Total Cholesterol and Lipoproteins in School Children: Prediction of Coronary Heart Disease in Adult Relatives

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SUMMARY The distribution of risk factors and the prevalence of coronary heart disease (CHD) were studied in 850 first- and second-degree relatives of 98 healthy index cases selected from 3666 school children surveyed for lipid levels in Rochester, Minnesota. Three groups of families were based on an index child's total plasma cholesterol level: 18 families with a child in less than the fifth percentile (low-cholesterol group), 47 with a child in the fifth to ninety-fifth percentiles (middle-cholesterol group) and 33 with a child in greater than the ninety-fifth percentile (high-cholesterol group). The children's cholesterol levels clustered with those of their relatives; mortality due to CHD before age 65 was increased by 2.5 times in grandfathers of index cases in the high-cholesterol group compared with those of the middle-cholesterol group (p < 0.016). The prevalence of CHD in all the grandfathers was associated with an index child's total cholesterol, more strongly associated with an index child's low-density lipoprotein cholesterol level and most strongly associated with an index child's high-density lipoprotein cholesterol level as a fraction of total cholesterol. This study establishes that childhood lipid and lipoprotein levels from a single cross-sectional survey identify families at elevated risk for CHD.

ATHEROSCLEROSIS underlies most coronary heart disease (CHD), but is difficult to study because a large proportion of the population with affected arteries has no easily detected manifestation of the disease. As a consequence, much of the emphasis in studies of CHD has been on the analysis of factors thought to be pathogenic. Goldstein et al. reported lipid abnormalities in 60% of a sample of men younger than 40 years of age and women younger than 50 years of age with myocardial infarction (MI). Heterozygous parents of children with one type of familial hypercholesterolemia have early onset of CHD while children who are homozygous often suffer a fatal MI before age 20 years. In a community-wide study, the rate of a first major coronary event in white adult males during a 10-year follow-up increased uniformly with an increase in initial cholesterol levels. Both the low-density lipoprotein (LDL) and high-density lipoprotein (HDL) fractions of serum cholesterol are stronger predictors of CHD in men older than age 50 years than is total cholesterol. Although an elevated LDL level appears to be atherogenic, an elevated HDL level may be antiatherogenic. Studies in children have provided frequency distributions of lipids and lipoproteins by age and sex and evidence that a person's cholesterol levels measured 2
years apart are highly correlated \((r = 0.6)\). Because atherosclerosis is a life-long process that begins in the first decade of life,\(^1\) it would be of interest to determine the value of a child’s serum lipid levels for predicting his or her risk of developing CHD. Such a determination would require a prospective study of several decades, but by studying the risk factor levels and the disease experience of adult relatives, one can test the hypothesis that elevated childhood levels of cholesterol are associated with increased coronary artery morbidity and mortality in their families. This hypothesis is supported by the evidence that lipid and lipoprotein levels aggregate in families regardless of ages studied\(^9,10\) and that first-degree relatives of adults with CHD have a 2.5- to 7-fold increase in the risk of early coronary death compared with relatives of controls.\(^11-14\)

In a recent study in Muscatine, Iowa,\(^15\) children with cholesterol levels above the ninety-fifth percentile in successive surveys 2 years apart identified adult relatives with a twofold excess of coronary mortality compared with relatives of children with cholesterol levels less than the ninety-fifth percentile in the same two surveys.

To confirm the generality of these findings, we ascertained 98 families in Rochester, Minnesota through school children with either elevated, normal or low total cholesterol levels. These families were studied to determine whether differences in total cholesterol levels in children from a single cross-sectional survey are predictive of differences in risk factor levels and disease experience in their adult relatives. In addition, the value of LDL and HDL cholesterol levels in children as predictors of CHD was evaluated.

**Materials and Methods**

**School Survey**

A survey of 5732 children attending Rochester schools was carried out in 1973 and 1974. Of 2939 boys contacted, 1857 (63.2%) participated in the survey; of 2793 girls contacted, 1809 (64.8%) participated. Nonparticipation was usually the result of absence from school because of illness or vacation. Examinations were carried out in the schools, early in the morning, after an overnight fast. Height, weight, triceps skinfold and blood pressure were measured before venipuncture. Cholesterol and triglyceride levels were measured for all participants; lipoprotein fractions were measured in 2421 of the 3666 children who agreed to participate. The specific laboratory methods, age and sex distributions for lipids and lipoprotein fractions, and the prevalence of different hyperlipoproteinemias are presented elsewhere.\(^16\) The precision of the measurements was ensured by the participation of the Mayo Clinic Specialized Center on Research Lipid Laboratory in the Center for Disease Control Cooperative Lipid Standardization Program.

**Family Selection**

Almost all medical care in Rochester is provided by the Mayo Clinic and the Olmsted Medical and Surgical Group. Medical records were reviewed and children with illness, those receiving medications that could secondarily affect serum lipid levels, and adoptees were excluded as possible index cases. From those eligible, 100 unrelated white children, ages 6–16 years, were selected as index cases. Families invited to participate were informed only of the relationship between adult lipid levels and atherosclerosis as well as the aims of the study, but not the child’s lipid levels. Among the 98 who agreed to participate, 33 had total serum cholesterol levels above the ninety-fifth percentile for their age and sex (the high-cholesterol group), 18 children had cholesterol levels below the fifth percentile (the low-cholesterol group) and 47 children had levels between the fifth and ninety-fifth percentile (middle-cholesterol group). Seventy-two index children also participated in a separate study of nutrient intake in which a 7-day diet diary was recorded by each child’s mother.\(^17\) Lipoprotein levels were measured in 58 of the 98 index children. The subgroups of children in the low-, middle- and high-cholesterol groups in which nutrition or lipoprotein measurements were made were representative of all index cases in those groups.

The 392 grandparents, 196 parents and 279 full siblings of the index cases were identified. No information was available on 17 persons. Of those remaining, 692 were living at the time of the study and 586 of these were examined at the Mayo Clinic. Among the others, three were former clinic patients for whom records were available and 103 (including 90 grandparents) supplied information by mail. Of the 158 deceased persons, 35 were former Mayo Clinic patients for whom records were available. Information on the remaining 123 was obtained by mail from the closest relative. In all, autopsy reports were obtained on 57 persons and the death certificates of the 101 others were reviewed. Medical histories were obtained on 99% of the parents, 99.6% of the siblings and 96.4% of the grandparents. Risk factor measurements, including serum cholesterol and triglycerides, blood pressure, plasma glucose levels, and body mass index (weight/height\(^2\)), were obtained on 98% of the parents, 96% of the siblings, 79% of the grandmothers and 47% of the grandfathers.

**Adjustment of Data and Definition of Disease**

Since the distributions of birth years and age at examination for each type of relative were not significantly different among the low-, middle- and high-cholesterol groups, the years at risk were considered similar and no age or time standardizations were considered necessary for risk factors, morbidity or mortality data. Standardization of lipid and lipoprotein measures was considered necessary for the index children because they were selected on the basis of their deviation from the mean cholesterol for their age and sex and because standardized predictor variables aid in the interpretation of different logistic models.\(^18\) A standardized value was defined as the difference between the raw value and the age- and sex-specific mean divided by the age- and sex-specific standard deviation.
The means and standard deviations were based on the sample of 3666 children screened in Rochester. The age intervals were 1 year. The presence of diabetes or hypertension was accepted if the subject was receiving appropriate drug therapy. The presence of MI was accepted if documented by an ECG. Angina, coronary insufficiency or intermittent claudication was accepted if diagnosed by a physician. A person was considered to have died from CHD if CHD was listed as the primary cause of death in the autopsy report or on the death certificate and was corroborated by the medical history.

**Statistical Methods**

We tested the hypothesis that the proportions of adults with different clinical manifestations of atherosclerosis were the same in the low-, middle- and high-cholesterol groups. Similar hypotheses for the proportions deceased and with specific causes of death were also tested. The null hypothesis of equality of mean levels of a risk factor in the three groups of relatives identified by the index child's cholesterol level was tested against the alternative that at least one group has a different mean from at least one other group using the nonparametric Kruskal-Wallis test.

Unless otherwise noted, the statistical contrasts reported in the results section were considered to be significant when the observed differences would have occurred by chance alone less than 5% of the time. When significant differences were detected among the low-, middle- and high-cholesterol groups in an overall test procedure, the three pairwise comparisons were made. In these *a posteriori* tests, a contrast was considered to be significant when the observed difference would have occurred by chance alone less than 1.6% of the time.

A multiple logistic regression model was applied to estimate the contribution of variability in different lipid and lipoprotein levels among index children to the prediction of CHD in grandparents. Under this model, the predicted probability of CHD as a function of K independent variables is estimated by

\[
P(\text{CHD}) = \frac{\exp(b_0 + \sum_{i=1}^{K} b_i X_i)}{1 + \exp(b_0 + \sum_{i=1}^{K} b_i X_i)}
\]

where \(b_i\) is the logistic regression coefficient for the \(i^{th}\) independent variable (e.g., LDL or HDL) and is used to compute an odds ratio for CHD per unit change in that independent variable. The intercept \(b_0\) provides a calibration of the model to give an approximate level of risk consistent with that observed in this sample. The \(b_i\)'s and \(b_0\) are estimated using the maximum likelihood method, which allows testing of the hypothesis that a specific \(b_i\) is significantly different from zero. The hypothesis test is based on the likelihood ratio criterion.

A comparison of the chi-square values associated with the likelihood ratios of different models having the same number but different specific independent variables provides a measure of the relative fit of these different models to the data. The fraction of variability in CHD among grandparents explained by the logistic regression \(R^2\) is reported as a measure of how well different models discriminate between those who have CHD and those who do not. The values of \(R^2\) can only be used as a guide to assess the relative strength of the relationship between different combinations of risk factors and CHD because appropriate probability levels cannot be assigned to \(R^2\) in logistic regression.

**Results**

Table 1 presents a summary of the characteristics of the 98 index children. The three groups were significantly different only for mean levels of total cholesterol, HDL and LDL cholesterol, total triglyceride and LDL triglyceride. Assessment of daily nutrient information reported in the diet diaries indicated no differences among the three groups for the intake of total calories, saturated fat, simple carbohydrates, total protein or dietary cholesterol.

Mean serum cholesterol levels in both siblings and parents of low-, middle- and high-cholesterol index cases showed significant stepwise differences (table 2). There were no significant differences among the three groups of parents for serum triglycerides, blood pressure, glucose levels or body mass index. Siblings of the high-cholesterol index cases had significantly higher mean levels of serum triglycerides and systolic blood pressure than the siblings of low-cholesterol cases. Among the three groups of living grandparents, there were no significant differences in mean levels of serum cholesterol, triglycerides, blood pressure, plasma glucose levels and body mass index. Each of the contrasts among the low-, middle- and high-cholesterol groups was consistent when male and female siblings, parents, or grandparents were considered separately.

The prevalence of disease among all the parents was low. One father in the high-cholesterol group and two fathers in the middle-cholesterol group were hypertensive; one father in the high-cholesterol group had an MI. One mother in the low-cholesterol group had cerebrovascular disease; one mother in the high-cholesterol group and two mothers in the middle-cholesterol group had angina. The percentages of living grandparents with coronary insufficiency, intermittent claudication, MI, cerebrovascular disease, diabetes or hypertension were not significantly different among groups identified by the low-, middle- and high-cholesterol children. Among the grandparents of high-cholesterol children, angina was significantly more common than among the grandparents of low-cholesterol children (21.1% and 5.3%, respectively). Although there were no significant differences in prevalence of MI among groups, the mean age at first MI was 62.3 years and 56.8 years for grandfathers of middle- and high-cholesterol index children, respectively, which suggests earlier CHD morbidity for living grandfathers of high-cholesterol children.

The overall death rate for grandfathers of high-cho-
Table 1. Characteristics of Index Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>47</td>
<td>33</td>
</tr>
<tr>
<td>Male/female</td>
<td>8/10</td>
<td>19/28</td>
<td>14/19</td>
</tr>
<tr>
<td>Age (years)</td>
<td>11.2 ± 2.5</td>
<td>10.2 ± 2.4</td>
<td>10.7 ± 2.6</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>103.0 ± 11.6*</td>
<td>172.4 ± 20.7</td>
<td>236.9 ± 37.9*</td>
</tr>
<tr>
<td>High-density</td>
<td>38.7 ± 10.2†</td>
<td>50.6 ± 11.0</td>
<td>54.9 ± 15.7</td>
</tr>
<tr>
<td>Low-density</td>
<td>49.9 ± 13.3*</td>
<td>110.7 ± 19.2</td>
<td>169.4 ± 42.4*</td>
</tr>
<tr>
<td>Very low density</td>
<td>12.7 ± 10.9</td>
<td>12.6 ± 12.4</td>
<td>15.2 ± 9.1</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>58.1 ± 31.8†</td>
<td>67.5 ± 35.5</td>
<td>85.2 ± 45.8</td>
</tr>
<tr>
<td>High-density</td>
<td>9.2 ± 3.3</td>
<td>8.3 ± 2.6</td>
<td>9.5 ± 2.7</td>
</tr>
<tr>
<td>Low-density</td>
<td>16.6 ± 10.7†</td>
<td>17.2 ± 5.1†</td>
<td>24.7 ± 8.8</td>
</tr>
<tr>
<td>Very low density</td>
<td>41.4 ± 31.4</td>
<td>39.4 ± 30.3</td>
<td>50.8 ± 33.1</td>
</tr>
<tr>
<td>BMI (weight/height²)</td>
<td>18.6 ± 2.4</td>
<td>17.8 ± 2.5</td>
<td>18.6 ± 2.5</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>13.0 ± 4.9</td>
<td>11.5 ± 6.1</td>
<td>14.5 ± 7.6</td>
</tr>
<tr>
<td>Total calories/day</td>
<td>2158 ± 321</td>
<td>2157 ± 471</td>
<td>2030 ± 415</td>
</tr>
<tr>
<td>Saturated fat (g% calorie)</td>
<td>34 ± 11</td>
<td>35 ± 11</td>
<td>32 ± 9</td>
</tr>
<tr>
<td>Simple carbohydrates (g% calories)</td>
<td>137 ± 39</td>
<td>144 ± 41</td>
<td>139 ± 33</td>
</tr>
<tr>
<td>Total protein (% calories)</td>
<td>77 ± 14</td>
<td>79 ± 20</td>
<td>79 ± 22</td>
</tr>
<tr>
<td>Dietary cholesterol (mg)</td>
<td>306 ± 74</td>
<td>311 ± 106</td>
<td>300 ± 83</td>
</tr>
</tbody>
</table>

*p < 0.016 vs middle group.
†p < 0.016 vs high group.

Abbreviation: BMI = body mass index.

Lester index cases was significantly higher than the rate for grandfathers of middle-cholesterol children (table 3). The most frequent primary cause of death for both grandfathers and grandmothers in all three groups was CHD, with the exception of the grandmothers in the low-cholesterol group. These grandmothers had the highest frequency of death due to diseases not related to CHD, cerebrovascular disease or malignancy. Among all groups, seven full siblings had died of causes unrelated to CHD or cerebrovascular disease.

There were no significant differences among the three groups of grandfathers for the relative frequency of death due to CHD, although the grandfathers of high-cholesterol children had the highest frequency (table 4). The relative frequency of CHD deaths among grandfathers of high-cholesterol index cases was significantly higher than that among grandfathers of middle-cholesterol children. The mean age at death for grandfathers who died from CHD showed a stepwise difference among the three groups (67.3, 64.2 and 62.6 years for low-, middle- and high-cholesterol groups, respectively). Death from CHD before age 65 years occurred two and a half times more frequently in the grandfathers of high-cholesterol children than in grandfathers of middle-cholesterol children.

Table 2. Age at Examination and Cholesterol and Triglyceride Levels in Living Relatives

<table>
<thead>
<tr>
<th>Relationship to index case</th>
<th>Cholesterol level</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full siblings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>57</td>
<td>94</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>13.2 ± 5.8</td>
<td>14.6 ± 6.6</td>
<td>14.3 ± 6.3</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>145.1 ± 32.7*</td>
<td>167.5 ± 29.4</td>
<td>200.7 ± 50.6*</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>66.5 ± 31.3†</td>
<td>73.2 ± 42.4</td>
<td>84.0 ± 42.0</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>35</td>
<td>94</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.9 ± 7.6</td>
<td>39.9 ± 5.9</td>
<td>41.4 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>169.4 ± 31.3*</td>
<td>214.2 ± 34.5</td>
<td>241.8 ± 54.6*</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>102.5 ± 55.5</td>
<td>121.6 ± 65.9</td>
<td>116.8 ± 68.2</td>
<td></td>
</tr>
<tr>
<td>Grandparents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>125</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.6 ± 9.7</td>
<td>67.5 ± 9.3</td>
<td>66.8 ± 9.5</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>231.3 ± 44.5</td>
<td>242.4 ± 45.9</td>
<td>248.1 ± 49.0</td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>136.3 ± 67.4</td>
<td>135.0 ± 76.9</td>
<td>142.7 ± 96.6</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.016 vs middle group.
†p < 0.016 vs high group.
TABLE 3. Total Mortality in Parents and Grandparents Deceased/Total (% Deceased)

<table>
<thead>
<tr>
<th>Relationship to index case</th>
<th>Cholesterol level</th>
<th>Low (2.9%)</th>
<th>Middle (19.6%)</th>
<th>High (21.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td>1/35</td>
<td>0/94</td>
<td>1/65</td>
<td></td>
</tr>
<tr>
<td>Grandmothers</td>
<td>11/35</td>
<td>18/92</td>
<td>14/65</td>
<td></td>
</tr>
<tr>
<td>Grandfathers</td>
<td>20/34</td>
<td>41/89</td>
<td>43/63*</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.016 vs middle group.

53 (51%) in the low-, middle- and high-cholesterol groups, respectively. The relative frequency of disease among grandfathers of high-cholesterol cases was significantly higher than among grandfathers of middle-cholesterol cases. Based on the same criteria, 24 grandmothers were classified as diseased, 143 were classified as without disease and 25 could not be included in either group. The relative frequencies of CHD for grandmothers (six of 32 [19%], eight of 79 [10%] and 10 of 56 [18%] in the low-, middle- and high-cholesterol groups, respectively) were not significantly different among groups.

Neither a grandchild's classification as low-, middle- or high-cholesterol nor his quantitative serum cholesterol level was a significant predictor of disease outcome in grandparents. Both were significant predictors of CHD in the 160 grandfathers. The chi-square values associated with the likelihood ratios, the relative magnitudes of the standardized coefficients and the R² measure of fit all indicate that the serum cholesterol level of an index child is a stronger predictor of disease in grandfathers than the categorization of being in the low-, middle- or high-cholesterol group. Total triglyceride levels in the index children did not predict disease status in either grandfathers or grandmothers.

Ninety-five of the 160 grandfathers were in 58 families identified by an index child who was measured for lipoproteins. Using the logistic model, the levels of total cholesterol, the cholesterol LDL (C-LDL), the triglyceride LDL (T-LDL) and the C-HDL as a fraction of the total cholesterol (C-HDL/total) in the index grandchild were each a significant predictor of CHD in the 95 grandfathers (models 1, 2, 3 and 4, respectively, in table 5). Total triglyceride levels, VLDL cholesterol, VLDL triglyceride, and T-HDL as a fraction of the total triglyceride in a grandchild were not significant predictors of disease in these grandfathers.

Based on estimates of standardized coefficients in models 1–4 as well as the R² and chi-square associated with the likelihood ratios, C-HDL/total in a grandchild was judged a stronger single predictor of disease than total cholesterol or C-LDL. The C-HDL/total was negatively associated with prevalence of disease while total cholesterol (model 1) and C-LDL (model 2) were positively associated with disease prevalence.

A model including both C-LDL and C-HDL/total (model 9) has the highest chi-square value among the models with two predictor variables (models 5–9), although such a model does not explain a significantly larger proportion of disease than does a model with either lipoprotein alone (in table 5, model 9 vs model 2, χ² = 2.83, model 9 vs model 4, χ² = 0.89). A model including both cholesterol and C-HDL/total (model 7) significantly improves the prediction compared with a model including total cholesterol only (model 7 vs model 1, χ² = 4.04). However, the addition of C-LDL to this model (model 10 vs model 7, χ² = 0.65) does not significantly increase predictability. A model including all the lipid and lipoprotein measures (not shown in table 5) increases the R² only 3% over model 10. Among grandmothers, none of the measures of lipoproteins in grandchild were significant predictors of CHD.

The relative frequency of CHD in grandfathers plotted against the standardized value of the index child's total cholesterol, C-LDL and C-HDL/total is shown in figure 1. The ninety-fifth percentile confidence intervals for the predicted probability of CHD are given for the mean levels and at 1 standard deviation from the mean. For all three measures of lipid metabolism, there are substantial differences in both the observed and predicted probability of CHD between grandfathers with an index grandchild below the mean and those with an index grandchild above the mean.

**Discussion**

The new finding from our study of Rochester families that both HDL and LDL cholesterol levels in grandchildren are stronger predictors than total cholesterol of CHD in grandfathers is consistent with the findings from several epidemiologic studies of adults. Both case-control and prospective studies of diverse populations over the last 30 years have established that...

TABLE 4. Death Due to Coronary Heart Disease* in Grandparents Deceased/Total (% Deceased)

<table>
<thead>
<tr>
<th>Age class</th>
<th>Grandfathers</th>
<th></th>
<th>Grandmothers</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (26.5%)</td>
<td>Middle (18.0%)</td>
<td>High (36.5%)</td>
<td>Low (5.9%)</td>
<td>Middle (5.4%)</td>
</tr>
<tr>
<td>All CHD deaths</td>
<td>9/34 (26.5%)</td>
<td>16/89</td>
<td>23/63†</td>
<td>2/35 (5.9%)</td>
<td>5/92 (5.4%)</td>
</tr>
<tr>
<td>CHD deaths ≤ 65 years</td>
<td>4/34 (12.5%)</td>
<td>8/89 (9.0%)</td>
<td>15/63†</td>
<td>1/35 (2.9%)</td>
<td>4/92 (4.3%)</td>
</tr>
</tbody>
</table>

*Death due to CHD is primary cause of death.
†p < 0.016 vs middle group.
Abbreviation: CHD = coronary heart disease.
both elevated LDL cholesterol and elevated total cholesterol levels are directly associated with development of CHD and that there is an inverse relationship between HDL and CHD that is independent of cholesterol LDL or total triglyceride levels. Healthy persons with a parental history of CHD have lower levels of HDL than those with a negative family history of CHD.

In our study, total triglyceride levels were not predictive of CHD. This finding agrees with a recent study in Muscatine that showed that relatives of children with elevated total triglyceride levels but total cholesterol levels less than the seventy-fifth percentile were not at increased risk for CHD mortality. The accumulated evidence from several large studies does not support a causal relationship between total triglyceride levels and CHD.

The general finding in Rochester of increased total mortality among grandparent's of low-cholesterol children compared with grandparents of middle-cholesterol children is consistent with several studies that showed an inverse relationship between serum cholesterol and overall mortality. The proportion of deaths due to cancer in our study was not significantly different among the three groups of relatives, although other studies have reported an inverse relationship between serum cholesterol levels and incidence of cancer.

The similarity in the findings from both Rochester and Muscatine that cholesterol levels in school children are related to cholesterol levels in first-degree relatives and CHD experience in their grandparents exists despite several differences between the two populations and study designs. First, the index cases in Muscatine were selected on cholesterol levels from surveys 2 years apart, whereas those in Rochester were based on single measurements. Several studies have reported that half of the children with a cholesterol level above the ninety-fifth percentile fall below this level on repeated measurements. Second, the mean cholesterol levels for the low-, middle- and high-cholesterol groups of index cases were each at least 13 mg/dl higher and the mean triglyceride levels were each at least 20 mg/dl higher in Muscatine than for the corresponding group in Rochester. The accuracy of lipid measurements in Muscatine were also ensured by the Center for Disease Control. Third, the fraction of cholesterol in each of the lipoprotein particles in children with hyperlipidemia may vary. Fourth, the number of relatives per family and the number of families surveyed in Muscatine were higher than in Rochester. Finally, the overall CHD mortality rates in Muscatine are substantially higher than national figures, whereas those in Rochester are substantially lower. Consideration of these differences and the consistency of the results between the two studies suggests that predictability of CHD in adults using childhood cholesterol levels is a characteristic of many populations.

The differences in lipid and lipoprotein levels among the index children in Rochester could not be explained by the variability in nutrient intake reported in seven-day diet diaries. A genetic analysis suggests that the shared genetic influences on variability in serum cholesterol levels are stronger in the high-cholesterol group families in Rochester compared to the mid-

\[ \chi^2 = -2 \ln \left( \text{likelihood ratio of complete vs reduced model} \right) \]
\[ p (\text{CHD under reduced model}) = \exp(b_0)/(1 + \exp(b_0)) \]

**Abbreviations:** C-LDL = low-density lipoprotein cholesterol; T-LDL = triglyceride low-density lipoprotein; C-HDL/Total = high-density lipoprotein cholesterol as a fraction of total cholesterol.
dle- and low-cholesterol groups. Data from the 33 high-cholesterol families support a hypothesis that there is segregation of a dominant allele at a locus with a major effect on cholesterol levels in addition to additive polygene and individual environmental factors. Heterogeneity among groups in the genetic and environmental factors contributing to lipid variability is associated with the mean level of serum cholesterol as well as increased CHD in grandfathers of high-cholesterol index children. Similarly, the high-cholesterol families in Muscatine show evidence of segregation at a single locus influencing serum cholesterol levels, but no such evidence exists for low- or middle-cholesterol families in that study.

The findings in Rochester raise several questions. Studies of cord blood suggest that at birth, neither the level of total cholesterol nor the level of HDL cholesterol is predictive of CHD prevalence in adult relatives. At what age, then, between birth and 6 years do the levels of cholesterol, LDL and HDL become predictive? A larger study than the one reported here would allow an investigation of the disease outcome in male and female relatives of male and female index children separately at different ages with different lipid and lipoprotein levels. The specific roles of LDL and HDL cholesterol in lipid metabolism and in the pathogenesis of CHD still need further elucidation. Although the relationship between lipid and lipoprotein levels in childhood and later development of disease is unknown, we can infer from our study that children between the ages of 6 and 16 years with elevated LDL or low HDL are probably at increased risk for CHD in adulthood. While an accurate prediction of risk for CHD should include levels of multiple risk factors for the individual as well as information about the family, we conclude from this study that childhood lipid and lipoprotein levels from a single cross-sectional survey can identify families at increased risk for CHD.

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Aneurysmal Coronary Artery Disease

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SUMMARY To examine the clinical and historical features and the natural history of aneurysmal coronary disease, we reviewed the registry data of the Coronary Artery Surgery Study (CASS). Nine hundred seventy-eight patients, representing 4.9% of the total registry population, were identified as having aneurysmal disease. No significant differences were noted between aneurysmal and nonaneurysmal coronary disease patients when features such as hypertension, diabetes, lipid abnormalities, family history, cigarette consumption, incidence of documented myocardial infarction, presence and severity of angina, and presence of peripheral vascular disease were examined. In addition, no difference in 5-year medical survival was noted between these two groups. These findings suggest that aneurysmal coronary disease does not represent a distinct clinical entity but is, rather, a variant of coronary atherosclerosis.

ANEURYSMAL coronary disease is characterized by abnormal dilatation of a localized or diffuse segment of the coronary arterial tree. This involvement has also been termed coronary ectasia or dilating arteriosclerosis; destruction of the vessel media is the usual histologic feature. Frequently, aneurysmal disease coexists with coronary atherosclerosis and has raised the question of whether aneurysmal disease is a variant of atherosclerotic coronary disease or a distinct entity. The presence of dilated coronary segments, even in the absence of obstructive disease, is believed to result in alterations in blood flow and stasis, which predispose these patients to myocardial ischemia and infarction.

Although many reports on aneurysmal coronary disease have been published, the number of patients in each report has been small. We therefore evaluated a large group of patients with aneurysmal coronary disease from the registry data of the multiinstitutional Coronary Artery Surgery Study (CASS), sponsored by the National Institutes of Health (NIH). We examined the clinical and historical features and the natural history of coronary aneurysmal disease to determine whether it represents a distinct clinical entity or a variant of coronary atherosclerotic disease.

Materials and Methods

Between July 1975 and May 1979, clinical, laboratory and angiographic data were collected in a standardized fashion and entered into a registry of consecutive patients undergoing coronary arteriography for clinically suspected coronary artery disease at 15 participating clinical centers of CASS. Patients who were subsequently shown to have normal coronary arteries were included in the registry. Patients studied for suspected coronary artery disease who were found to have another form of heart disease were excluded. Those who underwent coronary angiography for evaluation of other conditions, such as valvular heart disease, cardiomyopathies and congenital heart disease, were also excluded even if subsequent evidence showed that coronary artery disease was a major clinical problem.

A total of 20,087 patients from the participating institutions was entered into the CASS registry. The patients who had undergone cardiac surgery were not included. Each patient was interviewed at the time of hospitalization for coronary angiography by a trained data technician or the responsible physician. The base-
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