Probability of Middle-Aged Men Developing Coronary Heart Disease in Five Years

By Ancel Keys, Ph.D., Christ Aravanis, M.D., Henry Blackburn, M.D., F. S. P. van Buchem, M.D., Ratko Buzina, M.D., B. S. Djordjevic, M.D., Flaminio Fidanza, M.D., Martti J. Karvonen, M.D., Ph.D., Alessandro Menotti, M.D., Vittorio Puddu, M.D., and Henry L. Taylor, Ph.D.

SUMMARY

Characteristics of 11,132 men aged 40–59 years and free from coronary heart disease (CHD) at entry were related to follow-up experience, using multivariate analysis. In 5 years among 2,404 U.S. railroad men and 8,728 European men there were 615 cases of CHD, 214 of whom died from CHD or suffered definite nonfatal infarction.

With five entry characteristics (age, systolic blood pressure, serum cholesterol, smoking habit, and body mass index), multiple logistic solutions for Europeans and Americans, separately, gave estimates of the individual probability of CHD. Classified by deciles scores for these probabilities, the expected and observed CHD cases were highly correlated (r = 0.930–0.981). Predictions based on European data applied to Americans, and vice versa, gave similar high correlations but American incidence was excessive compared with European experience.

Application of the analysis coefficients obtained from data in Europe and in the U.S. railroad to 6,221 other U.S. men 40–59 years of age, CHD-free at entry, gave good prediction of relative risk (r = 0.94) for observed versus predicted cases in deciles of risk score; however, the actual numbers of cases were underpredicted.

From single measurements of a few characteristics the multiple logistic solution usefully estimates the relative risk of CHD for individuals. Age, systolic pressure, and serum cholesterol are universally powerful predictors of risk. Variables not measured in this study or not yet identified contribute to the risk of CHD among American men.

Additional Indexing Words:
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CORONARY HEART DISEASE (CHD) is now commonly held to have a multivariable causality; in other words, several, perhaps many, variables promote the disease.

Follow-up studies of persons judged to be free of CHD at entry examination have identified several characteristics associated with increased risk of development of CHD in future years. Age, arterial blood pressure, and serum cholesterol concentration uniformly emerge as important risk factors in follow-up studies in the Twin Cities, Minnesota, Framingham, Massachusetts, Los Angeles, California, Albany, New York, Chicago, Illinois, and London, England. In those studies, cigarette smoking emerged as anything from a relatively small to a very important risk factor. Overweight was associated with increased risk of CHD in most of these studies but observed
associations between relative weight and blood pressure raise doubts about the independent contribution of overweight to risk.

In this situation, where several variables act simultaneously, and perhaps interact, to influence the development of CHD, and where some of those variables are intercorrelated, a multivariate analysis is required to estimate the probability of the disease appearing within some specified period of time in the future. Cross tabulations of persons into classes of each of the variables—high and low, or high, medium, and low, etc.—are better than considering each variable separately. However, as pointed out by Truett et al., that method of analysis and avoidance has great limitations with more than two or three variables, and loses much information provided from measurements of continuous variables.

It is necessary to estimate “risk” quantitatively. It is not true that certain persons are at risk and others are not but it will be agreed that different persons differ in degrees of risk. The problem, then, is probabilistic; the need is to be able to estimate, from information on the entry status in regard to risk variables, the probability that clinical CHD will occur in a given time. The present paper presents the results of the development of such estimates from data obtained in the International Cooperative Study on the Epidemiology of Cardiovascular Disease, which started examination and follow-up work in 1958. The material considered here includes the experience of 5 years of follow-up of 11,132 men, a total of 55,660 man-years. In addition, the predictive power of that experience is tested with another series of 6,221 men followed 5 years.

The Subjects and their Follow-up

The primary subjects comprised men aged 40–59 years and judged to be CHD-free at the time of their entry examination in the International Cooperative Study on Cardiovascular Epidemiology. Of the total of 11,132 considered here, 2,404 were full-time employees of U. S. railroads and 8,728 were men in geographically specified areas in Finland, Italy, Greece, The Netherlands, and Yugoslavia. Ten of the 13 cohorts in Europe were “chunk” samples of specified rural areas comprising, on the average, over 95% of all men aged 40–59 years resident in the areas. One cohort, N = 864, represented a 4/9ths statistical sample of men aged 40–59 years in Zutphen, a small town in central Holland. One cohort, N = 758, was a sample of men aged 40–59 years in four specified occupations in the Rome division of the Italian state railroad system. Men on the faculty of the University of Belgrade made up one cohort. The recruitment and entry characteristics of the men in all of the cohorts have been reported in detail.

Table 1 summarizes the numbers of men in the present study. Among the U. S. railroad men, 210 developed CHD, including 78 men who died from CHD or who had definite infarctions (hard CHD) and 79 other men who developed classical angina pectoris. Among the European men the CHD incidence rate was around half that of the Americans: 48% for hard CHD, 44 for angina pectoris (AP), and 53 for any CHD. Definitions of any CHD are given later under Diagnostic Criteria.

The proportions of the total CHD incidence accounted for by hard CHD and by AP are similar in the Europeans and the Americans. Hard CHD accounted for 37.1% of the U. S. cases and 33.2% of the cases in Europe. The slight discrepancy between ratios of hard CHD to AP cases in the U. S. (= 1.00) and in Europe (= 1.10) is far from approaching significance. However, in Europe the relative frequency of CHD other than hard CHD or AP is significantly higher (< 0.02) than among the American men. In Europe there were 150 men with CHD diagnoses other than CHD death, infarction, or AP; if that diagnosis in Europe were in the same

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**Table 1**

**Numbers of Men in Various Studies**

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>N at risk</th>
<th>Hard CHD</th>
<th>AP</th>
<th>Any CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. S. railroad men</td>
<td>2,404</td>
<td>78</td>
<td>79</td>
<td>210</td>
</tr>
<tr>
<td>European men</td>
<td>8,728</td>
<td>136</td>
<td>124</td>
<td>405</td>
</tr>
<tr>
<td>Four-pool total</td>
<td>6,221</td>
<td>223</td>
<td>118</td>
<td>*</td>
</tr>
<tr>
<td>(Framingham)</td>
<td>(1,337)</td>
<td>(52)</td>
<td>(31)</td>
<td>*</td>
</tr>
<tr>
<td>(Albany)</td>
<td>(1,735)</td>
<td>(50)</td>
<td>(19)</td>
<td>*</td>
</tr>
<tr>
<td>(Chicago, Paul)</td>
<td>(1,891)</td>
<td>(64)</td>
<td>(58)</td>
<td>*</td>
</tr>
<tr>
<td>(Chicago, Stamler)</td>
<td>(1,258)</td>
<td>(57)</td>
<td>(10)</td>
<td>*</td>
</tr>
</tbody>
</table>

*Soft criteria not comparable.

Abbreviations: N at risk = men aged 40–59 years and CHD-free at entry who were followed for 5 years; Hard CHD = CHD death or definite infarction; AP = classical angina pectoris; and Four-pool = Framingham + Albany + Chicago, Stamler + Chicago, Paul.
proportion to hard CHD + AP as in the U. S. men, the expectation would be 90 men. The meaning is obscure.

Table 1 also shows data on the four-pool, the combined material of men aged 40–59 years and judged CHD-free at entry into the studies at Framingham, Albany, and in the two studies in Chicago. In table 1 there is a major discrepancy between these and our studies in regard to the relative frequency of AP compared with hard CHD. More detailed examination of the four-pool data shows extremely large differences between the cohorts in the reported frequency of AP. It is very likely that diagnostic criteria for angina were not comparable. However, there is no evidence that hard-CHD diagnoses differed among the cohorts.

Later in this paper the material on hard CHD in the four-pool will be used to test the multiple logistic solutions obtained for the European and U. S. data. The reported incidence of hard CHD in the four-pool (35.8 per 1,000 men in 5 years) was closely similar to that in the U. S. railroad men (32.4). The discrepancy does not remotely approach statistical significance. However, the evaluation of such comparisons requires consideration of the distribution of risk factors in the two sets of men. Such consideration will be made in due course in this paper.

Methods

The procedure and methods used in the entry and 5-year reexaminations have been described in detail but a brief summary may be useful.

Standing height and body weight were recorded with the subject barefoot and in light underwear. From those data the body mass index was calculated as BMI = weight (kg) divided by the square of height (meters). BMI seems to serve all the purposes of “relative weight” with the advantages of not being dependent on tables of so-called “standards” or “averages” that change from time to time and from population to population. Studies on height-weight data in several populations indicate BMI to be a better measure of relative body weight than ponderal indices in which height enters as the cube or weight as the cube root in the ratio.

Arterial blood pressure was recorded with the auscultatory method with the subject in the supine position, having avoided smoking and exercise for at least 30 min. Most examinations were made in the morning, and in any case the effort was made to avoid examining anyone within 2 hours of a heavy meal and to provide calm and relaxed conditions.

Blood was drawn by venipuncture with a minimum of stasis and allowed to clot. The serum was separated by centrifugation, 0.100-ml portions were dried on filter paper, and duplicates were sent by airmail to the Laboratory of Physiological Hygiene at the University of Minnesota. Cholesterol was estimated by a modification of the method of Abell et al.

Smoking habits were elicited by a standard questionnaire administered by a person using the language of the area. After various analyses, for the present purposes the questionnaire material was condensed so as to place each man in one of the following smoking classes: 3 = nonsmokers, including both men who had never smoked regularly and men who had apparently stopped permanently; 4 = men smoking regularly but fewer than an average of five cigarettes daily; 5 = five to nine cigarettes’ daily; 6 = 10 to 19 cigarettes daily; 7 = 20 to 29 cigarettes daily; and 8 = 30 or more cigarettes daily.

Occupation was the sole basis of classification of physical activity of the U. S. railroad men. In the U. S. railroad cohort the men in sedentary jobs, i.e., executives, dispatchers, and clerks (including only clerks who had no duties requiring physical work), were coded class 1, physical activity sedentary, while 835 switchmen were coded class 2, moderate physical activity on the job. No U. S. men were rated class 3, habitual, heavy occupational activity. In the present material, 342 of the total of 2,404 U. S. men could not be securely classified in regard to occupational activity and so were omitted from analyses concerning that variable.

In Europe, the range of physical activity was much greater than in the U. S. cohort, and a large proportion (53% of the men in the present analysis) was placed in physical activity class 3, while only 20.9% were sedentary in their work. The most common occupation of the European men was small-scale farming with a minimum of power equipment. Nevertheless, the answer, “farmer,” to the question as to occupation did not necessarily result in being rated as class 3 activity; questions were asked about the actual activity.

Diagnostic Criteria

Diagnostic criteria were set forth in detail in the American Heart Association Monograph 29, pages 14–19. The present analysis is concentrated on two categories of CHD: Hard CHD, meaning death from CHD or definite
myocardial infarction, and any CHD. In addition to cases of hard CHD, defined in the
monograph, any CHD used here included four categories: (1) classical angina
pectoris, (2) clinical judgment of definite heart disease and etiology specified
as myocardial infarction by history, and (3) follow-up clinical diagnosis of
possible heart disease with etiology specified by history as myocardial infarction
and any of Minnesota ECG codes17 1.2, 1.3, 5.1, 5.2, 6.1, 6.2, 7.1, 7.2, 7.4, or
8.3 at the 5-year examination, or Minnesota ECG codes 1.2 or
1.3 + 5.1 or 1.3 + 5.2 at the 5-year examination but not at entry.

It should be noted that in the present study, except in case of death, interim medical
history information from sources outside the present collaborating groups was not relied
upon for diagnoses. A major purpose of the International Cooperative Study on the
Epidemiology of Cardiovascular Disease was to compare cohorts in different regions. Because
the regions differed in respect to availability of medical care facilities and records, it would
obviously introduce bias if the records of the local medical care facilities became a prime
basis for decision about interim medical history.

This limitation on the use of local information obtained second hand had the advantage
that our diagnoses did not unduly reflect differences in the quality of medical records in
the different regions. On the other hand, undoubtedly the result was some underesti-
mate of incidence in all of the cohorts. For example, in the absence of classical angina
pectoris and of definite clinical evidence of heart disease at the 5-year examination, a very
real interim heart attack not accompanied by residual ECG evidence at 5-year examination
would not be listed as hard CHD with the agreed protocol in the present study.

The 5-year examinations involved on-the-spot checks of diagnosis by several internists
in an international team. The diagnostic opinions, together with the evidence of the
clinical history, physical examination, 12-lead ECG, and exercise test results, were centrally
reviewed by two of the present authors

(Henry Blackburn and Alessandro Menotti). The result, it is believed, is objective and
unbiased in regard to different cohorts.

The Multiple Logistic Equation

Several mathematical models may be proposed for the purpose of estimating the
relationship of one variable, say the development of a disease, to a series of other
variables, say predisease characteristics. All involve assumptions, and the real test of their
utility in a given situation is how well they work, that is, how well they classify the
persons into disease and no-disease categories on the basis of their predisease characteristics.
In this sense, the multiple logistic equation showed much promise in the application of it
to CHD incidence in the Framingham study by Truett et al.8 and by Walker and
Duncan.18

In the multiple logistic equation the probability of the development of CHD in an
individual is estimated as:

\[
P = \frac{1}{1 + e^{-a + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k}}
\]

where \( \alpha \) is a constant, \( X_1, X_2, \ldots, X_k \) are measurements of predisease characteristics,
e.g., age or systolic blood pressure, while \( \beta_1, \beta_2, \ldots, \beta_k \) are coefficients for the corresponding
variables, and \( e \) is the base of natural logarithms, 2.7183. The limits of \( P \) are zero, no
chance of CHD, and 1, absolute certainty of CHD. For a group of persons the sum of their
individual estimates for \( P \) should correspond with the number of persons in the group
observed to develop CHD.

Truett, Cornfield, and Kannel8 used the linear discriminant function in estimating the
constant and the coefficient in the above equation, assuming that in both the group of
persons who develop CHD and the group of those who do not the frequency distributions of
the "predicting" variables are multivariate normal, with equal variance and covariances.
Walker and Duncan18 developed a recursive
iteration procedure to provide maximum
likelihood estimates for the constant and
coefficients without assuming any particular
distribution of the values of the variables $X_1, X_2 \ldots X_4$. Practical comparison of results with the Walker and Duncan (W-D) and Truett and Cornfield (T-C) methods are presented below.

Trial of the Truett et al. method with data from the Framingham study produced good practical results. When the subjects were arranged in decile classes of $P$ and grouped in decile classes of $P$ there was a high correlation between the number of cases of CHD in the decile classes and the sum of the values of $P$ for the persons thus classified on the basis of seven variables: age, serum cholesterol, systolic blood pressure, relative body weight, blood hemoglobin concentration, smoking habit, and ECG (coded as $0 =$ normal, $1 =$ abnormal).

The agreement reported by Truett, Cornfield, and Kannel between observed and expected numbers of cases in the decile classes of estimated probability at Framingham is not, of course, a measure of the predictive power of their solution of the multiple logistic equation. Test of prediction requires application of the coefficients to an independent set of data. Application of the coefficients obtained by Truett, Cornfield, and Kannel from Framingham to data on the averages of men in 13 cohorts in the current International Cooperative Study showed a high correlation, with $r = 0.83$ for the 13 sets of values, between the observed CHD incidence rates and those expected. The fact that the total number of cases predicted was grossly discordant with the number observed could be explained, at least in part, by differences in length of follow-up and in diagnostic criteria.

A better test of the method of Truett et al. involved use of the method to solve the equation with data on a 20-year follow-up of Minnesota business and professional men and application of the coefficients to 5-year follow-up data on U. S. railroad men. The relative CHD risk of the railroad men proved to be usefully estimated.

Such indications of the value of the approach of Truett et al. do not rule out the possibility that the method of Walker and Duncan would yield even more useful results. However, as will be shown later in this paper, in our material the two methods produce substantially identical results. Solving the multiple logistic equation by the Walker and Duncan method is costly and requires sequestration of a block of uninterrupted time on an extremely powerful computer, such as the CDC 6600. Accordingly, in the present study, after some parallel runs with both methods, we have concentrated on the method of Truett et al., using a CDC 3300 computer.

Results

Five variables most commonly recorded or available and of greatest interest in regard to possible contribution to the etiology of CHD are age, systolic blood pressure, serum cholesterol concentration, a measure of relative body weight such as body mass index, and smoking habits. Results of solving the multiple logistic equation with these variables are given in table 2. Table 2 also gives the mean values for the five variables for each of the groups of cases and noncases. The mean values for the cases versus noncases tend to differ in the direction expected if, indeed, greater values in each of these variables is associated with increased risk of CHD. It will be noted also that for the three most universally established risk factors, age, blood pressure, and cholesterol, the difference between the cases and noncases is larger for hard CHD than for any CHD. This indicates that the more secure the CHD diagnosis, the more clearly is the disease related to age, blood pressure, and serum cholesterol. A similar trend is indicated for smoking habits. In BMI the differences in the means seem, superficially at least, to be trivial.

The ratios of the coefficients to their estimated standard errors, the equivalent of $t$ values, give a crude indication of the credence the coefficients actually merit. Systolic blood pressure, cholesterol, and smoking are indicated throughout to make a significant contribution, and the same is true for age except for its contribution to any CHD in Europe. For none of the four sets of material is there any
Table 2

<table>
<thead>
<tr>
<th>Cohort and solution</th>
<th>Criterion</th>
<th>Item</th>
<th>Age (yr)</th>
<th>Syst BP (mm Hg)</th>
<th>Chol (mg/100 ml)</th>
<th>Smoke</th>
<th>BMI</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. S. railroad</td>
<td>Any</td>
<td>(X), cases</td>
<td>50.92</td>
<td>147.5</td>
<td>249.0</td>
<td>5.41</td>
<td>25.89</td>
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<tr>
<td></td>
<td>(N = 2,404)</td>
<td>(X), noncases</td>
<td>49.53</td>
<td>138.2</td>
<td>238.4</td>
<td>4.92</td>
<td>25.34</td>
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<tr>
<td></td>
<td>A</td>
<td>Coeff</td>
<td>0.033</td>
<td>0.019</td>
<td>0.004</td>
<td>0.199</td>
<td>0.039</td>
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<td></td>
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<td>se</td>
<td>0.013</td>
<td>0.004</td>
<td>0.002</td>
<td>0.043</td>
<td>0.024</td>
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<tr>
<td>U. S. railroad</td>
<td>Hard</td>
<td>(X), cases</td>
<td>52.09</td>
<td>150.4</td>
<td>259.7</td>
<td>5.56</td>
<td>25.45</td>
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<td>(N = 2,404)</td>
<td>(X), noncases</td>
<td>49.57</td>
<td>138.6</td>
<td>238.6</td>
<td>4.95</td>
<td>25.39</td>
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<td>B</td>
<td>Coeff</td>
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<tr>
<td></td>
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<td>se</td>
<td>0.021</td>
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<td>0.003</td>
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<td>Europe</td>
<td>Any</td>
<td>(X), cases</td>
<td>51.83</td>
<td>149.9</td>
<td>236.3</td>
<td>4.95</td>
<td>24.8</td>
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<td></td>
<td>(N = 8,728)</td>
<td>(X), noncases</td>
<td>49.53</td>
<td>139.1</td>
<td>210.2</td>
<td>4.86</td>
<td>24.1</td>
<td></td>
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<tr>
<td></td>
<td>C</td>
<td>Coeff</td>
<td>0.066</td>
<td>0.019</td>
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<td>0.065</td>
<td>0.026</td>
<td>-11.888</td>
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<td>0.010</td>
<td>0.003</td>
<td>0.001</td>
<td>0.031</td>
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<td>Europe</td>
<td>Hard</td>
<td>(X), cases</td>
<td>52.30</td>
<td>151.4</td>
<td>241.5</td>
<td>5.07</td>
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<td>(N = 8,728)</td>
<td>(X), noncases</td>
<td>49.59</td>
<td>139.4</td>
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<td>4.86</td>
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<td></td>
<td>D</td>
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<td>0.103</td>
<td>0.016</td>
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<tr>
<td></td>
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<td>0.016</td>
<td>0.005</td>
<td>0.002</td>
<td>0.053</td>
<td>0.026</td>
<td></td>
</tr>
</tbody>
</table>

*All men were 40–59 years of age and CHD-free at entry.

Abbreviations: BMI = kg weight/(m height)^2; \(X\) = mean; and N = number of men.

indication that BMI makes a significant contribution to the risk or its evaluation.

Caution should be observed in making comparisons of the magnitudes of the coefficients for the several variables in an effort to evaluate the relative importance of those variables. First, allowance must be made for the fact that the magnitudes of the variables differ greatly. The coefficient for age is applied to a variable averaging around 50, while that for systolic pressure is applied to a variable averaging around three times larger. Consider hard CHD in Europe. The coefficient for smoking, 0.104, is 10 times that for cholesterol, but the product of the coefficient times the average value of the variable for cases is 2.4 for cholesterol and only 0.5 for smoking. The second consideration is the fact that in most cases the estimated standard errors of the coefficients are substantial in proportion to the coefficients themselves. Taken at face value, the “true” coefficient for cholesterol for hard CHD in the railroad cohort can only be narrowed down, with 95% confidence, to be somewhere between 0.003 and 0.015. Third, in regard to the discrimination of individuals in relative risk, attention should be paid to relative variation in the values of the variables; the range of possible contributions to risk of those variables should be considered, at least if we are interested in the relative importance of those variables in determining the range of risks of the individuals in possible prevention programs. In the present material, age ranges only from 40 through 59 years; the range is only 20% of the mean. Systolic blood pressure, however, varies in this material over a range of about 90 to 240 mm Hg; the range is about 100% of the mean.

The success with which the results of the multiple logistic solution identifies groups of men with different future (5-year) incidence rates of CHD is examined in figures 1 through 4. Figure 1 concerns the incidence of hard CHD \((N = 78)\) among U. S. railroad men as related to age, systolic blood pressure, serum cholesterol, smoking habit, and body mass index, using the coefficients in solution B in table 2.

The top decile class of estimated probability contained 23 of the total of 78 cases; in the top quintile of probabilities the incidence rate is 19 times that in the bottom quintile.
Figure 1

CHD deaths and infarctions (HARD CHD) in 5 years among 2,404 U. S. railroad men aged 40–59 years and CHD-free at entry. Cases were expected in the decile classes of probability calculated from the coefficients in solution B in table 2 for age, systolic blood pressure, serum cholesterol, smoking habit, and body mass index. D10/T is the ratio of cases found in the top decile of probability to total cases. Q5/Q1 is the ratio of cases in the top to those in the bottom quintile.

Figure 2 corresponds to figure 1 but for any CHD diagnosis (210 cases) among the railroad men, using solution A in table 2. The correlation is not quite so high as between observed and expected numbers of cases in the deciles in the result with hard CHD but the difference cannot be claimed to be significant.

Figures 3 and 4 correspond to figures 1 and 2, respectively, but for the material of 8,728 European men. Figure 3 treats hard CHD (136 cases) with solution D in table 2, while Figure 4 concerns any CHD (405 cases) using solution C in table 2. The results are closely similar to those found with the U. S. railroad men; the correlation between observed and expected numbers of cases in the deciles of probability is very high and there is a tendency, statistically not significant, for a better identification of high-risk men with hard than with any CHD criteria.

Predicting CHD in Europe from the U. S. and Vice Versa

The results presented so far in this report show the power of five variables in the multiple logistic equation in distributing observed CHD cases according to calculated probabilities. The numbers of observed cases proved to be very highly correlated with the numbers of expected cases, but note that this is not a test of true prediction. Such a test requires the application of a multiple logistic solution for one set of data to another independent set of data.

Figure 5 summarizes the result of predicting hard CHD in Europe from the results with U. S. railroad men (solution B in table 2).

In the top quintile there were 11.5 times as many cases as observed in the bottom quintile. Thirty percent of the European cases of hard CHD were found in the top decile of the probability distribution calculated from the U.S. coefficients; the regression is very far from y = x; there is a systematic difference between the Europeans and the Americans not accounted for by the five variables considered. The total number of hard CHD cases observed is only 136 of 238.4, or 57% of European expectation based on U. S. data for
HARD CHD among 8,728 European men with predictions based on solution $D$ in table 2 for age, systolic blood pressure, serum cholesterol, smoking, and body mass index.

Figure 3

men of the specified characteristics in five variables.

Figure 6 shows a similar picture in regard to the prediction of any CHD in Europe from the corresponding U. S. coefficients (solution $A$ in table 2). The prediction of relative risk within the European cohort is excellent, but the total of 405 cases observed is only 61% of the number expected from American experience.

The reverse prediction, the incidence of CHD among U. S. railroad men from experience in Europe, is summarized in figure 7 (hard CHD) and figure 8 (any CHD). The prediction of relative risk within the U. S. cohort is satisfactory but, as expected from the results noted above, the total incidence of CHD among the U. S. railroad men proved to be much greater than would correspond with European experience for men identical in respect to the five variables considered.

Finally, the U. S. railroad and European multiple logistic hard CHD solutions can be tested by applying them to the 5-year experience of hard CHD among 6,221 men aged 40–59 years and CHD-free at entry in the four-pool material of Drs. W. B. Kannel, Joseph T. Doyle, Jeremiah Stamler, and Oglesby Paul. The attempt to predict the four-pool experience from the U. S. railroad solution $B$ in table 2 is summarized in figure 9. As in the case of cross predictions between Europe and the U. S. railroad men, the correlation is very good between observed and predicted numbers of cases in the deciles of calculated probability. Identification of relatively high-risk men is also impressive, but the four-pool proved to have 41% more hard CHD cases than would have been expected, other things being equal.

The corresponding prediction of hard CHD in the four-pool from the experience of hard CHD in Europe is summarized in figure 10. The correlation between numbers of cases observed in the decile classes and those predicted from solution $C$ in table 2 for European men is very high ($r = 0.964$), and 15.6 times more cases were observed in the top quintile than in the bottom quintile of the probability distribution. However, the total incidence of hard CHD observed was 2.14 times greater than would be expected with European men of corresponding age, blood pressure, cholesterol, smoking habits, and body mass index. The risk of developing hard

Figure 4

Same as figure 3 but for ANY CHD and predictions based on solution $C$ in table 2.
CHD in the four-pool is greatly underestimated, but the relative risk of men with the four-pool is very well predicted by the European analysis.

**Walker-Duncan vs Truett-Cornfield Solutions**

In the foregoing analysis, the method of Truett et al.8 of solving the multiple logistic equation was used. That method involves the assumption that the distribution of the independent variables (e.g., blood pressure, cholesterol, and smoking) is multivariate normal, with equal variances and covariances in the “cases” and noncases. Those assumptions are patently unwarranted in the Framingham material used for the first trial of their method and are obviously not justified with the present material of data on men in Europe and employed by U. S. railroad companies. The method of Walker and Duncan,18 which does not require such assumptions, is therefore preferable on theoretical grounds.

Eighteen comparisons of results with the Walker-Duncan (W-D) and Truett-Cornfield
Besides important actuarial implications for insurance medicine, and for counseling about possible preventive measures, it appears that the relative influence of these variables, or at least their relative predictive power in regard to CHD developments, may be universal. However, the fact that the total incidence of CHD in one population may be poorly predicted from experience in another population requires careful examination.

Some of the discrepancy between hard CHD incidence in the four-pool analysis and that predicted from the experience of the U. S. railroad men could be attributed to differences in diagnostic criteria. Efforts were made to assure comparability, but that was only after the data had been collected. Possibly a more important reason for the difference observed could be in the fact that most of the men in the four-pool were reexamined two or more times in the 5 years of follow-up, while the U. S. railroad men were reexamined only at the end of the 5 years. Moreover, for the railroad men the decision was made to accept only diagnoses that could be directly verified by our own staff physicians at the time of the 5-year examination. These differences could well

**Discussion**

**Implications about Unknown Risk Factors**

The present data and analysis show, in several populations of middle-aged men, an excellent correspondence between the incidence rate of CHD observed and that calculated from simultaneous consideration, with the multiple logistic equation, of the characteristics of age, blood pressure, serum cholesterol, smoking habit, and a measure of relative weight at entry to follow-up. Further, it was found that the relative CHD risk of different men within a given population is well predicted from the results of the multivariate analysis of the experience of men in other far-distant populations differing in socioeconomic circumstances, language, and ethnic background.
result in differences in ascertainment and thus explain an incidence rate of hard CHD in the four-pool some 41% greater than in the railroad cohort.

No such explanations can be offered for the much more impressive difference between the U. S. railroad and the European men. Rules for clinical judgments and ECG criteria and the details of the examinations and their spacing were identical; yet the U. S. men had an incidence rate of hard CHD roughly double that of European men of the same age, blood pressure, serum cholesterol, and smoking habit. Even consideration of relative body weight and of physical activity does not change the discrepancy. The conclusion seems inescapable that the incidence of CHD is strongly influenced by one or more variables unrelated to any considered in these studies.

Still, the fact remains that consideration of only four variables (age, systolic blood pressure, serum cholesterol, and smoking habit) suffices to identify men whose likelihood of dying from CHD or having a definite infarction within 5 years is greatly above the average. By the same token, it is possible from these characteristics to identify men who are most unlikely to become CHD victims in 5 years.

**Applications**

The present analysis concerns the 5-year experience of men aged 40–59 years who were free of evidence of CHD at the start. In the United States something like 10% of such men develop CHD in 5 years. It is desirable, then, to evaluate the likelihood of being included in the unfortunate 10%. The risk increases with age, and it is commonly agreed that it rises with arterial blood pressure, with serum cholesterol concentration, and with cigarette smoking. Each of these facts should be considered in providing health counsel, but a synthesis is needed to evaluate the overall risk. The solution to the multiple logistic equation provides a tool for that synthesis.

A high degree of discrimination of future risk is possible from only age, a casual systolic blood pressure measurement, a single serum
Table 3
Distribution of Individual Probability (P), of CHD by Any Criterion in 5 Years among Men in Europe Aged 40–59 Years and CHD-Free at the Start

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men at risk</td>
<td>873</td>
<td>873</td>
<td>872</td>
<td>873</td>
<td>873</td>
<td>873</td>
<td>873</td>
<td>873</td>
<td>872</td>
<td>873</td>
</tr>
<tr>
<td>Lowest P</td>
<td>0.0041</td>
<td>0.0138</td>
<td>0.0199</td>
<td>0.0235</td>
<td>0.0286</td>
<td>0.0344</td>
<td>0.0422</td>
<td>0.0518</td>
<td>0.0535</td>
<td>0.0941</td>
</tr>
<tr>
<td>Highest P</td>
<td>0.0138</td>
<td>0.0138</td>
<td>0.0235</td>
<td>0.0286</td>
<td>0.0344</td>
<td>0.0421</td>
<td>0.0518</td>
<td>0.0555</td>
<td>0.0941</td>
<td>0.7851</td>
</tr>
<tr>
<td>Sum of P</td>
<td>9.31</td>
<td>14.28</td>
<td>18.49</td>
<td>22.67</td>
<td>27.50</td>
<td>33.22</td>
<td>40.79</td>
<td>50.65</td>
<td>67.73</td>
<td>125.73</td>
</tr>
<tr>
<td>Cases</td>
<td>9</td>
<td>19</td>
<td>16</td>
<td>22</td>
<td>27</td>
<td>37</td>
<td>34</td>
<td>53</td>
<td>78</td>
<td>110</td>
</tr>
</tbody>
</table>

*Probability calculated with the following coefficients in the multiple logistic equation: alpha (the constant) = -11.3004; beta for age = 0.0648; beta for systolic blood pressure = 0.0196; beta for cholesterol = 0.0083; and beta for smoking = 0.0547.

Table 4
Prediction of Hard CHD (CHD Death or MI) in 5 Years among Men Aged 40–59 Years and CHD-Free at the Start in the Cohort under Study in Chicago by Dr. Oglesby Paul

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men at risk</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
<td>189</td>
</tr>
<tr>
<td>Lowest P</td>
<td>0.0018</td>
<td>0.0065</td>
<td>0.0093</td>
<td>0.0119</td>
<td>0.0147</td>
<td>0.0181</td>
<td>0.0223</td>
<td>0.0283</td>
<td>0.0372</td>
<td>0.0562</td>
</tr>
<tr>
<td>Highest P</td>
<td>0.0065</td>
<td>0.0093</td>
<td>0.0119</td>
<td>0.0147</td>
<td>0.0181</td>
<td>0.0223</td>
<td>0.0283</td>
<td>0.0372</td>
<td>0.0562</td>
<td>0.3771</td>
</tr>
<tr>
<td>Sum of P</td>
<td>0.004</td>
<td>1.509</td>
<td>1.985</td>
<td>2.498</td>
<td>3.190</td>
<td>3.786</td>
<td>4.726</td>
<td>6.089</td>
<td>8.759</td>
<td>18.944</td>
</tr>
<tr>
<td>Cases:*</td>
<td>Hard</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>A P</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

*Incidence of angina pectoris (A P) only, as well as of hard CHD.
†Probabilities calculated with multiple logistic solution for U. S. railroad men, coefficients being: alpha = -13.6427; beta for age = 0.0637; beta for systolic blood pressure = 0.0242; beta for cholesterol = 0.0091; and beta for smoking = 0.2367 (× 3 for nonsmokers, × 5 for less than 10 cigarettes per day, and × 7 for 20 or more per day).

cholesterol value, and an answer to a query about current cigarette smoking. Consider table 3, which deals with only those four variables. The multiple logistic solution assigned a probability of CHD (by any criterion) which ranged only from 4.1 to 13.8 chances per thousand among the 10% of the men at the low end of the distribution. Among those 873 men whose average probability of CHD in 5 years was calculated to be 10.7 chances in 1,000, the observed outcome was that CHD developed in nine men, making an incidence rate of 10.3/1,000. At the upper end of the distribution of risk were 873 men with calculated probabilities ranging from 94.1 to 185.1 chances in 1,000, the average being 144. In that group, 110 men developed CHD, giving an incidence rate of 126/1,000.

A physician or other health counselor, given a man's data on age, blood pressure, serum cholesterol, and smoking, can enter those numbers into the multiple logistic equation, together with the constant and the coefficients in table 2, and calculate his probability of developing CHD in 5 years. The answer would give guidance and perhaps persuasion about possible preventive measures as well as indicating a review of the patient's insurance policies. Actually, the calculation is exceedingly simple with modern programming calculators no bigger than a typewriter. When the coefficients are in storage, the time needed...
for the calculation is no longer than it takes to type the numerical data.

An example of application to a specific group of men is given in table 4, which concerns predictions of the incidence of CHD among Western Electric Company employees studied by Dr. Oglesby Paul in Chicago using for prediction the multiple logistic equation solution from data on CHD deaths and myocardial infarctions and on entry age, systolic pressure, cholesterol, and smoking of U. S. railroad men. The calculated probability of hard CHD in 5 years ranged from 1.8 to 37.7 chances per 1,000. The prediction was for 52.29 cases of hard CHD; in fact, 58 cases were observed, a difference that might easily be explained by some differences in ascertainment and details of diagnostic criteria, as noted earlier.

It was predicted that 81% of the cases in Dr. Paul’s series would be found in the top half of the probability distribution; 79% were actually observed there. It was predicted that the top quintile of P would contain 53% of the cases; 47% was the actual observation.

Table 4 also shows the distribution in Dr. Paul’s series of the cases of incidence of angina pectoris as the only evidence of CHD, in the decile classes of probability of CHD. The gradation of angina pectoris is not as steep as in the case of hard CHD, but the correlation is by no means negligible; r = 0.89, the Z transform being 1.42 with standard error of 0.38.

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References


Probability of Middle-Aged Men Developing Coronary Heart Disease in Five Years

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