 men who, though clinically well, changed to a low-cholesterol diet with moderate restriction of all fats. Most of these men were following the advice of their personal physicians who advocated

low-cholesterol diets and fat restriction for all middle-aged men. Prior to the diet change the mean and standard error of the serum total cholesterol concentration was 242.2 ± 14.0. After 3 to 7 months on the restricted diet the values were 229.9 ± 9.9. Though this difference is not statistically very impressive, it was important in the design of the systematic experiments to be mentioned below.

TABLE 7

Means and standard errors for serum total cholesterol, in mg. per 100 ml., in clinically healthy middle-aged men, matched as to age, with habitually different cholesterol intakes

The dietary intakes are indicated by the percentile ranks of the men in the total sample of 300 men of the upper economic bracket in the Twin Cities.

NO. MEN	FIRST YEAR		SECOND YEAR*	
	Intake Percentile	Serum Conc.	Intake Percentile	Serum Conc.
35	90	244.7 ± 5.9	90	246.0 ± 6.7
51	10	240.6 ± 8.8	10	244.0 ± 10.3
23	60	250.1 ± 7.1	25	250.3 ± 6.7
17	45	259.7 ± 8.3	70	252.5 ± 10.2

* Corrected for increased age from data of Keys et al. (30).

DIET AND SERUM CHOLESTEROL-CONTROLLED EXPERIMENTS

Like others (27, 28) we had consistently observed a marked decrease in the serum cholesterol concentration in hypertensive patients when treated by subsistence on the rice fruit diet (29). Studies were then made on 21 normotensive men before and during one month's subsistence on a modified rice-fruit diet in which salt was allowed as well as the substitution of potatoes for some of the rice. The results are summarized in Table 8. This diet, containing no cholesterol and extremely little fat—about 1 to 1.5 per cent of the total calories—immediately initiates a decline in serum cholesterol so that in 3 weeks the average is about 70 per cent of the value on an ordinary free diet (30).

More prolonged experiments were carried out on physically healthy schizophrenic men in an isolated metabolism building at the Hastings (Minnesota) State Hospital. In the first series of experiments 21 men were studied in collaboration with Dr. J. T. Anderson, for eight months of alternations of a month each on six diets of constant calorie, protein, mineral and vitamin content but differing in cholesterol and in total fat content. The basic diet was a modified rice-fruit diet, similar to that mentioned above but containing also some egg whites, fat-free bread and boiled green vegetables, to which were added vegetable fats or sugar and jelly to keep calories constant. The cholesterol was added in the form of egg yolks, the fat content of these substituting for an equivalent amount of vegetable fat. The men proceeded through these alternations in different order so possible cumulative effects of particular diet sequences were eliminated in the average serum changes shown in Table 9.

Table 9 clearly shows a pronounced effect of dietary (vegetable) fat and no significant effect of cholesterol in the range 0 to 650 mg. per day. Comparison

of the serum cholesterol values in the third and in the fourth weeks on each diet disclosed no significant difference, indicating that the diet effect was substantially completed in 3 weeks. Concordant results in studies on 3 men have been reported by Hildreth et al (32).

Further evidence on these questions was obtained in an experiment of 32 weeks' duration on 26 schizophrenic men similar to those mentioned above (31). The men, ranging from 27 to 46 years old, were paired off in 2 groups matched as to age, relative body weight, mental diagnosis and habitual physical activity. Two diets were devised, both providing 3400 Calories, 110 gm. of pro-

TABLE 8

Serum total cholesterol concentration, in mg. per 100 ml., before and after 3 weeks of subsistence on a modified rice-fruit diet

Mean values in 21 normotensive men, aged 22 to 45, grouped according to the control serum concentration, the last group including several men with marked idiopathic hypercholesterolemia.

NO. OF MEN	BEFORE	AFTER	CHANGE IN %
7	200	160	20
7	239	160	33
7	417	252	35
21	285.3	190.7	29.3

TABLE 9

Mean changes in serum total cholesterol concentration, in mg. per 100 ml., in 21 men after subsistence for 4 weeks on controlled diets

CHOL. MG./DAY	FAT, GM. DAILY			ALL EXPTS.
	15	72	114	
0	−64	−27	0	−46
600	−61	−21	0	−41
All Expts.....	−63	−24	0	—

teins and 700 mg. of cholesterol but in one (high fat) there were 140 gm. of fat and in the other (moderate fat) there were 70 gm. of fats. In both diets the fats were 90 per cent from animal and 10 per cent from vegetable sources. One group changed from the high to the moderate fat diet and in 4 weeks there was a mean decrease of 21 mg. of cholesterol per 100 ml. of serum. The other group made the reverse dietary change and the result was a mean increase of 27 mg. of cholesterol per 100 ml. of serum. Continued subsistence on these controlled diets for 32 weeks caused no significant further change in the serum and the difference between the serum cholesterol values on the two diets was maintained.

In all of the studies mentioned above the subjects, like the general population of the United States, had lived all their lives to the time of study on diets rela-

tively high in both total fats and cholesterol, and the experimental findings refer only to relatively short periods of change from this life-long pattern. In order to discover relationships with grossly different life-long diets studies were made on clinically healthy men in other countries.

The standard of comparison for such studies are the results on 1492 clinically healthy men in Minnesota as summarized in Table 10 (33). These standards are also valid, apparently, for other metropolitan areas in the United States (34).

The age trend, most clearly shown in the columns of percentages in Table 10, is striking and suggests the age trend commonly observed in the incidence of coronary artery disease. In the following comparisons with men in other countries this age trend is of particular interest.

TABLE 10

"Normal" values for the total cholesterol concentration, in mg. per 100 ml. of serum, for clinically healthy men in Minnesota

The data refer to 1492 men gainfully occupied in non-manual work in the metropolitan area of Minneapolis and St. Paul. Means and standard deviations (S.D.), and means expressed as percentages of the mean at age 25. These values refer to measurements using the Liebermann-Burchard reaction with the Bloor extract of bloods drawn in the basal state; for causal blood samples the values should be increased by about 5 per cent. With the Sperry-Schoenheimer method the values should be about 5 per cent lower, (33).

AGE	MEAN S. D.	%	AGE	MEAN S. D.	%
20	173 ± 31	94	50	248 ± 45	135
25	184 ± 34	100	55	256 ± 46	139
30	195 ± 40	106	60	253 ± 34	137
35	200 ± 43	109	65	237 ± 34	129
40	219 ± 39	119	70	225 ± 42	122
45	236 ± 37	128	75	212 ± 37	115

SERUM CHOLESTEROL VALUES IN OTHER COUNTRIES

In comparison with the United States the diet in Great Britain is interesting. The average fat consumption in Britain is high, though not so high as in the United States (about 11 per cent lower in Britain) and the pattern was not importantly changed during World War II and subsequent years. But the average cholesterol intake is much lower as indicated by the fact that the per capita consumption of eggs, meat and milk, as percentages of that in the United States, is, respectively, 52, 68, and 74 (from National Food Balance Data for 1949–50, supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations).

In the spring of 1950 it was possible to study 48 clinically healthy men employed in Slough, a suburb of London, and these 40 to 55 year-old men, together with the sample of 44 healthy younger men studied in London a few months previously (35) are compared with the Minnesota men in Table 11.

These Englishmen, then, conform closely to the Minnesota standards but this does not mean that the English and American populations are identical in these

respects. The men studied in London are not a true sample because, for one thing, their fat intake was somewhat higher than the national average. A careful study made by the Ministry of Health of food actually eaten by the men at Slough gave an average of 35.4 per cent of calories from fats. Since fat wastage is necessarily considerable between retail purchase and actual consumption, the retail average for these men might correspond to something like 38 per cent of calories from fats, as compared with a national average for Britain of 34.8. For comparison, the retail average for Minneapolis in the winter of 1948 was 41.1 per cent of total calories as fats (data supplied from the U. S. Department of Agri-

TABLE 11

Serum total cholesterol values in clinically healthy men in the London area

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 in England and of the means for equal ages in Minnesota.

AGE	MEAN	% OF VALUE OF	
		Age 25	Minnesota
20	178	96	103
30	193	104	99
40	228	123	104
50	238	129	101

TABLE 12

Serum total cholesterol values in clinically healthy men in Naples

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 and of the means for equal ages in Minnesota.

AGE	MEAN	% OF VALUE OF	
		Age 25	Minnesota
20	176	93	102
30	204	107	105
40	219	115	100
50	218	115	88

culture by Dr. Esther F. Phipard), the intake value being perhaps 36 to 38 per cent.

The important point about the data from England is that, with similar total fat intakes, the serum cholesterol values are also closely similar to those in Minnesota. But the cholesterol intake of these Englishmen was not much more than half that of the Minnesota men, owing to the strict rationing, since 1940, of eggs, butter and meats; margarine and cooking fats are abundant in Britain.

In Naples, Italy, similar studies were carried out on 83 clinically healthy men covering the age range 20 to 56 (36). In Naples the diet proved to be identical with the Italian national average for the percentage of total calories supplied by fats—20 per cent—and therefore about half the U. S. (and Minnesota) level. Serum cholesterol data are summarized in Table 12.

The picture is not different from that in the Englishmen through age 30 but thereafter the age trend does not continue as in England or the United States. From age 40 to age 50 in Minnesota there is a mean rise of 29 mg.; in Naples there is a fall of 1 mg. Statistical analysis, moreover, shows these differences to be highly significant.

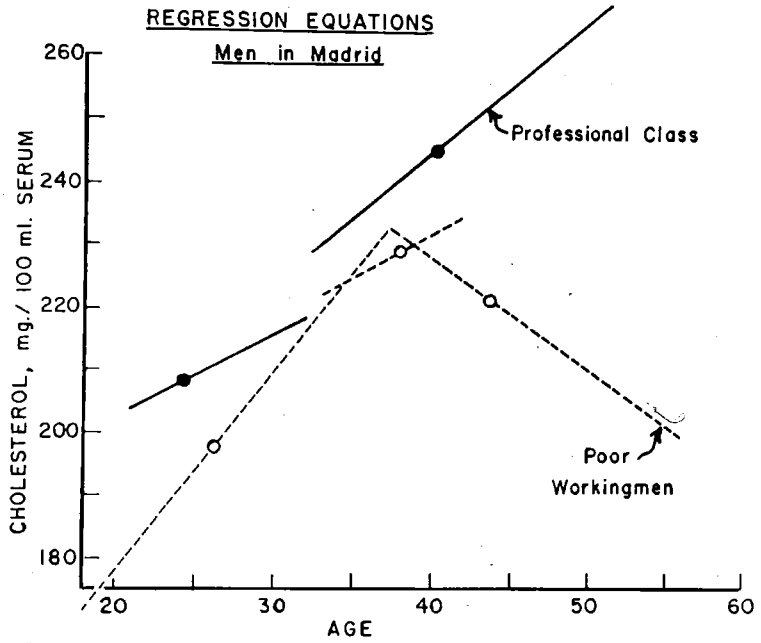

FIG. 1. Relationship of serum total cholesterol concentration to age in clinically healthy Spaniards in Madrid. The lines show the least-squares regression equations for the age ranges covered by these lines, the points being the means for each age series.

TABLE 13

Serum cholesterol values in 2 classes of clinically healthy men in Madrid

Means, in mg. per 100 ml., adjusted to basal conditions, together with percentages of the means at age 25 and of the means for equal ages in Minnesota.

AGE	POOR MEN			RICH MEN		
	Mean	% of Value of		Mean	% of Value of	
		Age 25	Minnesota		Age 25	Minnesota
20	166	91	95	193	98	111
30	199	109	102	201	102	103
40	209	114	95	230	117	105
50	197	105	79	251	127	101

In Madrid, Spain, similar studies were made on 55 poor men habitually always on a low-fat diet (about 22 per cent of calories from fats) and 57 prosperous professional men on a diet similar to that eaten by wealthy men in the United States. The poor men, moreover, were on a low-calorie diet, as indicated both by the dietary survey and by the body weights and measurements of skinfolds. The main findings on these two groups are indicated in Fig. 1.

The prosperous professional men in Madrid are not much different from the Minnesota standards, though they tend to be high at all ages, but they are in great contrast to the poor Madrilenos, especially after 30 years of age. Table 13 summarizes the data from Madrid in a form similar to that used in Tables 11 and 12.

THE FACTOR OF RELATIVE OBESITY

The foregoing analysis emphasizes the role of the total dietary fats in determining the serum cholesterol concentration. The question may be asked, however, as to the role of total calorie balance, particularly in view of the very low serum values in the undernourished poor men in Madrid. However, it seems that relative obesity is not the major factor, short of real undernutrition, when the men in England, in Naples and in Minnesota are considered. The mean relative body weights, as percentage of the Medical-Actuarial standards for height and age used in the United States were as follows: Minnesota 103, Naples 105, England 94. In spite of the relative leanness of the Englishmen, their serum concentrations were not lower than the Minnesotans. And the Neapolitan serum concentrations differ, after age 30, from the Minnesota values in spite of the fact they were a trifle fatter than the Minnesotans.

These facts are in harmony with our findings in Minnesota where we have studied the correlation between serum cholesterol and relative obesity. There is a positive correlation but it is small in men of equal ages in the general population (25). However, chronic severe undernutrition is almost always associated with low serum cholesterol concentrations (34, 37). This may be in part because the fat content of the diet in such cases is always low. We have consistently found increased values in men when they were actively gaining weight from simple overeating. In simple fasting the usual tendency for the serum cholesterol to rise may reflect the fact that the fasting man is primarily metabolizing fat; in a sense then he is on a high-fat diet (34).

THE DIET AND MORTALITY

All the data summarized here suggest an important chain of relations between the total fat content of the diet (or the proportion of fat calories of the total metabolized), the cholesterol (and lipoprotein) concentration in the blood, the development of atheroslerosis, and the mortality from degenerative heart disease. The vital statistics data for Italy (Table 1) clearly fit this pattern.

It is unfortunate that vital statistics data are not available for Spain but perhaps those from Portugal (Table 3) may serve to indicate what may be the case in Spain where the diet is similar. There seems to be no doubt that coronary disease and myocardial infarction are not common in Spain. This is agreed by the local doctors and is confirmed by a search through the public hospitals. But it is also of interest that the leading fashionable physicians do not lack cases among their rich patients and tell of many relatives and colleagues who have died from occulsions.

So far it has been possible to get fully comparable dietary and vital statistics data from 6 countries. Figure 2 gives a summary for men of two age ranges. This

is for "degenerative heart disease" as defined here to mean coronary disease, angina pectoris, infarction, chronic myocarditis and myocardial degeneration, i.e. categories 93 and 94 in the 1938 Revision of the International List and categories 420 and 422 in the 1948 Revision (1). Almost the same relation holds, moreover, if the total deaths from all heart disease are plotted against fat calories as a percentage of the total. This is because of the dominance of these categories in the cardiac total at these ages. Obviously the relation shown in Fig. 2 is too regular and too marked to be explained on the grounds of possible differences between countries in the criteria for death certification. Whether or not choles-

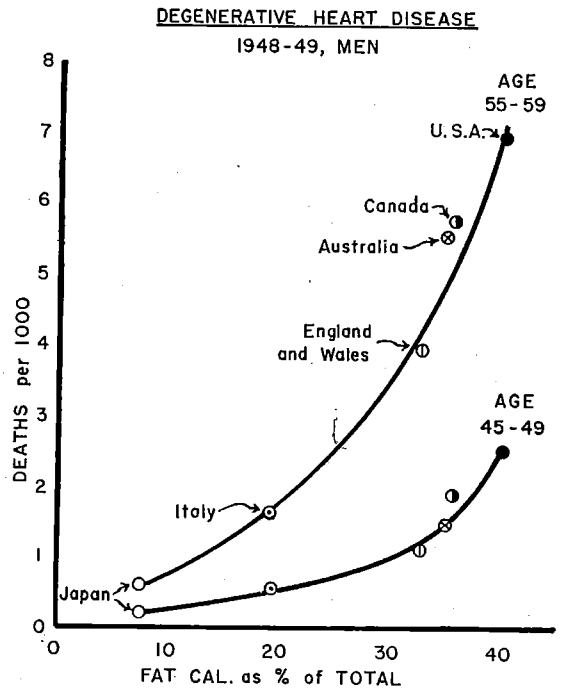

FIG. 2. Mortality from degenerative heart disease (categories 93 and 94 in the Revision of 1938, categories 420 and 422 in the Revision of 1948, International List. National vital statistics from official sources. Fat calories as percentage of total calories calculated from national food balance data for 1949 supplied by the Nutrition Division, Food and Agriculture Organization of the United Nations.

terol, etc., are involved, it must be concluded that dietary fat somehow is associated with cardiac disease mortality, at least in middle age.

There is other impressive evidence to this same effect. World War II brought with it dietary alterations in many areas and a reduction in dietary fat was prominent for several years in lands conquered by Germany. In Norway, the public health and vital statistics records were well maintained and it is clear that not long after the national dietary change began there was a marked decline in mortality from circulatory disease, particularly from arteriosclerotic heart disease (38). At first this change in mortality was attributed to a reduction in dietary cholesterol (39), but detailed analysis indicates that a reduction in total dietary fats was the responsible factor (40).

DISCUSSION

The argument and evidence assembled here make a consistent picture which holds promise of a preventive hygiene but many details are lacking. The mechanism of the action of the diet on the blood cholesterol concentration has not really been examined. This is an important part of the blood cholesterol level (41). We should like to know how, apart from dietary peculiarities, hypercholesterolemia tends to run in families (42, 43, 44). Moreover, there is much reason to believe that other factors besides the blood concentration are important in the actual development of arteriosclerotic heart disease. Why are men and women so different, until well beyond the female reproductive age range, in susceptibility? So far the blood studies have been made mostly on men but at least to age 30 or a little older there seems to be no difference in the blood adequate to account for the sex difference in coronary disease incidence in the United States.

Recognition of all those limitations should not interfere with the analysis of the facts now at hand. It may be hoped that efforts to discover and to understand mechanisms will be pursued vigorously. There is, however, obviously a fruitful

TABLE 14

Fat calories as a percentage of the total calories in the U. S. National food supply since 1910

Computed by Dr. E. Phipard from official data of the U. S. Department of Agriculture.

	%		%		%
1910	31.8	1930	35.0	1950	40.2
1920	33.0	1940	38.3		

field for epidemiological research as yet scarcely touched. And it is not too soon to begin the application, by educational means, of epidemiological findings.

The present high level of fat in the American diet did not always prevail and this fact may not be unrelated to the indication that coronary disease is increasing in this country. Table 14 shows the average fat calories as a percentage of the national food calorie supply from 1910 (the beginning of reliable data) through 1950. In the past 40 years the contribution of fats to the total metabolism in the United States has risen by more than 25 per cent; in the past 20 years the rise has been almost 13 per cent. In the fact of all the evidence, is this situation desirable? One may seriously ask whether the current nutritional and dietetic teaching in this country is as completely on the right track as some may suppose. Complete indifference to the amount of the fat in the diet is the attitude currently expressed by both technical and popular books and articles on diet.

From the statistics of the U.S. Department of Agriculture it is clear that the biggest contributor to the fats in the American diet is fats and oils as such, excluding butter, which comprise 46.5 per cent of the total. Meats, poultry and fish combined make a poor second at 22.1 per cent. Any attempt to reduce the total fat intake must, then, begin with cooking fats and oils.

CONCLUSIONS

The material discussed above covers too large a field to be summarized except in terms of the conclusions which emerge from it. These are:

1) Compared with other countries where records are comparable, the total age-specific death rate over most of the span of adult life is excessively high in the United States and this American inferiority is more marked with men than with women.

2) The excessive death rate of adults in the United States is attributable to an excessive mortality from "degenerative" heart disease—coronary disease, angina pectoris, myocardial infarction, chronic myocarditis and myocardial degeneration. These conditions cannot be clearly separated in vital statistics and probably share some common features in basic etiology.

3) The concentration of total cholesterol in the blood serum bears an important relationship to the development of atherosclerosis and its sequelae and related clinical conditions. Similar relationships exist with the concentrations of certain "giant molecules" (S_f 10–20, S_f 12–20) and of certain lipoprotein fractions separable by precipitation methods.

4) Measurements of total cholesterol and of S_f 12–20 particles in the serum afford highly significant differentiation between *groups* of men who are clinically healthy and *groups* of men who have or are likely to develop coronary heart disease. There is no important difference between the cholesterol and the S_f 12–20 measurements in this regard, particularly with men before old age.

5) These measurements of total cholesterol or of S_f 12–20 concentrations in the serum have very little practical value for individual diagnosis or prognosis, the index of forecasting efficiency being of the order of 20 per cent.

6) The total cholesterol concentration in the serum of man is substantially independent of the dietary cholesterol intake over the whole range of possible human diets.

7) The total cholesterol concentration in the serum of men habitually on diets characteristic of the United States changes directly with changes in the total fat content of the diet. The response to the new diet begins in a few days and reaches a new plateau in a few weeks, this new plateau being relatively stable for at least several months. There is no indication of a difference in animal versus vegetable fat in evoking the serum response.

8) Comparison of men from populations always living on different amounts of total fat intake indicates that in youth and to the early thirties the serum cholesterol concentration is relatively independent of the diet if there is calorie sufficiency. But from the thirties through the fifties the serum concentration is increasingly dependent on the amount of total fat in the diet.

9) The different age-specific death rates of men 40 to 65 years old from degenerative heart disease in different countries are directly related to the differences in those countries in the proportion of the total calories derived from total fats. The relationship in the case of women is much less clear.

10) For the 40 years of records available, the proportion of fat calories in the total American food consumption has steadily increased. On the basis of compari-

sons with other countries at present this rise in fat consumption might be predicted to be associated with an increase of the order of 50 to 100 per cent in mortality from degenerative heart disease for men aged 40 to 65. U. S. vital statistics are, in fact, compatible with this prediction.

11) The facts and relationships indicated here are of such importance as to warrant a large extension of this type of epidemiological research. It is difficult to escape the conclusion that public health programs must take cognizance of the information already at hand.

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REFERENCES

1. World Health Organization. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Sixth Revision of the International Lists of Diseases and Causes of Death, Adopted 1948. Vol. 1. W.H.O., Geneva, 1948.
2. Jones, H. B., Gofman, J. W., Lindgren, F. T., Lyon, T. P., Graham, D. M., Strisower, B., and Nichols, A. V.: Lipoproteins in Atherosclerosis. Amer. J. Med., 11: 358, 1951.
3. Keys, A.: "Giant Molecules" and Cholesterol in Relation to Atherosclerosis. Bull. Johns Hopkins Hosp., 88: 473, 1951.
4. Keys, A.: Cholesterol, "Giant Molecules," and Atherosclerosis. J. Amer. Med. Assoc., 147: 1514, 1951.
5. Gertler, M. M., Garn, S. M., and Lerman, J.: The Interrelationship of Serum Cholesterol, Cholesterol Esters, and Phospholipids in Health and in Coronary Artery Disease. Circulation, 2: 205, 1950.
6. Gertler, M. M., Garn, S. M., and White, P. D.: Diet, Serum Cholesterol and Coronary Artery Disease. Circulation, 2: 696, 1950.
7. Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A., and Strisower, B.: Blood Lipids and Human Atherosclerosis. Circulation, 2: 161, 1950.
8. Schoenheimer, R. and Breusch, F.: Synthesis and Destruction of Cholesterol in the Organism. J. Biol. Chem., 103: 439, 1933.
9. Gould, R. G.: Lipid Metabolism and Atherosclerosis. Amer. J. Med., 11: 209, 1951.
10. Frantz, I. D., Jr., Schneider, H. S., and Hinkelman, B. T.: Relationships Between the Levels of Dietary, Liver and Serum Cholesterol and Hepatic Cholesterol Synthesis. Circulation, 6: 467, 1952.
11. Keys, A.: Human Atherosclerosis and the Diet. Circulation, 5: 115, 1952.
12. Chaikoff, I. L., Bloom, B., Siperstein, M. D., Kiyasu, J. Y., Reinhardt, W. O.,

DAUBEN, W. G., AND EASTHAM, J. F.: C^{14}-Cholesterol. 1. Lymphatic Transport of Absorbed Cholesterol-4-C^{14}. J. Biol. Chem., 194: 407, 1952.

13. BIGGS, M. W., KRITCHEVSKY, D., COLMAN, D., GOFMAN, J. W., JONES, H. B., LINDGREN, F. T., HYDE, G., AND LYON, T. P.: Observations on the Fate of Ingested Cholesterol in Man. Circulation, 6: 359, 1952.
14. MESSINGER, W. J., POROSOWSKA, Y., AND STEEL, J. M.: Effect of Feeding Egg Yolk and Cholesterol on Serum Cholesterol Levels. Arch. Internal Med., 86: 189, 1950.
15. COOK, R. P. AND THOMSON, R. O.: The Absorption of Fat and of Cholesterol in the Rat, Guinea-pig and Rabbit. Quart. J. Exp. Physiol., 36: 61, 1951.
16. KESTEN, H. D. AND SILBOWITZ, R.: Experimental Atherosclerosis and Soya Lecithin. Proc. Soc. Exp. Biol. & Med., 49: 71, 1942.
17. RODBARD, S., BOLENE, C., AND KATZ, L. N.: Hypercholesteremia and Atheromatosis in Chicks on a Restricted Diet Containing Cholesterol. Circulation, 4: 43, 1951.
18. STAMLER, J. AND KATZ, L. N.: Production of Experimental Cholesterol-induced Atherosclerosis in Chicks with Minimal Hypercholesterolemia and Organ Lipidosis. Circulation, 2: 705, 1950.
19. HORLICK, L. AND HAVEL, L.: The Effect of Feeding Propylthiouracil and Cholesterol on the Blood Cholesterol and Arterial Intima in the Rat. J. Lab. & Clin. Med., 33: 1029, 1948.
20. SPERRY, W. M. AND STOYANOFF, V. A.: Effects on Long Continued Cholesterol Feeding in Rats. J. Nutrition, 9: 131, 1935.
21. GREENBERG, L. D. AND RINEHART, J. F.: Plasma Cholesterol Levels of Cholesterol Fed Control and Pyridoxine Deficient Monkeys. Proc. Soc. Exper. Biol. & Med., 76: 580, 1951.
22. MOSES, C.: Dietary Cholesterol and Atherosclerosis. Amer. J. Med. Sci., 224: 212, 1952.
23. STEINER, A.: Cholesterol Metabolism and Arteriosclerosis. Amer. J. Med., 6: 117, 1949.
24. OKEY, R. AND STEWART, D.: Diet and Blood Cholesterol in Normal Women. J. Biol. Chem., 99: 717, 1933.
25. KEYS, A.: The Physiology of the Individual as an Approach to a More Quantitative Biology of Man. Fed. Proc., 8: 523, 1949.
26. WILKINSON, C. F., JR., BLECHA, E., AND REIMER, A.: Is There a Relation Between Diet and Blood Cholesterol? Arch. Int. Med., 85: 389, 1950.
27. KEMPNER, W.: Treatment of Hypertensive Vascular Disease with Rice Diet. Amer. J. Med., 4: 545, 1948.
28. SCHWARTZ, W. B. AND MERLIS, J. K.: Nitrogen Balance Studies on Kempner Rice Diet. J. Clin. Inves., 27: 406, 1948.
29. CHAPMAN, C. B., GIBBONS, T., AND HENSCHEL, A.: The Effect of the Rice-Fruit Diet on the Composition of the Body. New England J. Med., 243: 899, 1950.
30. KEYS, A., MICKELSEN, O., MILLER, E. V. O., AND CHAPMAN, C. B.: The Relation in Man Between Cholesterol Levels in the Diet and in the Blood. Science, 112: 79, 1950.
31. ANDERSON, J. T. AND KEYS, A.: Dietary Fat and Serum Cholesterol. Fed. Proc., in press.
32. HILDRETH, E. A., MELLINKOFF, S. M., BLAIR, G. W., AND HILDRETH, D. M.: The Effect of Vegetable Fat Ingestion on Human Serum Cholesterol Concentration. Circulation, 3: 641, 1951.
33. KEYS, A., MICKELSEN, O., MILLER, E. V. O., HAYES, E. R., AND TODD, R. L.: The Concentration of Cholesterol in the Blood Serum of Normal Man and Its Relation To Age. J. Clin. Invest., 29: 1347, 1950.
34. KEYS, A., BROZEK, J., HENSCHEL, A., MICKELSEN, O., AND TAYLOR, H. L.: The Biology of Human Starvation. 2 Vols: Minnesota Press, Minneapolis, 1950.
35. TANNER, J. M.: The Relation Between Serum Cholesterol and Physique in Healthy Young Men. J. Physiol., 115: 371, 1951.

36. KEYS, A., FIDANZA, F., SCARDI, V., AND BERGAMI, G.: The Trend of Serum Cholesterol Levels with Age. Lancet, 263: 209, 1952.
37. HORST, W.: Beitrag zum Lipoidstoffwechsel bei Chronischer Unternährung. Klin. Wscher., 28: 184, 1950.
38. STRØM, A. AND JENSEN, A. R.: Mortality from Circulatory Diseases in Norway 1940–45. Lancet, 260: 126, 1951.
39. MALMROS, H.: The Relation of Nutrition to Health. A Statistical Study of the War-time on Arteriosclerosis, Cardiosclerosis, Tuberculosis and Diabetes. Acta Med. Scand. Suppl., 245: 137, 1950.
40. PIHIL, A.: Cholesterol Studies. II. Dietary Cholesterol and Atherosclerosis. Scand. J. Clin. and Lab. Invest., 4: 122, 1952.
41. BYERS, S. O., FRIEDMAN, M., AND ROSENMAN, R. H.: Review: On the Regulation of Blood Cholesterol. Metabolism, 1: 479, 1952.
42. BOAS, E. P. AND ADLERSBERG, D.: Familial Hypercholesteremia (Xanthomatosis) and Atherosclerosis. J. Mt. Sinai Hosp., 12: 84, 1945–1946.
43. WILKINSON, C. F., JR., HAND, E. A., AND FLIEGELMAN, M. T.: Essential Familial Hypercholesteremia. Ann. Int. Med., 29: 676, 1948.
44. ADLERSBERG, D.: Hypercholesteremia with Predisposition to Atherosclerosis. An In-Inborn Error of Lipid Metabolism. Amer. J. Med., 11: 600, 1952.