Genetic–Epidemiologic Study of Early-onset Ischemic Heart Disease

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SUMMARY A genetic–epidemiologic study was undertaken of a white Colorado population of 207 patients who had a myocardial infarction before age 55 years. Nineteen independent variables were compared between the 207 cases and 621 controls, matched 3:1. The highest risk ratios were associated with a positive family history for ischemic heart disease (IHD). The heritability of IHD was 63% when families with the monogenic forms of hyperlipoproteinemia were included, and 56% when they were excluded. A risk index was developed that incorporates family history into a data base of risk factors, which can be readily assessed by the clinician obtaining a screening history, physical and standard laboratory tests. A scale of 0–10 was devised and the predictive value of the index was tested against another data set. The efficiency of the index was maximal at a screening level of 5. This study suggests that it is logistically feasible to seek patients at high risk for intensive management in a clinical setting (high-risk strategy) using risk indices similar to the one developed for this study, which emphasize the very important familial component to IHD.

THE CONCEPT that ischemic heart disease (IHD) is the product of genetic and environmental factors is generally accepted, but the relative contributions of heredity and environment have remained more obscure. Epidemiologic studies have provided risk figures for several environmental factors, but have not attempted to incorporate the family history into risk indices. In this study we assessed the relative contribution of the genetic history as a risk factor, among other risk factors. The study is not restricted to the genetic transmission of lipid and lipoprotein abnormalities. We have incorporated family history into a preliminary risk index to be used in a clinical setting, and attempted to evaluate the issue: Is a high-risk strategy for prevention of IHD a practical option?

Patients and Methods

Our cases were 207 patients who had sustained and survived myocardial infarction at ages 35–54 years. Diagnosis of infarction was made by traditional clinical, electrocardiographic and enzymatic methods. Thirty-three white women and 174 white men were referred to us in three community hospitals and the University of Colorado Medical Center. The stated reason for recruitment of patients into the study was to assess risk factors in subjects who have heart attacks at younger ages. The 207 patients constitute a convenience sample about which there was no prior knowledge concerning specific risk factors. Age of onset of the heart disease was the single specified determinant for entry. The intake period for this study began in January 1976.

A control group of 621 subjects was matched 3:1 with the patients for age, sex and race. These subjects were drawn from over 3000 subjects who were self-referred to two community-wide heart disease screening programs in which our group participates. On the basis of the screening evaluation, all control subjects were judged to be free of IHD before and at the time of intake.

All subjects completed a questionnaire and were examined according to a protocol that obtained height (without shoes), weight (in indoor clothing), blood pressure and fasting cholesterol and triglycerides. Certain data were obtained in one group and not the other. Information on juvenile diabetes and hypertension in first-degree relatives and IHD in second-degree relatives was called for in the protocols of patients with infarcts, but only in the protocol of one of the screening programs. Therefore, these three factors were compared in a subset of only 140 patients matched 1:1 with controls of the same age, sex and race.

Lipid and lipoprotein determinations were performed in our laboratory by the methods outlined for the Lipid Research Clinics Program. Blood pressures were taken according to the protocol of the Pooling Project Research Group, except that diastolic pressure was taken as the abrupt muffling of sound (phase IV). The threshold for diagnosis of hypertension in a patient or first-degree relative was 140/90 mm Hg. Only first-degree relatives 12 years and older were included in the family study because a blood pressure of this level is not found as a ninety-fifth percentile discriminant until this age. Relative weight was determined according to published standards of the Metropolitan Life Insurance Company.

The self-administered questionnaires were designed to cover a priori risk factors that have been implicated in IHD in previously published studies, as well as potential risk factors that were proposed for this investigation. The format of the questionnaire permitted direct transcription to computer keypunch cards, but
also included spaces for narrative regarding diet, exercise, stress and behavior that were interpreted by a physician who read the responses and coded the risks.

Nineteen independent variables were checked against the dependent variable, myocardial infarction. Differences between the patients and controls were analyzed by chi-square and risk ratios (relative risk or odds ratio) were calculated by the standard method of the dividend of the cross products of a $2 \times 2$ contingency table. Heritability of liability was calculated by the method of Falconer. The monogenic forms of lipoproteinemia were segregated by clinical profile and family studies that revealed distinct bimodality. Sensitivity (Se) was taken as true positives (TP) divided by true positives plus false negatives (FN). Specificity (Sp) was determined by dividing true negatives (TN) by the sum of true negatives and false positives (FP). Efficiency was found by dividing the sum of true positives and true negatives by the grand total.

## Results

The mean ages of the patients were 46.2 years for men and 49.7 years for women. Thirty-one probands were identified as having single-gene forms of lipoproteinemia. Table 1 displays the risk factors in descending order of risk ratio. The highest risk ratio (10.4) is associated with family history of a first-degree relative who has the onset of IHD before age 55 years and the next highest, IHD in a first-degree relative before age 65 years (RR = 7.1). A serum of plasma cholesterol greater than 270 mg/dl had a risk ratio of 4.3. This level of 270 mg/dl corresponds to the highest quintile in the study of the Pooling Project Research Group. Cholesterol > 240 mg/dl corresponds to the two highest quintiles and > 220 mg/dl to the three highest quintiles. The risk ratio and significance decreased at each level of cholesterol, but a statistically significant difference was observed at all three levels between patients and their controls.

Cigarette smoking (more than a half pack per day at the time of infarction) was almost twice as frequent in the patient group as among controls. The level of more than a half pack appeared from the data of the Pooling Project to represent a useful discriminating threshold. The presence of juvenile diabetes in a first-degree relative provided a higher risk ratio than the actual presence of diabetes in the patient himself, but was based on fewer cases and had a similar $p$ value (< 0.05). Diabetes in a first-degree relative or in the patient himself were tentatively taken as equivalent risks. Exercise deficiency is displayed as the inverse of the question regarding adequacy of exercise (in order to provide a risk ratio). The judgment of adequacy was made by a physician reviewing the written report and narrative provided by the subject on the questionnaire. More than 1 hour per week of sustained, rhythmic, aerobic exercise divided into at least three periods no more than 2 days apart was the minimum level accepted for adequate exercise. In the control

### Table 1. Independent Variables in Patients with Early-onset Ischemic Heart Disease Compared with Matched Controls and Presented in the Descending Order of Risk Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
<th>%</th>
<th>Controls</th>
<th>%</th>
<th>Risk Ratio</th>
<th>$p &lt;$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD—1° relatives younger than 55 years</td>
<td>99/207</td>
<td>48</td>
<td>50/621</td>
<td>8</td>
<td>10.4</td>
<td>0.001</td>
</tr>
<tr>
<td>IHD—1° relatives younger than 65 years</td>
<td>126/207</td>
<td>61</td>
<td>112/621</td>
<td>18</td>
<td>7.1</td>
<td>0.001</td>
</tr>
<tr>
<td>J. diabetes—1° relative</td>
<td>9/140</td>
<td>6</td>
<td>2/140</td>
<td>1</td>
<td>4.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholesterol &gt; 270 mg/dl</td>
<td>50/207</td>
<td>24</td>
<td>43/621</td>
<td>7</td>
<td>4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking &gt; ½ pack/day</td>
<td>141/207</td>
<td>68</td>
<td>217/621</td>
<td>35</td>
<td>4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke—1° relatives younger than 55 years</td>
<td>10/207</td>
<td>5</td>
<td>9/621</td>
<td>1</td>
<td>3.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Exercise deficiency</td>
<td>199/207</td>
<td>96</td>
<td>546/621</td>
<td>88</td>
<td>3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (in patient)</td>
<td>12/207</td>
<td>6</td>
<td>14/621</td>
<td>2</td>
<td>2.7</td>
<td>0.05</td>
</tr>
<tr>
<td>IHD-2° relatives younger than 65 years</td>
<td>59/140</td>
<td>42</td>
<td>32/140</td>
<td>23</td>
<td>2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Cholesterol &gt; 240 mg/dl</td>
<td>77/207</td>
<td>96</td>
<td>130/621</td>
<td>21</td>
<td>2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>BP ≥ 160/100 mm Hg</td>
<td>44/207</td>
<td>21</td>
<td>81/621</td>
<td>13</td>
<td>1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Hypertension—1° relative</td>
<td>41/140</td>
<td>29</td>
<td>26/140</td>
<td>19</td>
<td>1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Cholesterol &gt; 220 mg/dl</td>
<td>120/207</td>
<td>58</td>
<td>304/621</td>
<td>49</td>
<td>1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke—1° relatives younger than 65 years</td>
<td>25/207</td>
<td>12</td>
<td>43/621</td>
<td>7</td>
<td>1.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Type A behavior</td>
<td>56/207</td>
<td>27</td>
<td>124/621</td>
<td>20</td>
<td>1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Triglycerides &gt; 200 mg/dl</td>
<td>47/207</td>
<td>23</td>
<td>99/621</td>
<td>16</td>
<td>1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>BP ≥ 140/90 mm Hg</td>
<td>60/207</td>
<td>27</td>
<td>138/621</td>
<td>22</td>
<td>1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Imprudent diet</td>
<td>155/207</td>
<td>75</td>
<td>422/621</td>
<td>68</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Relative weight &gt; 1.20</td>
<td>83/207</td>
<td>40</td>
<td>211/621</td>
<td>34</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Relative weight &gt; 1.20 excluding monogenic cases</td>
<td>80/176</td>
<td>45</td>
<td>174/621</td>
<td>33</td>
<td>1.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: IHD = ischemic heart disease; 1° = first degree; 2° = second-degree; J. diabetes = juvenile-onset diabetes; BP = blood pressure.
group, 12% of the subjects were achieving this level, while in the patient group only 4% were exercising this actively at the time of infarction.

Other findings from the family history and examination that appeared to offer promise in constructing risk formulas included history of stroke in first-degree relatives (RR = 3.5), history of IHD in second-degree relatives (RR = 2.4), and evidence of hypertension in first-degree relatives (RR = 1.8). The latter two observations could be useful in risk predictions for children. The strategy of initiation of preventive measures in high-risk pediatric patients cannot wait until the occurrence of IHD in first-degree relatives, because by the time a parent infarcts in his forties his children are likely to have already reached adulthood.

The risk ratio for systolic blood pressure higher than 160 mm Hg or diastolic pressure higher than 100 mm Hg was below 2 (1.8), but was significantly different ($p < 0.01$) in patients with infarcts compared with their controls. The difference was less but still significant ($p < 0.05$) at the level of 140/90 mm Hg (RR = 1.4).

Type A behavior was judged by a physician from the checked responses and the narrative report in the questionnaire on a scale of 1-4 for A to B. There was no significant difference if grades 1 and 2 (tendency to type A) were compared with grades 3 and 4 (tendency to type B). However, when comparing the extremes, grade 1 with grade 4, a difference was noted at the 0.05 level, and a risk ratio of 1.5 was calculated. Similarly, there was no difference between the two groups in triglycerides at 140 mg/dl, but a difference appeared at 200 mg/dl ($p < 0.05$).

Comparing the relative weight $> 1.20$ between the two groups, we could not find a significant difference. This finding seemed to contradict clinical experience but was compatible with what has been found in the older patients by the Pooling Project Research Group. However, the profile of a patient with monogenic hyperlipoproteinemia includes a diminished responsiveness to dietary intervention. Our monogenic patients with high lipids and lipoproteins were seldom overweight. Deleting the 31 monogenic patients from the group unmasked the increased risk (RR = 1.7; $p < 0.01$) with obesity that is traditionally associated with IHD and lipid abnormalities of the multifactorial inheritance type. Relative weight thus appears to be a valid risk factor in the majority of cases, but is not applicable in subjects who have a single-gene lipoproteinemia.

Dietary history is difficult to obtain as a screening procedure or in the usual physician-patient encounter. The protocol for this study was either inadequate to determine a difference in diet between the two groups, or a significant difference did not actually exist. We suspect that the former explanation is correct. If genetic hyperresponders to dietary challenge can be segregated, a convincing difference may be demonstrable.

High-density lipoproteins (HDL) would be predicted to provide useful additional information on risk. Because the more laborious ultracentrifugation may not be essential in preliminary screening determinations, the simpler biochemical test for HDL cholesterol is now part of our community screening program. During the intake period for the majority of patients in this study, $\alpha$ lipoproteins were taken as the more practical screening procedure. Some differences in $\alpha$ lipoproteins were found between the two groups, but are not discussed because the data are incomplete.

Heritability for early-onset IHD had to take into account that first-degree relatives should have reached ages when clinical manifestations appear. The midpoint of the age range (35-54 years) of the patients with infarcts was taken as the lower limit for a negative history of IHD. Clearly, infants, children and young adults who are first-degree relatives of probands with early-onset IHD cannot be entered into the data base for heritability calculations. Another subset of subjects who may be eliminated from such calculations are those with demonstrable monogenic heart disease associated with a hyperlipoproteinemia. Heritability for early-onset IHD, based on the data from all 207 families, was calculated as 0.63. Heritability after eliminating the 31 monogenic families was 0.56.

**Genetics**

Even after eliminating the families with apparent monogenic hyperlipoproteinemia, the heritability in our study of IHD that produced myocardial infarction before 55 years of age is 56% — that is, the contribution of heredity (as calculated in this study) appears to exceed the contribution of the environment. This observation must be considered in etiologic studies, risk index development and in strategies of prevention.

Falconer's model\(^3\) and Edwards' model\(^4\) of multifactorial inheritance are based on a continuous distribution of liability to a disease. The model of Morton et al.\(^5\) proposes that diseases attributed to multifactorial inheritance are caused by the small effects of many genes in most cases, but in a smaller number of cases are determined by single genes of large effect. We applied such a model to congenital heart disease\(^6\) and find it even more applicable to IHD.

Although the frequency rate of monogenic forms of hyperlipoproteinemias is apparently small in the general population — less than 1% — it is relatively high among patients with early-onset IHD. In our study, 15% of patients 35-54 years of age who survived myocardial infarction had a monogenic disorder. Goldstein and co-workers\(^7\) calculated that 20% of their patients who had myocardial infarcts before 60 years of age had a hyperlipoproteinemia of single-gene etiology. The evidence is convincing that among patients with liability to IHD there are single major gene influences. Interest has centered on monogenic disorders of lipid metabolism, yet there is no reason to believe that major gene influences are confined to lipid pathways. In our series, the risk ratio is greater for family history of IHD than for the highest quintile of cholesterol levels. In fact, the majority of subjects who
have myocardial infarctions are in the second, third, and fourth quintiles for cholesterol, as are the majority of subjects who do not have IHD. Of course, these quintiles for cholesterol in the United States and Northern Europe yield levels above the highest quintile in many other countries and societies.

It is useful to segregate those groups in which a specific etiologic mode has been demonstrated. The monogenic hyperlipoproteinemias represent a category that may be segregated from the heterogeneous population of IHD. Genetic studies emphasize the clinical profiles of these patients, but the usual epidemiologic study does not. We recognized 31 patients who had monogenic hyperlipoproteinemias: 10 had familial hypercholesterolemia, eight had familial triglyceridemia, and 13 had familial combined hyperlipidemia. Family studies and lipoprotein analyses in the control group were confined to those in which a hyperlipidemia was detected by screening. The number of probands in the control group who had monogenic hyperlipidemia was so small as to make the calculation of risk ratios unrealistic. No type IIa hypercholesterolemia subjects were encountered among the controls, and only two type IIb and three type IV control subjects were discovered.

From this modest data base we propose that genetic factors in IHD have not received enough emphasis in traditional epidemiologic studies. Analyzing risk factors such as smoking, diet, obesity, cholesterol and hypertension as if they were independent of hereditary predisposition may be misleading. IHD is familial, and the contribution of heredity appears to exceed that of environment based on heritability as calculated in this study. How environmental risks interact with hereditary predisposition is an appropriate area for investigation. In terms of clinical management of individual patients and families at risk, it will become more important to define the pathogenetic components of the disease and the predisposition. Then the specific metabolic, immunologic or coagulation diathesis may receive selective and intensive therapeutic intervention and be subjected to genetic analysis of the separate factors in a given subject.

### Table 2. Risk Index (Maximum Score = 10)

<table>
<thead>
<tr>
<th>Family history</th>
<th>Lipids</th>
<th>Other risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD 1° &lt; 55 = 3</td>
<td>Cholesterol &gt; 270 = 2</td>
<td>Smoking = 1.5</td>
</tr>
<tr>
<td>IHD 1° &lt; 65 = 2.5</td>
<td>Cholesterol &gt; 240 = 1</td>
<td>Diabetes = 1</td>
</tr>
<tr>
<td>IHD 2° &lt; 65 = 1</td>
<td>Cholesterol &gt; 220 = 0.5</td>
<td>No exercise = 1</td>
</tr>
<tr>
<td>Stroke 1° &lt; 55 = 1</td>
<td>Triglycerides &gt; 200 = 0.5</td>
<td>BP &gt; 140/90 = 0.5</td>
</tr>
<tr>
<td>Stroke 1° &lt; 65 = 0.5</td>
<td>(Select highest single cholesterol plus triglyceride value to a maximum of 2 for this column)</td>
<td>Relative wt &gt; 1.20 = 0.5</td>
</tr>
<tr>
<td>(Select highest value in this column)</td>
<td></td>
<td>Type A = 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Add all values in this column)</td>
</tr>
</tbody>
</table>

Abbreviations: IHD = ischemic heart disease; 1° = first-degree relative; 2° = second-degree relative; BP = blood pressure.
twofold risk over the prior probability in the population. A risk score of 4.5 carries a prediction of a sixfold increase in risk over the general population risk; 5 is a fifteenfold increase; and at 5.5, where the specificity becomes 100%, the curve becomes asymptotic and the resultant projection reaches \( \infty \).

For screening in the clinical setting the level of 5 would be recommended as most efficient. For management of risk factors in a program of prevention, there is a twofold increase in risk even at as low a level as 3. An obvious goal would be to lower the risk score in a given patient as far as can be achieved.

The development of this risk index from a small data base and its subsequent testing in an even smaller population must be taken only as a feasibility study. Another data base with the same independent variables or additional variables may produce a risk index of greater sensitivity and efficiency and possibly less redundancy. We see opportunity for refinement within our own projected studies. Certainly, larger numbers of cases and matched controls for the three variables in which we had only 140 subjects in each group would be valuable. Our study could advantageously be replicated with 300-400 consecutive or randomized cases with controls in which there would be additional variables such as inherited clotting factors, B-cell and T-cell types, more precise dietary information, and extended information on second-degree relatives, as well as a weighting system to take into account the number of affected family members. We are currently incorporating this risk index into clinical practice with the clear recognition that an index derived in this study or in subsequent studies would still require testing of sensitivity, specificity and efficiency in other populations. The ultimate test would, of course, be a prospective study, but the active intervention in risk factors taking place in Western industrialized countries would most likely contravene the predictions.

### Implications for High-risk vs Low-risk Strategies of Prevention

Low-risk strategies, advocating changes in lifestyle, diet, exercise and smoking habits suitable for the entire population, are being implemented. We would attribute much of the declining mortality from cardiovascular diseases during the past decade to these low-risk strategies. The experience in North Karelia, Finland — the area of highest cardiovascular mortality in the world — supports the concept of population-wide attack on risk factors. Just 5 years after its inception, the program in Finland has been associated with a 20% decline in deaths from myocardial infarctions.\(^9\)

One argument against deliberately seeking those at highest risk (high-risk strategy) has been based on the inability of present methods to detect such patients, and the unfavorable cost-benefit ratio in case-finding. We believe our data support what experienced clinicians have long appreciated: IHD is familial and cardiovascular diseases cluster in high-risk families. A reasonable extension of this observation is to develop methods that are readily applicable to a clinical setting to identify high-risk individuals and families. These individuals and families are most in need of, and will benefit most from, aggressive medical management of risk factors, including intensive pharmacologic and physiologic programs of intervention. The awareness of the familial nature of IHD is becoming so prevalent in the public sector that there is frequently insistence on the part of family members for risk evaluation after a coronary event in a close relative. Logistically, this is an ideal time to screen high-risk individuals.

Lifestyle modification is an excellent first step in reducing mortality and morbidity from cardiovascular disease. A further step, the deliberate seeking for intensive management of those at high risk, using a genetic-epidemiologic data base and risk index of the type we have presented, appears to be a practical option in routine clinical care.

### References

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Clinical Judgment and Statistics
Lessons from a Simulated Randomized Trial in Coronary Artery Disease

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PHILIP J. HARRIS, M.B., D.PHIL., AND ROBERT A. ROSATI, M.D.

SUMMARY A simulated randomized clinical trial in coronary artery disease was conducted to illustrate the need for clinical judgment and modern statistical methods in assessing therapeutic claims in studies of complex diseases. Clinicians should be aware of problems that occur when a patient sample is subdivided and treatment effects are assessed within multiple prognostic categories. In this example, 1073 consecutive, medically treated coronary artery disease patients from the Duke University data bank were randomized into two groups. The groups were reasonably comparable and, as expected, there was no overall difference in survival. In a subgroup of 397 patients characterized by three-vessel disease and an abnormal left ventricular contraction, however, survival of group 1 patients was significantly different from that of group 2 patients. Multivariable adjustment procedures revealed that the difference resulted from the combined effect of small imbalances in the distribution of several prognostic factors. Another subgroup was identified in which a significant survival difference was not explained by multivariable methods.

These are not unlikely examples in trials of a complex disease. Clinicians must exercise careful judgment in attributing such results to an efficacious therapy, as they may be due to chance or to inadequate baseline comparability of the groups.

CLINICAL JUDGMENT in chronic illness involves a knowledge of the natural history of the disease, the ability to assess the validity of therapeutic claims and a means of applying what is known to the individual patient. Much has been written about the natural history of angina pectoris. The literature has emphasized the importance of multiple factors in determining outcome and of the heterogeneity of patients grouped together under the diagnosis of angina pectoris. This complexity makes the clinician's task of interpreting therapeutic claims particularly difficult. In this paper, a simulated randomized clinical trial in patients with coronary artery disease is presented to illustrate the effects that the heterogeneity of patients with angina pectoris may have on the results of clinical experiments. The role of statistics and clinical judgment in solving the problems encountered is explored. The randomized design is used because it represents the ideal method of treatment allocation in clinical experiments. The problems and the approaches to their solutions apply equally well to both randomized and nonrandomized clinical studies.

Methods

The subjects in this simulated trial consisted of the medically treated patients with angiographically proved coronary artery disease contained in the Duke University data bank. The data bank has been described previously. Briefly, baseline historical, physical examination, laboratory, electrocardiographic, stress test, chest x-ray, angiographic data and follow-up information on 1073 medically treated
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