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Coronary Heart Disease among Minnesota Business and Professional Men Followed Fifteen Years

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THE high incidence of coronary heart disease in the United States indicates that among any group of currently "healthy" middle-aged men a significant number of them may be expected to develop the disease within a few years. Comparison of pre-disease characteristics of such men with those of their fellows who do not develop the disease should reveal characteristics associated with different degrees of susceptibility, thereby providing methods to identify coronary-prone persons to whom preventive efforts could be directed. Potentially even more important, the data from a longitudinal epidemiologic study should be useful to test hypotheses and to provide clues as to etiology.

This reasoning led to the start, in the winter of 1947-48, of a long-term study on 281 Minnesota business and professional men, then aged 45 to 55 and clinically "healthy."[1] These men, with few lapses, have had 15 successive detailed annual examinations with special attention to the cardiovascular system and items that may be relevant to coronary heart disease. Their personal physicians cooperated by reporting the status in cases of death or of interim illness.

During 15 elapsed years 32 men developed coronary heart disease. There have been 17 "coronary" deaths in this group. In addition, 16 men developed changes in status that indicate "possible" coronary heart disease.

The present paper reports the data on these men, and on the group as a whole, for relative body weight, body fatness, blood pressure, and cholesterol concentration in the serum.

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Subjects

The business and professional men who are the subjects of this study were originally recruited in 1947 in an epidemiologic program planned to cover about 300 men, then aged 45 to 55, who would be examined annually for as many years as possible to reveal the incidence of coronary heart disease as related to pre-disease characteristics.

The men were selected as follows. For public relations reasons, a few prominent local men were admitted but the real source of supply was from corporations, which provided the names of 1,000 men considered to be stable in their employment. Letter solicitation of these men, accompanied by mass media publicity, yielded 916 volunteers. After eliminating a few men judged unacceptable from their replies to a questionnaire, first selection was made of the 50 most overweight, the 50 most underweight, and another 50 men who were reported by the athletic directors of the local YMCAs and athletic clubs to be especially active in their programs. The remaining places to a total of 300 were filled by drawing names at random from the roster of men available.

When these men were first examined early in 1948, a number of them were found to have overt heart disease, bleeding peptic ulcer, diabetes or other unacceptable disability. Neither blood pressure nor obesity was, per se, a cause for exclusion. At the end of the first examination three men withdrew. The result is that the original "healthy" cohort consisted of 281 men. The age distribution of these men (in 1948) is indicated by the percentages within ages 45, 46—18.9; 47, 48—17.8; 49, 50—26.0; 51, 52—19.6; 53, 54—17.7 per cent.

The coverage of the men in 15 consecutive annual examinations averaged 93.0 per cent. Among 249 survivors, 198 have never missed a year and 222 have been examined on at least 12 annual occasions. Most of the missed examinations were accounted for by the men having moved from the area to become residents of other states.

The Staff accepted no responsibility for medical advice to the subjects. The results of the examinations were made available to their personal physicians who received routinely a brief summary after each examination. When it appeared to be warranted, the subject was urged to consult his own physician but in so doing the effort was made to avoid expressions of opinion.

Procedure and Methods

Each year from December 1 to about the 18th and from about January 6 through February most of the men reported to the Laboratory for examination but a few others, primarily men who had moved away from the area, came in for examination at other times. Information about the health status of men who missed examination entirely was obtained from them or their physicians, or both, each year.

The men always came to the Laboratory by appointment in the morning, without breakfast and having avoided any strenuous activity after rising. After disrobing and having rested at least 10 minutes or more, they were given a physical examination during which the blood pressure (supine) was recorded three times about 5 minutes apart with the auscultatory method, with use of a mercurial manometer. The means of these readings in systole and in the fifth (disappearance of sound) phase of diastole were used for analysis. A blood sample was drawn without stasis from an arm vein, a 12-lead electrocardiogram was taken in supine rest, nude weight was recorded, a 6-foot postero-anterior chest x-ray was taken, and qualitative urinalysis was done. Each year after the first examination the interim medical history and complaints were recorded twice, once by the examining physician and again by a senior staff member.

Relative body weight was computed by use of the tables in the Medico-actuarial Investigations.[2] These tables provide an arbitrary set of standards suitable for the present purposes and have the virtue of being more universally available than any other.

The thickness of the skinfolds (subcutaneous fat) was measured with calipers in 1948, 1949, 1951, and 1954. Measurements were made over the tip of the scapula and over the triceps muscle of the arm midway between the elbow and the tip of the acromion. The sum of these two skinfolds (Σ skinfolds) was used in the present analysis. The technic was standardized in 1954, as recommended by the Anthropometry Committee of the National Research Council Food and Nutrition Board.[3] The measurements of skinfolds in earlier years are not strictly comparable but comparison among the men, in the same year, are valid.

Total serum cholesterol was estimated by the Bloor method each year until 1953, when both the Bloor method and a modification of the Abell method[4] were used in duplicate. From 1954 on only the modified Abell method was used. Comparison of the Bloor and modified Abell data for the same 270 serum samples in 1953 showed that the Abell value could be reliably estimated for these men by multiplying the Bloor value by the factor 0.85. This adjustment was applied to the data for 1948-53 so that all cholesterol values covering the 15 consecutive yearly examinations should be comparable. Many other tests and measurements were made during one or more of the yearly examinations. The findings from these other procedures will be reported separately.

The present analysis concerns the "natural characteristics" of the men before the recognition of clinical coronary heart disease. A few men, including several who later developed the disease, drastically altered their diets or their physicians prescribed antihypertensive drugs; only the data recorded before these changes are included in the present analysis.

Table 1 summarizes the cases of definite coronary heart disease. Myocardial infarction occurred in 22 men, seven other men developed angina pectoris with electrocardiographic evidence of myocardial ischemia and one man died suddenly under circumstances that we believe justify the attending physician's conclusion of coronary heart disease. Two men, without hypertension or important electrocardiographic abnormalities, developed classical angina pectoris confirmed independently by several cardiologists.

The diagnosis of "possible coronary heart disease" was made for 16 additional men, none of whom had hypertension or other "noncoronary" conditions that would explain the changes in serial examinations. The changes observed in these men were nonspecific electrocardiographic changes, "positive" exercise tests plus, in several cases, atypical chest pains. Four of these men developed progressive heart failure, which finally led to death in one case.

Results

Deaths

During 15 elapsed years (through January 1963) 32 deaths occurred among the original 281 men in the cohort. Besides 17 deaths definitely attributed to coronary heart disease, it may have been involved in three other cases. Other definite causes of death were accidents (2), leukemia (2), ruptured aneu-

Table 1

Men With Coronary Heart Disease

Serial no. of subject		Onset	Death
Coronary heart disease with myocardial infarction			
228	History,* abnormal ECG since	1950	....
242	ECG documented infarct, angina since	1950	....
467	History, ECG ischemia, sudden death	1951	1952
247	ECG documented infarct, sudden death	1952	1952
269	ECG documented infarct, sudden death	1952	1959
445	History, ECG ischemia, infarct 1961, sudden death	1953	1962
298	ECG documented infarct, infarct autopsy	1954	1955
370	ECG documented infarct, infarct autopsy	1954	1959
455	History, ECG ischemia, angina	1955	....
385	ECG documented infarct	1955	1955
436	ECG documented infarct, angina, sudden death	1955	1960
272	ECG documented infarct	1956	....
426	Angina, infarct autopsy	1956	1957
454	ECG documented infarct, sudden death	1956	1960
332	ECG documented infarct, angina	1957	....
438	ECG documented infarct, angina, heart failure	1957	....
374	ECG documented infarct	1958	....
267	ECG documented infarct, infarct autopsy	1958	1958
365	ECG documented infarct, confirmed by transaminase	1958	1958
432	ECG documented infarct, angina	1959	....
474	ECG documented infarct	1959	....
342	ECG documented infarct, angina	1959	1961
Coronary heart disease without documentation of infarction			
Classical angina pectoris plus ECG ischemia			
340	Angina, ECG ischemia	1951	....
476	Angina from 1951, ECG ischemia from 1960; sudden death; severe coronary atherosclerosis and myocardial fibrosis at autopsy	1951	1960
260	Angina from 1952, ECG ischemia from 1955; died in surgery (for cancer); severe coronary atherosclerosis and myocardial fibrosis at autopsy	1952	1956
451	Angina from 1953 (possibly 1948), ECG ischemia from 1953	1953	1955
263	ECG ischemia progressive from 1952, atypical chest pains from 1957, heart failure from 1959, acute angina pectoris in 1961	1952	....
337	Angina from 1961, ECG ischemia from 1959	1959	....
234	Angina from 1961, ECG ischemia from 1961	1961	....
Classical angina pectoris			
320	Angina from 1957, ECG normal except for frequent extrasystoles; two minor ''strokes'' with small residue	1957	....
286	Angina from 1959, ECG normal except for low voltage and frequent extrasystoles; intermittent claudication	1957	....
Sudden death			
227	ECG ''borderline'' ischemia from 1948; collapsed in garden clutching chest and muttering about ''heart attack''; died in minutes	1951	1951

*Means a typical infarct history verified by the attending physician.

rysm of the aorta (2), cancer (3), cerebral thrombosis, suicide, and pulmonary insufficiency.

The death rate in this cohort has been low. U. S. Vital Statistics for white men of this age distribution indicate expectation of 72 instead of the 32 deaths observed until now. Life insurance experience on "unimpaired lives"[5] provides a better basis for comparison. For the period covered here the actuarial prediction would be 47 deaths. The experience of our group with coronary heart disease is less disparate from other expectations. From the U. S. Vital Statistics the expectation would be about 24 instead of 17 deaths attributed to coronary heart disease.

The favorable mortality may be related to the method of recruitment, which resulted in a group of unusually successful men, stable in occupation and residence. Possibly the annual examinations helped to restrict mortality by calling attention to conditions needing treatment. Favorable mortality was achieved although high blood pressure alone was not a reason for exclusion and the group included an unusually large proportion of very obese men.

Characteristics before Coronary Heart Disease

The main purpose of this report is to compare, in respect to the measurements considered here, the pre-disease characteristics of the men who developed coronary heart disease with the contemporary characteristics of their fellows who did not develop the disease. An obvious approach is to examine the distribution of the "coronaries" and the "noncoronaries" above and below certain cutting points for the several variables. This is straightforward with the data from the initial examination but it is even more important to characterize more accurately the eventual coronary victims by utilizing, for each man, the data obtained in all years prior to the appearance of the disease. This introduces complications and necessitates a more elaborate analysis.

The approach adopted was, for each year, an array of measurement values for all men still "healthy" from lowest to highest for each variable, so as to classify, for each year, every man into centile positions within the cohort. Table 2 summarizes the distributions thus obtained for 1948 and, to conserve space, only the median values for the same centile

Table 2

Values at the Centiles Indicated for the Distribution of All Men in 1948 and for the Medians of the Distributions for 1949-55 and 1956-62, Inclusive

Variable	Year	Centile								
		5	10	20	35	50	65	80	90	95
Relative weight	1948	77	80	87	94	100	106	115	121	128
	1949-55	78	83	89	96	101	106	116	121	127
	1956-62	80	85	90	97	101	106	116	120	126
Σ Skinfolds	1948	15	19	23	29	34	37	45	51	59
	1949-55	16	18	28	32	38	39	46	54	60
Systolic BP	1948	105	108	113	118	122	127	133	140	149
	1949-55	106	109	113	118	123	128	134	147	158
	1956-62	110	115	119	126	130	138	144	156	168
Diastolic BP	1948	60	60	61	70	71	78	80	87	91
	1949-55	66	69	71	75	78	81	86	90	97
	1956-62	68	68	72	78	80	83	89	93	98
Cholesterol	1948	165	176	193	209	221	234	253	264	289
	1949-55	162	175	190	203	223	237	257	276	288
	1956-62	172	186	200	218	232	248	269	288	300

Table 3

Distribution of Men with Coronary Heart Disease

Variable	Year	Centile			
		< 25	25-49	50-74	≧ 75
Relative weight	1948	7 (11)	6 (12)	7 (10)	12 (15)
	Last year	7 (12)	7 (12)	7 (11)	11 (13)
	All years	5 (10)	10 (15)	5 (9)	12 (14)
Σ Skinfolds	1948	7 (10)	6 (12)	7 (10)	12 (16)
	Last year	7 (8)	6 (13)	8 (13)	11 (14)
	All years	6 (10)	4 (9)	9 (12)	13 (17)
Systolic BP	1948	6 (8)	7 (10)	9 (15)	10 (15)
	Last year	2 (5)	6 (9)	8 (13)	16 (21)
	All years	1 (3)	11 (14)	7 (14)	13 (17)
Diastolic BP	1948	7 (10)	8 (10)	8 (16)	9 (12)
	Last year	9 (15)	4 (6)	3 (5)	16 (22)
	All years	3 (5)	12 (19)	5 (9)	12 (15)
Serum cholesterol	1948	4 (2)	5 (7)	9 (16)	14 (19)
	Last year	2 (5)	5 (6)	9 (15)	16 (22)
	All years	3 (5)	5 (9)	11 (15)	13 (19)

Distribution, among centile classes of the distribution for the entire "healthy" cohort, of the 32 men who developed definite coronary heart disease and, in parentheses, of these men plus the 16 who developed possible coronary heart disease. The distribution expected from chance alone is 8 men in each quartile for the "definite" and 12 for the "definite" plus "possible" men.

cutting points for 1949-55 and 1956-62. In table 2 the data on 281 men are represented for 1948; for the years 1949-55 and 1956-62 the average representation is 261 and 194 men, respectively.

Table 3 shows the distribution, among quartiles, of the contemporary distribution of all "healthy" men, of the 32 men who developed definite coronary heart disease plus, in parentheses, the 16 men with "possible" disease. All of the variables tend to concentrate the "coronaries" in the upper part of the distribution but there are important differences in significance. For relative body weight and skinfolds, this concentrating effect is more marked in the last pre-disease year and for the data over all pre-disease years than in the data for the first year (1948).

Considering the median cut first, only serum cholesterol is significant in the 1948 data, with $p = 0.01$ for the observed distribution of 23 men above and nine below the cholesterol median. With the data from the last pre-disease year, both systolic blood pressure and serum cholesterol are significant with $p = 0.004$ and $p = 0.001$, respectively. The data for all pre-disease years show significance for the sum of the skinfolds ($p = 0.025$), and serum cholesterol ($p = 0.004$), while the other variables are all statistically not significant.

The data indicate a steady progression of increasing risk as the cholesterol level is raised. The men in the bottom quartile of cholesterol at any time tended to have significantly less risk than the other men and the men in the top quartile had the greatest risk. Protection is indicated for men in the bottom quartile of either systolic or diastolic blood pressure for all years, with values of p less than 0.001 and $p = 0.007$, respectively.

In the combined material of definite plus possible coronary heart disease there is no evidence that any pre-disease measurements of relative weight or relative obesity (Σ skinfolds) have any relationship to the risk of developing the disease. For these 48 men blood pressure in the first examination was not significant but considering all pre-disease years there was excessive risk for men in the upper part of the blood pressure distribution,

while there was relative protection for men in the bottom quartile. The cholesterol data indicate a direct relation to risk extending over all cholesterol levels.

Combinations of Variables

The number of men in this study who developed coronary heart disease limits possibilities for useful detailed analysis of combinations of the characteristics considered here. However, since the serum cholesterol level seems to be of such importance, we asked whether men who developed the disease in spite of having relatively low cholesterol values had other characteristics that might have increased their risk.

There were 14 "coronaries" (eight definite plus six possible) who had below-median cholesterol values for all pre-disease years; for the last pre-disease year there were 11 in this category. Among these men, six were above the 80th centile of the systolic blood pressure distribution for both all and last pre-disease years. Detailed comparison with the bivariate distribution among the men who remained "healthy" showed a highly significant difference in this respect. Analysis of other combinations indicated no significance for diastolic blood pressure or the sum of the skinfolds but the combination of systolic blood pressure and relative body weight was highly significant when the men were above the 80th centile in both of these variables.

The general conclusion seems warranted, then, that men who develop coronary heart disease in spite of having relatively low serum cholesterol values are men who tend to be at the upper extremes of blood pressure or relative body weight, or both.

Cholesterol in Alpha and Beta Lipoproteins

Various investigators have suggested that increased susceptibility to coronary heart disease may be associated with low levels of cholesterol in the alpha lipoprotein fraction of the blood level as well as with a high level of cholesterol in the whole serum or in the beta lipoprotein fraction.[6-9] Cholesterol was estimated separately in the alpha and beta lipoprotein fractions as well as in the whole serum in 1953 and 1955. Fractionation was made by paper electrophoresis in 1953 and by cold ethanol, similar to Cohn's method X, in 1955.[4] A few analyses were lost because of laboratory faults but these missing data are randomly distributed.

For the pre-disease data on all men, the coefficient of correlation between the concentrations of cholesterol in alpha and in beta lipoprotein cholesterol was found to be $r = -0.225$. This negative correlation is significant ($p = 0.01$), but it "explains" less than 5 per cent of the total variance of these two independent measurements.

For the men who remained healthy (N = 224) the mean cholesterol concentration in the alpha lipoprotein fraction was 45.29 (S.E. = ±0.87) mg. per 100 ml. The corresponding figures for definite (N = 22) and definite plus possible (N = 37) coronary heart disease were 39.45 ± 1.68 and 39.51 ± 1.39; these differ significantly from the values for the "healthy" men with $p = 0.05$ and $p = 0.01$, respectively. Statistical analysis without the assumption of normality of the distributions gave essentially the same results. At the median cut, tables for the summed binomial distribution gave $p = 0.001$.

So we asked whether increased susceptibility of men with low alpha lipoprotein values could account for men who developed the disease in spite of low total serum cholesterol. We had data on 12 men who developed the disease and were below the median for total cholesterol; all but two of the 12 were below the median in the alpha fraction ($p = 0.02$).

But more detailed analysis did not support the hypothesis that alpha lipoprotein cholesterol contributes much independent significance. Further, it was found that the ratio of α/β lipoprotein cholesterol is not as powerful as the total cholesterol measurement in distinguishing between men who remained healthy from those who later developed the disease. This ratio is skewed; for the 224 men who remained healthy, the cutting points for the 10th, 25th, 50th, 75th, and 90th centiles were 0.131, 0.154, 0.190, 0.239, and 0.320, respectively. The distribution at the quartile

cut of the definite "coronaries" differs from that of the healthy group with $p = 0.03$. Other cuts, as well as all cuts with the definite plus possible coronaries, were not statistically significant.

Comparison with Other Samples

Socioeconomic Features

The men in the present study are not a statistical sample of American men or even of middle-aged men in Minnesota. They were drawn from men in the upper socioeconomic class in the metropolitan area of St. Paul-Minneapolis; one fourth are (or were) presidents or vice-presidents of substantial corporations; more than half of the group were college men. This is a native-born and educated group, almost all with ancestral origins in the British Isles, the Scandinavian countries (mainly Norway and Sweden), and Germany.

Other similar follow-up programs show contrasts. At Framingham, Massachusetts, the U. S. Public Health Service attempted to study a statistical sample of adults, aged 29 to 62 at the outset, in the population.[10-14] Only 65.5 per cent of the men in the sample actually entered the study, and among these men 31 per cent were foreign born, fewer than 20 per cent had any education beyond high school and 42 per cent went no further than grade school.

The New York State Department of Health study at Albany, New York, concerns volunteers among male civil service employees of the State.[15-17] The group includes a few Negroes and large Jewish and Italo-American minorities. More than two thirds of these men were in subprofessional or low professional grades of the civil service.

In California, a stratified sample of civil service employees of the City of Los Angeles was selected for study but 25 per cent of those invited failed to participate.[18] Among the men in the follow-up study 16.5 per cent are Negroes and some other "non-whites" were included. Few of the men in the Los Angeles study are in an upper economic bracket.

In Chicago, one follow-up study concerns men employed by a large public utility company.[19-21] Among these men, about 20 per cent were foreign born and only 21 per cent had sedentary occupations. Only about 11 per cent of these men are on salary, the others receiving hourly wages. Another study in Chicago concerns male employees of a large manufacturing corporation.[22] This group was composed chiefly of second and third generation Americans of Polish and Bohemian ancestry. In general, these are men with relatively modest incomes and educational backgrounds.

Medical Selection

The samples of men in the several follow-up studies differed medically at the outset. Whereas in the Minnesota study men with already evident heart disease, diabetes, or metabolic disorder were excluded at the outset, most of the other studies did not make such exclusions. Among men aged 45 to 62 in the Framingham study, 14 per cent were judged to have atherosclerotic or "definite hypertensive heart disease." In the Albany study 7 per cent of the men had hypertensive or coronary heart disease or diabetes at entry. In the Chicago study of utility company employees, there were included in the study 49 men with "definite hypertensive heart disease," and 66 men with "definite" and 155 men with "suspect coronary heart disease." In the other study in Chicago, however, men judged to be already suffering from heart disease were excluded. In the Los Angeles study, among 692 men aged 40 to 54, there were 45 cases of heart disease at the outset and among 433 men aged 55 to 70, 81 were judged to have heart disease at entry.

The inclusion of men with already evident cardiovascular disease makes the significance of characteristics at entry and the events in the follow-up somewhat different from the Minnesota study. It may well be that the antecedent characteristics of men who develop completely new disease are somewhat different from those of men who, already known to be diseased, develop new "events." For example, the factors influencing the risk of

Table 4

Incidence of Elevated Serum Cholesterol Values

Group	Initial age range	% Men with values under 220	% Men with values 260 or more
Minnesota, 1948-1955, inclusive	45-55	47	20
Minnesota, 1956-1962, inclusive	53-63	37	27
Framingham	45-62	44	23
Albany	39-55	45	22
Chicago, Stamler, et al.	40-59	26	47
Chicago, Paul, et al.	40-55	31	37

a second heart attack may not be identical with those that make for susceptibility to the first attack. In the several publications it is not possible clearly to identify the subsequent experience of these different classes of men in the published reports on the several studies.

Cholesterol Levels

Absence of published distributions of relative weight and of blood pressure in the other studies prevents proper comparison in these respects. Fatness (Σ skinfolds) was not measured in the other studies. However, data are available for serum cholesterol which are summarized in table 4. Essentially identical methods were used in all of these studies, and there is no reason to ascribe differences in the results to the methods used.

In our Minnesota study there is some variability in the distribution of cholesterol values from year to year and a general trend for the values to rise over the years from 1948 through 1959. From 1960 on, there is some tendency to reverse this trend. The average median cholesterol value for 1955 through 1959 was 239.6, for the years 1960 and 1961 the medians were 233 and 232, and for 1962 the median was 222, resembling the level in the first 3 years 1948-1950 when the median ranged from 218 to 224.

The cholesterol distributions at Framingham and Albany are closely similar to those in the early years in Minnesota; later, in 1956-62, fewer of the Minnesota men had values under 220 mg. per cent and more of them were in the 260 or above category. These three samples of men are significantly different in this regard from the Chicago men, who were characterized by somewhat higher cholesterol values.

Comparison among Studies—Cholesterol-Risk Relationship

Data for comparison in regard to the relationship of risk of coronary heart disease to the pre-disease serum cholesterol were provided from Framingham by Dr. Thomas R. Dawber and from Albany by Dr. Joseph T. Doyle, Jr. Including the Minnesota study the data cover 4,069 men, among whom 251 men developed definite coronary heart disease. In order to reduce age heterogeneity, the younger (aged 30 to 49 at entry) and the older Framingham men (aged 50 to 59 at entry) are separated; so the analysis concerns four groups of men.

The relevant data are set forth in table 5, which gives the incidence rate of new coronary heart disease for men classified into five classes in respect to pre-disease serum cholesterol level. In all four series the incidence rises sharply with increasing pre-disease serum cholesterol level.

Graphical plots of these data on relative incidence rate at given average serum cholesterol levels suggest that a similar general relationship is involved in all four series but that it is not a simple linear function; an exponential or a logarithmic function is suggested. Accordingly, exploration was made with the equation (1) $y = a + bX^k$, where y is relative risk (incidence rate as the last colume in table 5) associated with cholesterol level X, expressed in mg. per 100 ml. Trial computations showed that the least squares solutions for the constants a and b gave the least "unexplained" variance with values of k close to 3.0, though almost equally good solutions were obtained in the range of k between 2.0 and 3.0.

Such computations were made with the 20 sets of observed relative incidence rates in the last column of table 5 and the corresponding mean cholesterol values for the five cholesterol classes in table 5. The computations

were made both unweighted and also weighted according to the number of cases in each class ("New C.H.D." in table 5). Results are given in table 6 in which no weights were applied for equations (1) through (4) but were used in equation (5). Figure 1 shows the result of using equation (3) for the prediction of number of cases of coronary heart disease developing in the four groups of men.

It may be suggested that only the cholesterol concentration in excess of some limiting value can possibly contribute to risk. Part of the total cholesterol is in the alpha-lipoprotein fraction of the serum, presumably not a risk factor, and in any case cholesterol values less than 100 mg. per 100 ml. do not occur in healthy men in these populations. Accordingly, trial was made with the cholesterol value, in mg. per 100 ml., reduced by 100, as in equation (4) in table 6.

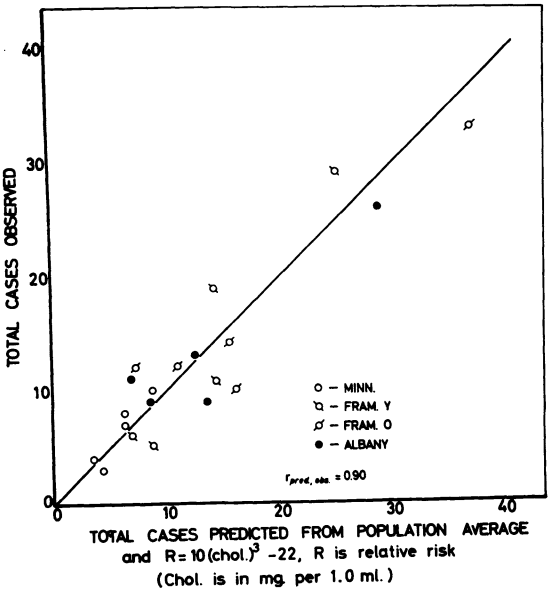

Figure 1

Prediction of incidence of number of cases of new coronary heart disease from the pre-disease cholesterol level by means of equation (3), table 6.

Table 5

*Serum Cholesterol Level and Subsequent Risk of Coronary Heart Disease (CHD)**

Group	Cholesterol, mg. % Range	Cholesterol, mg. % Mean	No.	New CHD	Annual rate per 1000	Rate as % of group
Minnesota	<200	179	85	4	3.13	41.3
	200-219	211	55	3	3.64	48.0
	220-239	230	59	7	7.91	104.0
	240-259	250	43	8	12.41	163.6
	≧ 260	281	39	10	17.10	225.4
	All	221.0	281	32	7.59	100.0
Framingham	<200	180	445	6	1.69	29.7
	200-219	210	275	5	2.27	39.9
	220-239	230	317	11	4.34	76.3
	240-259	250	218	19	10.89	191.3
	≧ 260	285	282	29	12.85	225.8
	All	224.9	1537	70	5.69	100.0
Framingham	<200	181	148	12	10.14	59.1
	200-219	210	113	12	13.27	77.3
	220-239	230	116	14	15.09	87.9
	240-259	250	78	10	16.03	93.4
	≧ 260	288	135	33	30.56	178.1
	All	229.8	590	81	17.16	100.0
Albany	<200	178	457	11	4.02	58.9
	200-219	210	294	9	5.11	74.9
	220-239	230	304	13	7.14	104.7
	240-259	249	247	9	6.09	89.3
	≧ 260	292	359	26	12.09	177.2
	All	228.4	1661	68	6.82	100.0

*Minnesota men initially 45-55 followed 15 years, Framingham men 30-49 and 50-59 followed 8 years, and Albany men 39-55 followed 6 years.

Table 6

Equations for Predictions of Coronary Heart Disease from Serum Cholesterol

Equation	a	b	SEE	% of variance "explained"	$r_{y, y}$
(1) $y = a + bX^2$	−81.5	34.9	28.6	79.3	0.891
(2) $y = a + bX^{2.5}$	−46.3	18.4	27.9	80.2	0.896
(3) $y = a + bX^3$	−22.4	10.0	27.4	80.8	0.899
(4) $y = a + b(X\text{-}1)^3$	28.3	30.4	26.5	82.2	0.908
(5) $y = a + bX^3$, weighted	− 2.8	8.5	27.4	81.2	0.902

Least squares solutions of equations for predicting relative risk of future coronary heart disease from serum cholesterol (X, in mg. per 1.0 ml.). y is per cent of average risk of population group. SEE = standard error of estimate; r = correlation coefficient.

Undoubtedly, other equation forms besides the exponential with k = 3 could be found to describe the data satisfactorily. But the point here is not to do an elaborate job of curve-fitting; we are concerned only to see whether one common relationship between serum cholesterol and subsequent incidence holds for all these population groups. The results in table 6 are consistent with this hypothesis, and this is particularly evident in figure 1, in which observed and predicted incidence rates are plotted.

Similar least-squares solutions were obtained for each of the population groups separately. As expected, the correlations between observed and predicted incidence rates (absolute, not relative in this case), tended to be higher than when a single equation was found for all four groups, the values being r = 0.96 for Minnesota and for Framingham ages 50 to 59, r = 0.85 for Framingham ages 30 to 49, and r = 0.95 for Albany, when k = 3.0.

Interrelationships among Variables

The American businessman is commonly pictured as fat, subject to high blood pressure, and characterized by a high level of serum cholesterol. It is an easy step to the implication that the variables of relative weight, body fatness, arterial blood pressure, and serum cholesterol are all intercorrelated. American businessmen—and American men in general—do tend to be heavier and fatter than men in most other populations, and serum cholesterol levels are usually high in the United States,[23-29] but there is little reason to believe that Americans are peculiar in regard to the frequency distribution of arterial blood pressure.[30-32] Carefully standardized studies on men in Italy, Greece, Yugoslavia, Finland, and the Netherlands, to be reported elsewhere, show close similarities in the blood pressure distribution to the present findings in Minnesota and in samples of men in the Northwest sector of the United States. Finally, within the U. S. population the available evidence fails to support the common assumption of a high correlation among these variables except in the case of relative weight and body fatness.

Even the correlation between relative weight and relative body fatness is far from perfect as shown by table 7, which shows the joint distribution of these two variables for our Minnesota men in 1948. If we define as "obese" the top 30 per cent of the men in regard to skinfold thickness, and, similarly, as truly "overweight" the upper 30 per cent of the relative weight distribution, table 7 shows that only 68 per cent of the truly overweight men are also obese. Further, among the truly overweight men, 23.5 per cent are actually under the median in body fatness.

Figure 2 shows the average relative body weight and systolic blood pressure of our Minnesota men (in 1948), classified according to centile position in the array of serum cholesterol concentration. Clearly in this population there is no significant relationship between either of these variables and serum cholesterol. Figure 3 shows the average systolic blood pressure of these same men distributed into centile classes of relative body

weight and here there *is* a highly significant relationship. As the relative weight rises, the average blood pressure rises; the data suggest a curvilinear relationship.

Analysis of bivariate distributions above and below the population medians of the Minnesota men who developed definite or possible coronary heart disease show a similar picture. Aside from the tendency of these men to be concentrated in the above-median classes for these variables, the intervariable relationships are generally similar to that indicated in table 7 and figures 2 and 3; relative weight and the sum of skinfolds are related, serum cholesterol is unrelated to the other variables, and there is a relationship between blood pressure and both relative weight and the sum of the skinfolds.

Intra-individual Variability

The relationship discerned in the Minnesota and other follow-up studies between the incidence of C.H.D. and the various pre-disease measurements are necessarily affected by intra-individual variability in the measurements concerned. Even though technical measurement error is small, spontaneous biological variation must be reckoned with, especially in blood pressure and serum cholesterol.

When blood sampling is repeated at intervals with free-living healthy men who are stable in their habits, including the diet, the average intra-individual standard deviation is of the order of 20 to 25 mg. per 100 ml.[30] Even with men on a rigidly constant regimen of diet and physical activity under locked metabolic ward conditions this figure is still

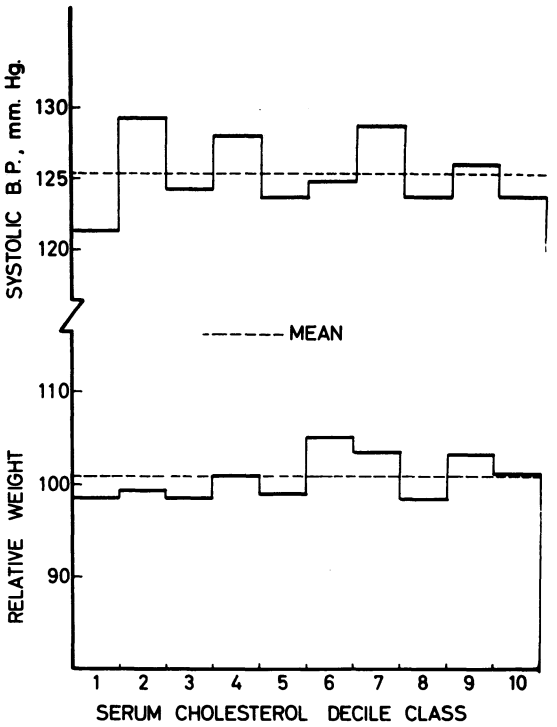

Figure 2

Mean values for systolic blood pressure and for relative body weight of the men (N = 280) classified in cholesterol deciles; 1949 data.

Table 7

Joint Distribution of Relative Body Weight and the Sum of the Skinfolds in the Data of 1948 (N = 281). The Table Gives the Number of Men in the Decile Classes of the Two Variables

Σ Skinfolds decile	Relative body weight decile										
	1	2	3	4	5	6	7	8	9	10	No.
1	20	6	1	1							28
2	6	11	7		1		1	2			28
3	1	7	8	4	1	2	3	2			28
4	1	2	5	8	7	4	1				28
5		2	4	2	2	7	6	4	1		28
6			2	4	5	2	5	8	2		28
7				5	3	6	6	2	6		28
8			1	1	6	4	3	7	2	5	29
9				1	3	3	2	1	12	6	28
10				2			1	3	5	17	28
Total no.	28	28	28	28	28	28	28	29	28	28	281

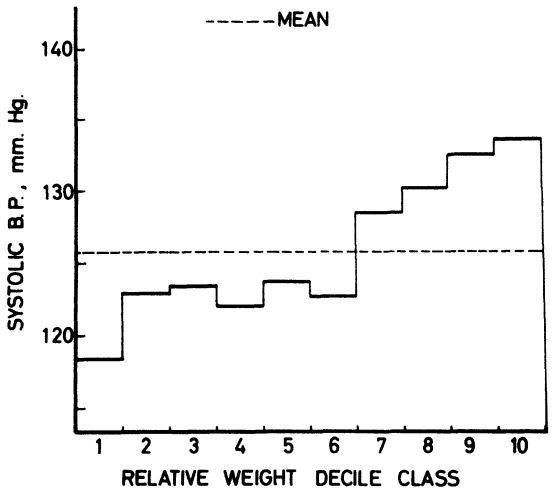

Figure 3

Mean values for systolic blood pressure of the men (N = 280) classified in relative body weight deciles; 1949 data.

12 mg. per cent, the standard error of measurement being 4 to 5 mg. per cent.[33]

In this Minnesota study, as well as in those at Framingham and Albany, it is conservative to estimate an average of about 20 mg. of cholesterol per 100 ml. for the intra-individual standard deviation, the corresponding inter-individual value (among individuals), being only about twice as large, i.e., about 40 to 45. With respect to any cutting point selected for classification then, a considerable number of misclassifications will occur if each individual is characterized only by a single blood sample. Moreover, if the cutting point is at any value other than the median, bias will occur, and this bias will increase the further the cut is from the median.

We cannot discuss in detail the effects of intra-individual variability but it must be noted that, in general, estimates of the power of a measurement to discriminate between coronary-prone and less susceptible individuals that disregard these factors must necessarily underestimate the true degree of relationship between risk of the disease and the variable in question.

These considerations apply to any variable, of course. Among the variables of concern here the ratio of intra-individual to inter-individual variability is small for relative body weight and is somewhat larger for the sum of the skinfolds (because of measurement error). But, for neither of these variables does it appear that much improvement in their prognostic value would result from replications of measurements on many occasions.

But blood pressure and serum cholesterol are in a different category. An indication of the relative intra-individual variability of the variables of concern is given in table 8,

Table 8

Variability from 1948 to 1949 of 281 Men as Indicated by Shift in Decile Class in Respect to Each of 5 Variables. The Table Gives Per Cent of Men Who Remained in the Same Decile Class, Those Who Shifted One Class, etc.

Shift 1948 to 1949	Relative weight	Σ Skin-folds	Blood pressure Systole	Blood pressure Diastole	Serum chol.
Increased 5 or more deciles	..	..	2.8	3.2	0.4
Increased 4 deciles	..	..	2.8	4.6	1.8
Increased 3 deciles	0.4	1.4	5.0	7.8	6.4
Increased 2 deciles	1.4	5.0	9.6	12.5	8.5
Increased 1 decile	19.0	15.7	15.8	10.0	17.1
No change	59.9	53.0	23.5	19.9	30.6
Decreased 1 decile	17.2	19.2	18.9	14.9	18.5
Decreased 2 deciles	1.4	4.3	11.0	12.1	9.3
Decreased 3 deciles	..	1.0	6.4	8.2	3.5
Decreased 4 deciles	0.7	0.4	2.8	3.6	2.5
Decreased 5 or more deciles	..	..	1.4	3.2	1.4
Sum of % times square of decile change	62.5	104.6	439.2	604.3	327.9

which gives the average difference in decile classification, disregarding sign, between two successive years (1948 and 1949) for the same men. This rough measure of relative intra-individual variability has the advantage that it eliminates contribution to the variability by any systematic trend between years and, moreover, the scale is the same for all variables.

Four-Year Follow-Up of Industrial Employees in Chicago

Just before this manuscript was to be submitted for publication, Dr. Oglesby Paul kindly sent us a pre-publication copy of his report on the follow-up of 1,882 men initially aged 40 to 55, employed by an industrial corporation in Chicago.[22] After 4 years, 47 men had angina pectoris, 28 had suffered myocardial infarction, and there were 13 sudden "coronary" deaths. There was no significant difference in relative body weight between the men who developed coronary heart disease and those who did not but skinfold thickness did have some discriminatory value. Elevated blood pressure was associated with some increased risk but, as elsewhere, serum cholesterol level was more significantly prognostic. The average for the men who continued healthy was 247.3 mg. per 100 ml., the average for the eventual angina cases was 263.6, for those who suffered infarcts was 275.2, and 284.5 for those who died from coronary heart disease.

The available data do not permit comparison in all details of the Chicago study with the Minnesota, Framingham, and Albany studies, and in any case comparison will require caution. The cholesterol levels in this Chicago population are substantially higher than in the other populations. Most important, among the coronary cases, the ratio of angina pectoris to infarction was 1.68 in Chicago but only 0.45 in Minnesota, 0.46 for the younger (30 to 49) and 0.56 for the older Framingham (50 to 59) men.

Summary

Relative weight, body fatness (skinfold thickness), blood pressure, and serum cholesterol are reported from 281 Minnesota business and professional men, initially clinically healthy and aged 45 to 55, who were followed by annual examinations since the winter of 1947-48. In 15 elapsed years, coronary heart disease developed definitely in 32 men and possibly in 16 other men.

The incidence of coronary heart disease tended to be higher among men above the median at first examination in relative weight, body fatness, systolic and diastolic blood pressure, and serum cholesterol concentration but these segregations were not statistically significant except with serum cholesterol, which was associated with $p < 0.001$. The data for the last pre-disease year on the men who developed coronary heart disease showed a significant relationship between incidence and systolic blood pressure as well as for cholesterol. Average data over all pre-disease years showed significantly reduced risk among the men in the bottom quartile for diastolic as well as for systolic blood pressure, while the cholesterol level was significantly prognostic over the entire range of that variable. The few men who developed coronary heart disease with low cholesterol values tended to be in the top 20 per cent of the distribution of blood pressure or relative weight or both.

Relative weight showed a high but still imperfect correlation with body fatness. Arterial blood pressure tended to be elevated in extremely obese or grossly overweight men. Serum cholesterol was not significantly related to any of the other variables.

Men who developed coronary heart disease tended to have low values for cholesterol in the alpha-lipoprotein fraction in the serum but the ratio of cholesterol in the alpha- to the beta-lipoprotein fraction of the serum was no more prognostic than total cholesterol alone.

Comparison with similar follow-up data from Framingham, Massachusetts, Albany, New York, and Chicago, show a high degree of concordance. In all series relative weight had least significance and the incidence of coronary heart disease rose continuously with the serum cholesterol level. With men classi-

fied according to pre-disease cholesterol level, about 80 per cent of the total variance in relative subsequent risk is accounted for by regression of risk on the cholesterol value raised to any power from 2 to 3 and the correlation between observed and predicted relative risk is of the order of $r = 0.9$.

Acknowledgment

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References

1. Keys, A., Taylor, H. L., Simonson, E. L., and Blackburn, H.: The C. V. D. research program of the Laboratory of Physiological Hygiene—An explanation and a letter to "Guinea Pigs." Journal-Lancet **81**: 291, 1961.
2. Association of Life Insurance Medical Directors and the Actuarial Society of America: Medico-actuarial mortality investigation. Vol. 1. New York, 1912.
3. Committee on Nutritional Anthropometry, Food and Nutrition Board, National Research Council (A. Keys, Chairman): Recommendations concerning body measurements for the characterization of nutritional status. Body Measurements and Nutrition (ed. J. Brozek). Wayne Univ. Press, Detroit, 1956, p. 1. Also published in Human Biol. **28**: No. 2, 1956.
4. Anderson, J. T., and Keys, A.: Cholesterol in serum and lipoprotein fractions. Clin. Chem. **2**: 145, 1956.
5. Society of Actuaries: Select basic table, intercompany experience for 1946-'49. Tr. Soc. Actuaries **2**: 506, 1950.
6. Barr, D. P., Russ, E. M., and Eder, H. A.: Protein-lipid relationships in human plasma. II. In atherosclerosis and related conditions. Am. J. Med. **11**: 468, 1951.
7. Nikkilä, E.: Studies on the lipid-protein relationships in normal and pathological sera and the effect of heparin on serum lipoproteins. Scandinav. J. Clin. & Lab. Invest. **5**: suppl. 8, 1953.
8. Azerad, E., Lewin, J., and Ghata, J.: Etude de la repartition du cholesterol dans les deux fractions α- et β- lipoproteines du serum chez l'homme normal et chez 24 sujets atteints d'infarctus du myocarde. Bull. et mém. Soc. méd. hôp. Paris **74**: 703, 1953.
9. Dodds, C., and Mills, G. L.: Influence of myocardial infarction on plasma-lipoprotein concentration. Lancet **1**: 1160, 1959 .
10. Dawber, T. R., Moore, F. E., and Mann, G. V.: Coronary heart disease in the Framingham study. Am. J. Pub. Health **47**: 4, 1957.
11. Dawber, T. R., Kannel, W. B., Revotskie, N., Stokes, J., III, Kagan, A., and Gordon, T.: Some factors associated with the development of coronary heart disease. Six years' follow-up experience in the Framingham study. Am. J. Pub. Health **49**: 1349, 1959.
12. Kagan, A., Gordon, T., Kannel, W. B., and Dawber, T. R.: Blood pressure and its relation to coronary heart disease in the Framingham study. Hypertension **7**: 53, 1959.
13. Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N., and Stokes, J., III: Factors of risk in the development of coronary heart disease—six-year follow-up experience. Ann. Int. Med. **55**: 33, 1961.
14. Dawber, T. R., and Kannel, W. B.: Susceptibility to coronary heart disease. Mod. Concepts Cardiovas. Dis. **30**: 671, 1961.
15. James, G., Hilleboe, H. E., Filippone, J. F., and Doyle, J. T.: Cardiovascular Health Center-II. First year's operation A. General observations and hypertension. New York State J. Med. **55**: 774, 1955.
16. Doyle, J. T., Heslin, A. S., Hilleboe, H. E., Formel, P. F., and Korns, R. F.: A prospective study of degenerative cardiovascular disease in Albany: Report of three years' experience—1. Ischemic heart disease. Am. J. Pub. Health **47**: 25, 1957.
17. Doyle, J. T., Heslin, A. S., Hilleboe, H. E., and Formel, P. F.: Early diagnosis of ischemic heart disease. New England J. Med. **261**: 1096, 1959.
18. Chapman, J. M., Goerke, L. S., Dixon, W., Loveland, D. B., and Phillips, E.: The clinical status of a population group in Los Angeles under observation for two to three years. Am. J. Pub. Health **47**: 33, 1957.
19. Stamler, J., Lindberg, H. A., Berkson, D. M., Shaffer, A., Miller, W., and Poindexter, A.: Prevalence and incidence of coronary heart

disease in strata of the labor force of a Chicago industrial corporation. J. Chron. Dis. **11**: 405, 1960.

20. Berkson, D. M., Stamler, J., Lindberg, H. A., Miller, W., Mathies, H., Lasky, H., and Hall, Y.: Socioeconomic correlates of atherosclerotic and hypertensive heart diseases. New York Acad. Sc. **84**: 835, 1960.
21. Stamler, J., Berkson, D. M., Lindberg, H. A., Miller, W., and Hall, Y.: Racial patterns of coronary heart disease. Geriatrics **16**: 382, 1961.
22. Paul, O., Lepper, M. H., Phelan, W. H., Dupertuis, C. W., MacMillan, A., McKean, H., and Park, H.: A longitudinal study of coronary heart disease. Circulation **28**: 20, 1962.
23. Keys, A., Fidanza, F., and Keys, M. H.: Further studies on serum cholesterol of clinically healthy men in Italy. Voeding (Amsterdam) **16**: 492, 1955.
24. Higginson, J.: Atherosclerosis, diet, and serum cholesterol in the South African Bantu. *In* Cardiovascular Epidemiology (ed. by A. Keys and P. D. White). New York, Hoeber-Harper, 1956, p. 34.
25. Keys, A.: Calories and cholesterol. Geriatrics **12**: 301, 1957.
26. Scrimshaw, N. S., Trulson, M., Tejada, C., Hegsted, D. M., and Stare, F. J.: Serum lipoprotein and cholesterol concentrations. Comparisons of rural Costa Rican, Guatemalan, and United States populations. Circulation **15**: 805, 1957.
27. Brozek, J., Buzina, R., and Mikic, F.: Population studies on serum cholesterol and dietary fat in Yugoslavia. Am. J. Clin. Nutr. **5**: 279, 1957.
28. Padmavati, S., Gupta, S., and Pantulu, G. V. A.: Dietary fat, serum cholesterol levels and incidence of atherosclerosis and hypertension in Delhi. Indian J. M. Res. **46**: 245, 1958.
29. Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N. P., and Keys, M. H.: Lessons from serum cholesterol studies in Japan, Hawaii, and Los Angeles. Ann. Int. Med. **48**: 83, 1958.
30. Bays, R. P., and Scrimshaw, N. S.: Facts and fallacies regarding the blood pressure of different regional and racial groups. Circulation **8**: 655, 1953.
31. Biörck, G.: Further studies in Sweden. *In* Cardiovascular Epidemiology (ed. by A. Keys and P. D. White). New York, Hoeber-Harper, 1956, p. 69.
32. Takahashi, E., Kato, K., Kawakami, Y., Ishiguro, K., Kaneta, S., Ohba, E., Yano, S., Ito, Y., Shiraishi, M., Murakami, N., Sugawara, T., Meguro, Y., and Suzuki, Y.: Epidemiological studies on hypertension and cerebral hemorrhage in Northeast Japan. Tohoku J. Exper. Med. **74**: 188, 1961.
33. Keys, A., Anderson, J. T., and Grande, F.: Prediction of serum-cholesterol responses of man to changes of fats in the diet. Lancet **1**: 959, 1957.

Amyl Nitrite and Angina Pectoris

From observations during the attack, and from an examination of numerous sphygmographic tracings taken while the patients were free from pain, while it was coming on, at its height, passing off under the influence of amyl, and again completely gone, I find that when the attack comes on gradually the pulse becomes smaller, and the arterial tension greater as the pain increases in severity. During the attack the breathing is quick, the pulse small and rapid, and the arterial tension high, owing, I believe, to contraction of the systemic capillaries. As the nitrite is inhaled the pulse becomes slower and fuller, the tension diminished, and the breathing less hurried. On those occasions when the pain returned after an interval of a few minutes, the pulse, though showing small tension, remained small in volume, and not till the volume as well as tension of the pulse became normal, did I feel sure that the pain would not return.—T. L. Brunton. "Use of Nitrite of Amyl in Angina Pectoris." *The Lancet,* **2**: 98, 1867.