

## PRIMARY PREVENTION OF CORONARY HEART DISEASE BY DIET\*

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THE subject of diet, atherosclerosis, and coronary heart disease was covered by Ancel Keys<sup>1</sup> at the *Conference on Atherosclerosis and Coronary Heart Disease* held on January 15, 1957, and sponsored by the New York Heart Association. Among the major conclusions from Dr. Keys' epidemiologic studies of more than a decade ago were the following:

1) There were very great differences between populations in the incidence of atherosclerosis and the mortality of coronary heart disease at given ages.

2) These differences were not explained by race, nationality, or climate or any *nondietary* factor studied.

3) The differences appeared to be closely correlated with the average serum cholesterol concentration in samples of the population.

4) Both the serum cholesterol concentration and the frequency of ischemic heart disease were unrelated to the amount of protein in the diet but there was a close correlation with the proportion of fats in the habitual diet.

5) Different dietary fats differed in their effect on serum cholesterol and, probably, on atherosclerosis; the common meat and dairy fats that dominated the American diet had a powerful tendency to raise the serum cholesterol level.

One month after that conference, in February 1957, the Diet and Coronary Heart Disease Study Project (usually known as the Anti-Coronary Club) originated in an executive order of the Commissioner of Health of the City of New York, and the pioneer investigation of the primary prevention of heart disease by diet was begun. The above-mentioned conclusions of Keys instilled a fair degree of confidence that

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a public health approach to the prevention of coronary heart disease through diet could be attempted.

There was more scientific background. A study by the Public Health Service of the population aged 45 to 62 years residing in Framingham, Mass.,<sup>2</sup> revealed that men with serum cholesterol levels below 225 mg. per cent proceeded from normal hearts (with relation to coronary heart disease) to clinical coronary disease at the rate of 13 per thousand after 4 years of observation at 2-year intervals. This compared with an incidence of 80 per thousand after 4 years in men entering the study with serum cholesterol levels over 260 mg. per cent. Nonobese men revealed an incident of new attacks of coronary heart disease at a rate of 28 per thousand per 4 years; the incidence was 57 per thousand per 4 years in obese persons. Hypertensive subjects had an incidence of 100 new attacks per thousand persons per 4 years, compared with 17 in normotensive persons. Put in another way: if the risk of the development of coronary heart disease in obese hypercholesterolemic men aged 45 to 62 years was 14 times greater than in men of normal weight with lower cholesterol levels, and if a change in diet could alter both of these abnormalities, it would follow that the attack rate after dietary change might be lowered.

The work of Kinsell,<sup>3</sup> which was confirmed by Ahrens,<sup>4</sup> Beveridge,<sup>5</sup> and Malmos,<sup>6</sup> provided an aid to a practical dietary approach; namely, that in subjects trained in a metabolism ward or taught to follow formula diets, the substitution of oils high in polyunsaturated fatty acids (corn, cottonseed, safflower, soybean, sunflower) for the dietary saturated fats would lower the blood cholesterol. This permitted us to construct a diet (the Prudent Diet) in which foods with predominantly saturated fatty acids (butter, whole-milk cheese, ordinary margarines, and hydrogenated shortenings) and foods containing such acids in significant amounts (beef, pork, lamb, and eggs) could be reduced in quantity or eliminated.

These foods could be replaced by those with predominantly unsaturated types of fatty acids (vegetable oils, fish, most nuts) and with leaner meats such as poultry and veal. The diet of our subjects on entry to the study was composed approximately of 18 per cent protein, 42 per cent carbohydrate, and 40 per cent fat. The division of total fat was as follows: saturated fatty acids, 46 per cent of total fat; monounsaturated fatty acids, 40 per cent; and polyunsaturated fatty acids, 14 per cent.

The experimental diet averaged 19 per cent calories from protein, 48 per cent from carbohydrate, and 33 per cent from fat. The distribution of the fatty acids in terms of per cent of total fat was as follows: saturated fatty acids, 33 per cent; monounsaturated fatty acids, 33 per cent; and polyunsaturated fatty acids, 34 per cent.

The Prudent Diet has a P/S ratio\* 1.25-1.50. The usual American diet has a P/S ratio of 0.3-0.4. Food-table analysis of the study diet pattern shows an upper limit of 400 mg. of dietary cholesterol and 1.6 gm. of dietary sodium.

The nutritionists emphasized inclusion of adequate amounts of citrus fruits, green vegetables, and grains and cereals in the diet. This insured a predominance of complex carbohydrates in the total diet rather than simple sugars. The overweight subjects were placed on a diet that averaged 1,600 calories and contained 19 per cent of the total calories as fat, and a P/S ratio of 0.6-0.7. When weight reduction was completed, this was changed to the standard diet by the addition of 1 oz. of vegetable plus additional calories when needed from bread, nuts, fruits, and vegetables.

Specific inquiry was made in relation to calories derived from sugar, syrups of all types, honey, jam, jelly, sweetened carbonated beverages, candy, and gelatin. We calculated the range of the percentage of calories per day from these sources in 303 subjects on entry and in no subject did it exceed 6.5 per cent (range was 4.7 to 6.5 per cent). The diet did not exceed 5 per cent of calories from these sources of refined sugar.

Our over-all purpose was to investigate a dietary approach to the prevention of coronary heart disease. Our diet was to be nutritionally adequate, palatable, and composed of American foods available in every community. Would such a diet lower the serum cholesterol? The main objective would be accomplished when we could determine that a favorable change in the serum cholesterol level produced and maintained by diet would be associated with a favorable change in morbidity and mortality from coronary heart disease.

## METHOD

*Experimental group.* Since the inception of the Anti-Coronary Club in 1957, 1,242 male volunteers aged 40 to 59 years enlisted. The volunteers responded initially to a radio and press call for participants in the

\*The P/S ratio, without consideration of technical qualifications, is substantially the amount of polyunsaturated fatty acids divided by the amount of saturated fatty acids present in a given diet pattern.

TABLE I. NEW CORONARY DISEASE EVENTS AND INCIDENCE IN STUDY AND CONTROL SUBJECTS FREE OF CORONARY HEART DISEASE, 40 TO 59 YEARS OF AGE

	<i>Experimental</i>		<i>Control</i>
	<i>Active</i>	<i>Inactive</i>	
Number of subjects	941	532	457
Years of experience	3,954	3,207	3,122
Confirmed new events	17	24	32
Incidence per 100,000 person-years of experience	430	748	1,025

study. Subsequent volunteers were derived largely from referrals made by the original members of the Anti-Coronary Club. This report considers the 941 subjects of this total who were free of prior evidence of clinical coronary heart disease. The remaining 301 subjects have been excluded from this report because of a history of clinical or electrocardiographic evidence of coronary heart disease on entry to the study.

Table I shows that as of November 30, 1967, the end of the observation period regarding the occurrence of new coronary disease events for this report, 941 men had accumulated 3,954 person-years of experience while in an active status. Active status denotes regular attendance approximately every five weeks for venipuncture and serum cholesterol determinations and consultation with a nutritionist; every 10 weeks for a clinical and nutrition review session by a panel of physicians; and a yearly medical history, with physical, laboratory, electrocardiographic, and roentgenographic examinations.

By the end of the period of observation, 532 of the 941 subjects had lapsed into an inactive status in which they accumulated 3,207 person-years of experience. Subjects in inactive status were appraised annually as to health and nutritional status but did not return regularly to the Anti-Coronary Club for venipuncture, nutritionist, or physician panel sessions. For about two thirds of this inactive group this appraisal of health took the form of an annual physical and laboratory examination; in the remainder, communication was maintained by phone or by a mail questionnaire. It has been determined that in no case was the onset of a new coronary disease even the cause for the shift of a subject to inactive status.

*Control group.* The first objective of the Anti-Coronary Club was to determine whether the experimental or Prudent Diet was capable of lowering the serum cholesterol level and whether the experimental subjects would find the prudent diet palatable and be able to adhere to it. After sufficient time had passed and an affirmative answer to these questions had been obtained, a control group was enlisted for comparison with the experimental group regarding serum cholesterol changes and incidence of coronary heart disease.

Starting in 1959, the control group was recruited from men who had voluntarily appeared for examination at the cancer detection clinics of the New York City Department of Health. These subjects were considered similar to the experimental subjects in the specific sense that they showed health consciousness and were willing to participate in a dietary program of a Department of Health. Potential control subjects were induced to participate in the study by the offer of an annual comprehensive cardiovascular examination as an additional routine service. This proposal was made to every male aged 40 to 59 attending the Cancer Detection Clinics; about one third accepted. These were assigned to the study as controls. They were not told that they were part of a diet and heart disease study. The control group included in the analyses in this report consists of 457 subjects who showed no initial evidence of coronary heart disease by the same criteria applied to the experimental group.

The validity of comparing coronary heart disease incidence in the experimental group on the diet used in the study and the control group that maintained its usual diet depends on the comparability of other factors such as demographic and risk factors associated with coronary heart disease as they exist in the two groups on entry. Accordingly, a detailed demographic analysis of the experimental and control groups was performed. This analysis indicates that the significantly lower incidence observed in the experimental group compared with the total control group could not be ascribed to demographic differences<sup>7</sup>

The experimental and control groups were compared regarding entry levels of the three risk factors identified by the Framingham study,<sup>2</sup> i.e., hypercholesterolemia (serum cholesterol 260 mg./100 ml. or more), hypertension (diastolic pressure of 95 mm. Hg. or more), and obesity, defined as at least 15 per cent more than optimum weight as presented in tables of the Metropolitan Life Insurance Company for height, build,

and sex, and further modified by subjective evaluation of a panel of physicians on the basis of skin-caliper measurements and appearance. The two groups were quite comparable regarding the proportion with initial hypercholesterolemia. However, the experimental group had higher proportions with initial obesity and hypertension than did the control group. In view of these findings, it would be expected that the experimental group might experience a higher frequency of coronary heart disease than the control group.

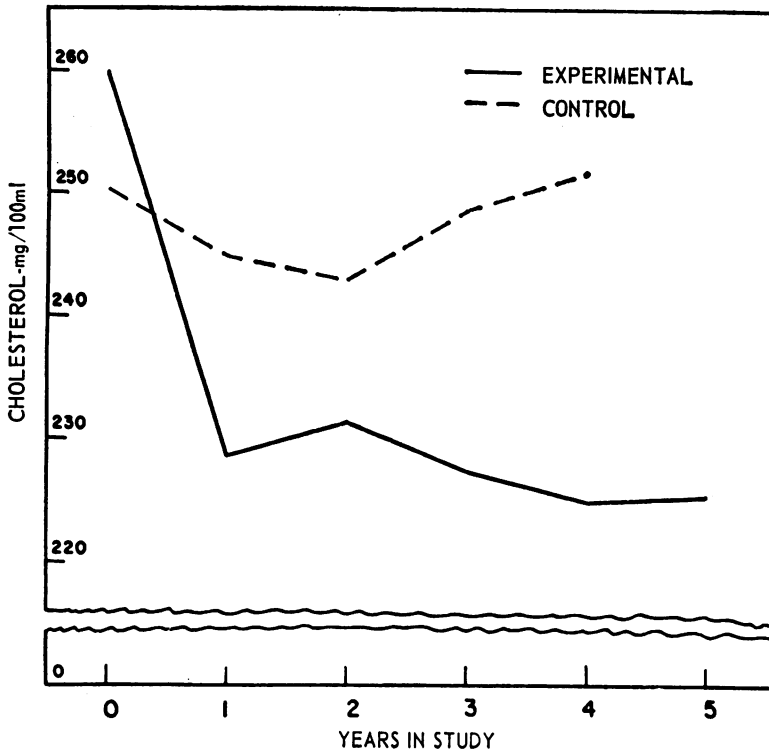
*Diagnostic criteria.* The classification of new events that represented myocardial infarction was that used by the Cooperative Study of the American Heart Association,<sup>8</sup> which included the following categories: 1) myocardial infarction, definite; 2) myocardial infarction, definite by ECG alone; 3) coronary thrombosis, definite; 4) coronary sclerosis, definite by autopsy; 5) ECG abnormalities, definite, associated with coronary artery disease; 6) angina pectoris, definite with ECG changes; and 7) angina pectoris, definite without ECG changes. The clinical and electrocardiographic criteria for new coronary events were based on those recommended by the New York Heart Association.<sup>8</sup>

The chief cardiologist of the project assigned a classification of "definite events" when in his judgment criteria for one of the above categories were met. He used data from the physical examination of subjects, mail and phone follow-up of inactive subjects, and information reported by subjects and their associates. Records from the subjects' complete records on all such "definite" events were then submitted to another cardiologist whose sole function on the project was their critical review and evaluation. This cardiologist did not know whether the record under review was that of an experimental or a control subject; however, submission of a record for his review implied at least the suspicion of disease.

## RESULTS

*Serum cholesterol.* Until 1965 the serum cholesterol level was determined by the Anderson-Keys modification of the method of Abell and Kendall with a technical error of 2.5 per cent. From then on the autoanalyzer technique was used.

The accompanying figure shows the trends in the average level of serum cholesterol of the 478 experimental subjects and 420 control subjects 40 to 59 years old still active in the experimental and control groups



Average serum-cholesterol levels of men 40 to 59 years old with no prior coronary heart disease in active experimental and control groups by years in study.

as of December 31, 1963. In the experimental group, a highly significant drop of about 30 mg./100 ml. serum from an average initial level of 260 mg./100 ml. was observed after one year in the study. Thereafter the concentration of serum cholesterol leveled off at about 225 mg./100 ml. In the control group the serum cholesterol level fell about 7 mg./100 ml. during the first two years, but rose thereafter so that by the end of the fourth year the average level had returned to its initial concentration.

In the experimental group a cohort of 104 men aged 40 to 59 years, followed for more than 7 years up to October 1967, had an average benchmark cholesterol level of 253.1 mg./100 ml. After six months, this average had decreased to 228.4 mg./100 ml. and has fluctuated slightly around that level ever since. The lowest average level was 220.5; the highest, 229.5 mg./100 ml.

In the control group a corresponding cohort of 197 men aged 40 to 59 years have been followed for six years up to October 1967. This group had an average benchmark cholesterol of 251.9 mg./100 ml. At the end of the first year of observation, this had fallen to 245.5 mg./100 ml. and has remained at that level ever since with little variation.

*Serum triglycerides.* To test the effect of the experimental diet on serum triglycerides,<sup>9</sup> as well as to validate the comparability of the control group from this aspect, we measured serum triglyceride levels<sup>10</sup> in 30 men who have been members of the experimental group for more than one year, in 53 men who were members of the experimental group but had not yet started on the study diet, and in 34 members of the control group. For the experimental group the average serum triglyceride level was 122.0 mg. per cent for those who had not started the diet, compared with 88.0 mg. per cent for those already on the diet. This difference is highly significant statistically ( $p < 0.005$ ). The 34 subjects from the control group had an average level of 120.9 mg. per cent, a level not significantly different from that of the 53 men in the experimental group before they were placed on the experimental diet ( $p = 0.86$ ).

At a later date the serum triglyceride levels on 37 different subjects in the experimental group for more than one year were measured by another chemical method.<sup>11</sup> Their triglycerides averaged 86.7 mg. per cent with a standard deviation of  $\pm 34.4$  mg. per cent.

These results suggest that adherence to the Prudent Diet not only does not elevate the serum triglycerides but indeed may be effective in lowering it.

*Serum vitamin E and A levels.* Serum vitamin E and A determinations were made in 176 subjects and 50 subjects respectively. For vitamin E, the subjects were measured from the prediet period for up to four years. For vitamin A the measurements were determined for more than one year on the diet. The levels of both vitamins remained within normal limits for the observed periods.

*Composition of depot fat.* The development and greater availability of gas liquid chromatography as an analytical tool enabled us to determine the pattern of fatty acids in the adipose tissue lipids of 78 subjects who followed the experimental diet for one to four years.<sup>12</sup> The major change associated with prolonged adherence to the study diet was in the



polyunsaturated fatty acid components of the depot fat and particularly in the proportion of linoleic acid, which increased from a mean of 9.7 per cent initially to 18.9 per cent in the group of subjects who had been on the diet more than three years. The increase in the linoleic acid and in the more highly unsaturated and longer chain fatty acids was achieved at the expense of myristic, palmitic, and oleic acids. This trend was independent of weight and cholesterol levels.

The analysis of depot fat, since it is related to the linoleate content of the diet, has served us as a useful method in distinguishing between adherents and nonadherents to the experimental diet and in substantiating the validity of the dietary interview as a determinant of dietary adherence.

*New coronary events, incidence, active experimental subjects compared to controls.* Table I shows data accrued by the experimental and control groups in terms of number of subjects, their accumulated person-years of experience, the number of confirmed new coronary events, and incidence rates per 100,000 person-years. During the 3,954 person-years of active experience accumulated by the 941 experimental subjects, 17 new coronary events occurred. This represents an over-all incidence rate of 430 per 100,000 person-years of experience.

Similarly, the 457 men of the control group in comparable age categories have accumulated 3,122 person-years of experience and 32 new coronary events, resulting in an over-all incidence of 1,025 per 100,000 person-years of experience.

*Inactive experimental group.* As seen in Table I, confirmed new coronary disease events have been detected among those in the experimental group who shifted to inactive status. The observed incidence rate was 748 per 100,000 person-years of experience. It should be noted (Table II) that the incidence of new coronary disease events in the inactive group increased as the active experimental group become inactive. The active and control groups showed a somewhat steady incidence from 1963 through 1967 despite an increase in the number of new events.

It is difficult to interpret precisely the findings in the inactive experimental group, since it is not known to what extent this group may have followed the study diet. Moreover, the detection of new coronary disease events which have occurred may not be as complete for this group as for the active experimental and control subjects. However, the incidence in this inactive experimental group is intermediate between

TABLE II. NEW CORONARY DISEASE EVENTS AND INCIDENCE IN STUDY SUBJECTS INITIALLY FREE OF DISEASE

As of	Person-years of experience			Confirmed new events			Incidence per 100,000		
	Experimental			Experimental			Experimental		
	Ac- tive	In- active	Con- trol	Ac- tive	In- active	Con- trol	Ac- tive	In- active	Con- trol
12/31/63	2,357	1,482	1,224	9	7	13	382	472	1,062
12/31/65	3,425	2,062	2,184	15	17	22	438	824	1,007
11/30/66	3,689	2,634	2,652	15	21	27	407	797	1,018
11/30/67	3,954	3,207	3,122	17	24	32	430	748	1,025

Active. Experience accumulated while regularly attending study facilities at specified appointment dates.

Inactive. Experience accumulated while attending study facilities annually or with successful regular contact by mail or phone since active attendance at panel or nutritionist sessions were discontinued. No professional supervision of diet in this phase.

Note. The number of confirmed active events contains two cases who never adhered to the experimental diet. The number of confirmed inactive events contains three such cases.

that of the active experimental and control subjects. This suggests that the difference in incidence between the active experimental and control subjects may be due to the Anti-Coronary Club program.

*Changes in risk-factor status that result from participation in the study.* Since the incidence of coronary heart disease in the experimental subjects was significantly lower than that of the control group during their period of participation in the study, it is of interest and importance to recognize the changes which took place in their status with respect to the three risk factors considered in this study.<sup>18</sup> For the 332 subjects in the active experimental group and the 329 subjects in the control group who participated in the study for four years or more, risk-factor status was compared at time of entry to the study, after two years, and after four years of participation.

Table III indicates that the prevalence of hypercholesterolemia, obesity, and hypertension initially observed in the control group remained at substantially the same level after two years and four years of observation. On entry to the study approximately 46 per cent of subjects were obese and 11 per cent were hypertensive. The somewhat more variable proportions of subjects with hypercholesterolemia were 30 per cent and 32 per cent after two and four years, respectively, and may represent an additional manifestation of the slight downward trend observed initially followed by rebound upward of the serum-

TABLE III. PERCENTAGE OF RISK FACTORS AMONG 332 EXPERIMENTAL AND 329 CONTROL SUBJECTS AT ENTRY AND AFTER TWO AND FOUR YEARS

<i>Risk Factors</i>	<i>Experimental</i>			<i>Control</i>		
	<i>Entry</i>	<i>2 yr.</i>	<i>4 yr.</i>	<i>Entry</i>	<i>2 yr.</i>	<i>4 yr.</i>
None	16.6	61.3	59.0	34.0	35.8	35.3
Hypercholesterolemia*	42.8	20.7	19.9	38.3	30.4	32.2
Obesity**	56.3	15.7	17.8	45.3	45.8	44.1
Hypertension***	25.9	10.9	9.9	10.9	11.1	13.1
None	16.6	61.3	59.0	34.0	35.8	35.3
Any one	46.4	31.6	34.6	40.4	43.6	43.5
Any two	32.5	5.5	6.0	22.5	18.2	17.9
All three	4.5	1.6	0.3	3.0	2.4	3.3

\*Serum cholesterol of 260 mg./100 ml. serum or more.

\*\*At least 15 per cent more than optimum weight presented in the tables of weight of the Metropolitan Life Insurance Company for height, build, and sex, further modified by subjective evaluation of panel of physicians on basis of skin-caliper measurements and appearance.

\*\*\*Diastolic pressure of 95 mm. Hg. or more.

cholesterol level of the control group shown in the accompanying figure.

In the experimental group the prevalence of these risk factors decreased substantially after two years and remain depressed after four years. The prevalence of hypercholesterolemia declined from about 43 per cent to about 20 per cent, that of hypertension from about 26 per cent to about 11 per cent, while the proportion of obese subjects dropped from 56 per cent to 16 per cent. It should be noted that the initial prevalence of these risk factors for the experimental group was higher in each instance.

Table III also presents the distribution of the subjects in the experimental and control groups by the number of risk factors present for the same periods of observation. In the control group the distribution of the number of risk factors present after two and four years of observation have remained substantially the same as that observed initially. By contrast, the proportion of the experimental group with one or more of the risk factors has been a significant reduction in the number of subjects exhibiting a single risk factor, the most impressive changes are the decreased number of subjects with multiple-risk factors, and the increased number with none. At the time of entry to the study 32 per cent of the experimental subjects exhibited at least two of the risk factors considered here, while only 17 per cent had none; two and four years

TABLE IV. PER CENT DISTRIBUTION OF ACTIVE EXPERIMENTAL AND CONTROL SUBJECTS BY NUMBER OF CIGARETTES SMOKED PER DAY\*

<i>Number of cigarettes per day</i>	<i>Experimental</i>	<i>Control</i>
None	51.9	49.1
1-9	9.7	10.8
10-29	22.4	26.7
30-49	11.8	12.1
50-69	4.1	1.3
Mean	12.1	11.5
No. of subjects	478	420

\*At time of entry to study.

later, these proportions had changed to about 6 per cent and 60 per cent respectively.

In addition to changes in the prevalence of obesity, hypercholesterolemia, and hypertension described above, a study was made of the cigarette-smoking habits of all 478 active experimental and 420 active control subjects considered in this report. The distribution of number of the cigarettes smoked at time of entry to the study is shown in Table IV. Both groups contained a relatively large number of non-smokers; although there was a slight tendency for the experimental group to smoke more, the differences between the experimental and control subjects could easily be explained by chance variations.

In order to make these estimates of cigarette smoking current, a survey was conducted of all comparable subjects with more than two years of participation in the study who appeared at the study facilities during a two-month period. This group consisted of 195 experimental and 130 control subjects, and each was questioned concerning the number of cigarettes smoked at the time. This amount was then compared to that claimed at the time of entry to the study. Table V shows the proportion in each group that smoked more, the same, or less than the initial amount. Again, although there are seeming differences, these are not statistically significant. The smoking habits of the two groups have apparently remained comparable during the period of participation in the study.

TABLE V. CHANGE IN NUMBER OF CIGARETTES SMOKED PER DAY: DISTRIBUTION BY PERCENTAGE OF EXPERIMENTAL AND CONTROL SUBJECTS

<i>Change since enrollment</i>	<i>Experimental</i>	<i>Control</i>
More	3.1	3.8
Same	83.6	75.4
Less	13.3	20.8
Total	100	100
No. of subjects	195	180

### SUMMARY

The nutritional adequacy of the Prudent Diet, its acceptance by free-living ambulatory subjects, its capacity to lower serum cholesterol and triglyceride levels and, most important, its apparent influence on the significant reduction of new clinical coronary artery disease events make it, in our opinion,<sup>14</sup> an important public health modality for primary prevention of coronary heart disease.

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