Coronary Disease in Familial Hypercholesterolemia

By Julius Jensen, Ph.D., M.R.C.S., David H. Blankenhorn, M.D., and Valdemar Kornerup, M.D.

SUMMARY
A report of 20 years' experience with coronary disease in 11 Danish families with hypercholesterolemia and normal serum triglycerides is given. A significantly higher death rate was found in family members who inherited the trait of hypercholesterolemia than in those who did not. The death rate of hypercholesterolemic family members was significantly higher than that found in all other persons of their age and sex living from 1943 to 1964 in Denmark; the death rate for the normocholesterolemic families was not. Most hypercholesterolemic family members died from coronary disease and at an earlier age than is usual for persons with coronary disease in Denmark. There was nothing to indicate that increase in triglycerides rather than increase in cholesterol is related to coronary disease in these families. No environmental factor was found to account for the higher death rate among the members with hypercholesterolemia.

Additional Indexing Words: Serum triglyceride Sudden death Angina pectoris Xanthoma

It is important to decide whether patients with familial hypercholesterolemia but normal serum triglyceride levels* have a significantly greater incidence of coronary disease than do other members of the same population. The early reports of Harbitz and Mülle indicated that coronary disease was prevalent in familial hypercholesterolemia, but serum triglycerides were not examined. Much recent evidence indicates that elevated serum triglyceride levels are a frequent concomitant of hypercholesterolemia and Albrink and associates expressed the view that an increase in serum triglyceride concentration is the most characteristic abnormality in patients with coronary disease. Harlan and associates recently described a single large kindred with hypercholesterolemia and normotriglyceridemia and found “no evidence that familial hypercholesterolemia appreciably shortens the life of affected individuals, either male or female.” With such a variety of views, additional studies of families with hypercholesterolemia are indicated. This is one such study of 20 years' experience with the upper limit of this value has not been established beyond doubt. Occasionally persons in apparent health are found to have levels up to 400 mg%. Among 42 blood donors in Aarhus, examined as controls for this study, six had triglyceride levels of 200 to 400 mg%. Among 96 twins who answered a call in Los Angeles for twin volunteers for a cholesterol study, 28 individuals had triglyceride levels between 200 and 400 mg%, and two had a level of 445 mg%. In the families reported on here, all members had triglyceride levels below 200 mg% except for 14 individuals (see table 7).
coronary disease in 11 families with hypercholesterolemia and normotriglyceridemia.

**Methods**

In 1944, Kornerup\(^5\) studied 14 Danish families with extrapalpebral xanthomatosis. Twelve of them were re-examined by Piper and Orrild in 1954.\(^6\) In 1964, the present authors were given the opportunity to examine the families again and thus complete a 20-year study. Original records were made available by the previous authors, including information on family members who had died before 1954. The Bureau of Vital Statistics for Denmark provided death certificates of those who had died since 1954.

In 331 members of 11 of the 12 families, it was possible to determine whether or not they had inherited the trait of hypercholesterolemia and whether or not they had manifest coronary disease (table 1). Two hundred eight of them were personally examined during the 1964 study. The twelfth family (Kornerup's family V) had triglyceride levels above 400 mg% and was excluded from this study.

The presence of the hypercholesterolemic trait was diagnosed in any individual who had one of the three following criteria: (1) The blood cholesterol level was 350 mg% or more in persons 15 years of age or above; below the age of 15, 300 mg% was the upper limit of normal.\(^*\) These limits were based on Kornerup's study of control individuals. In persons above 15 years of age, he found a mean value of 219 ± 47 mg%. In children he found a mean value of 209 ± 40 mg%. In this study the limiting value can be set at 300 mg% for adults without affecting the results because one man with coronary disease had a cholesterol of 286 mg%, another 300 mg%, and all other family members with coronary disease whose cholesterol was known had levels above 360 mg%. (2) Xanthoma or xanthelasma was present. (3) Any of these conditions was present in at least one child and one parent or sibling.

If the blood of a descendant of a normocholesterolic member was not examined, this descendant was also considered normocholesterolic. These criteria are in accordance with the current concept that hypercholesterolemia is transmitted by a single dominant gene of variable penetrance.

A diagnosis of coronary disease was accepted if it had been made by Kornerup,\(^5\) by Piper and Orrild,\(^6\) or if it appeared in a hospital record or on a death certificate. In the current study a diagnosis was made by us in eight patients who gave a history of pain in the chest brought on by effort or emotional tension, frequently radiating into the neck or the arms. It was also made in one case in which a son of a hypercholesterolemic parent died suddenly at the age of 31 without other evidence of hypercholesterolemia or coronary disease.

**Findings**

In the 11 families, 181 members were classified as hypercholesterolemic and 150 as normocholesterolemic. Among the 181 with hypercholesterolemia, coronary disease was diagnosed in 59 (32.5%). Among the 150 normocholesterolemic family members, coronary disease was diagnosed in two (1.3%).

The cases of coronary disease among the hypercholesterolemic members were classified according to age and sex (table 2). The age at onset of symptoms was known in 43 cases (table 3). In the men the first symptoms appeared before the age of 40 in six (19.3%), and before the age of 50 in 14 (45.1%). In the women the first symptoms appeared before the

---

* Sera were examined in the Central Laboratory of Aarhus Kommunehospital, Aarhus University, under the direction of Professor R. Keiding. The cholesterol determinations were made by the method of Pearson and associates\(^7\) and the triglycerides by the method of Carlson.\(^8\)

---

### Table 1

Three Hundred and Thirty-one Members of Eleven Danish Families with Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th></th>
<th>Entire group</th>
<th></th>
<th>Members with coronary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Subtotal</td>
</tr>
<tr>
<td>With hypercholesterolemia</td>
<td>84</td>
<td>97</td>
<td>181</td>
</tr>
<tr>
<td>Without hypercholesterolemia</td>
<td>75</td>
<td>75</td>
<td>150</td>
</tr>
<tr>
<td>Total</td>
<td>159</td>
<td>172</td>
<td>331</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXVI, July 1967
FAMILIAL HYPERCHOLESTEROLEMIA

Table 2
Fifty-nine Family Members with Hypercholesterolemia and Coronary Disease Distributed According to Sex and Age When Seen During the Present Study or at Death

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men Alive</th>
<th>Men Dead</th>
<th>Women Alive</th>
<th>Women Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1</td>
<td>11</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>70-79</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>80-90</td>
<td>1*</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>30</td>
<td>5</td>
<td>17</td>
</tr>
</tbody>
</table>

*This man was 89 when examined; he died during the following year.

age of 40 in three (25%), and before the age of 50 in nine (75%).

There was only one juvenile case of coronary disease, a boy with monstrosus xanthomata, who died at 19 years of age. Another boy, aged 16, died suddenly on a football field some months after he had been examined by Korneirup who found his serum cholesterol to be 295 mg%.

Table 3
The Age at Onset of Coronary Symptoms in Thirty-one Male and Twelve Female Family Members with Hypercholesterolemia

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>40-49</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>50-59</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>70 and over</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>12</td>
</tr>
</tbody>
</table>

Ninety-five hypercholesterolemic and 60 normocholesterolemic family members over 9 years of age were alive in 1943. The expected death rate could be compared in each sex and age group with that actually experienced (tables 4 and 5). While the figures in each age group are too small for the differences between expected and actual deaths to be significant, the total differences between the expected and the actual for the hypercholesterolemic members are significant for each sex at the 1% level. The percentages of actual to expected deaths were: for the men

Table 4
Mortality Experience with Family Members Who Carried the Hypercholesterolemic Trait

<table>
<thead>
<tr>
<th>Age (yr)*</th>
<th>Men No.†</th>
<th>Death rate‡</th>
<th>Expected deaths§</th>
<th>Actual deaths**</th>
<th>Women No.</th>
<th>Death rate</th>
<th>Expected deaths</th>
<th>Actual deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-19</td>
<td>5</td>
<td>0.0345</td>
<td>0.1725</td>
<td>1</td>
<td>7</td>
<td>0.0273</td>
<td>0.1911</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>11</td>
<td>0.0479</td>
<td>0.5269</td>
<td>2</td>
<td>16</td>
<td>0.0431</td>
<td>0.6896</td>
<td>1</td>
</tr>
<tr>
<td>30-39</td>
<td>7</td>
<td>0.0709</td>
<td>0.4963</td>
<td>3</td>
<td>8</td>
<td>0.0678</td>
<td>0.5424</td>
<td>2</td>
</tr>
<tr>
<td>40-49</td>
<td>9</td>
<td>0.1450</td>
<td>1.3050</td>
<td>4</td>
<td>10</td>
<td>0.1314</td>
<td>1.3140</td>
<td>3</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>0.3157</td>
<td>2.8413</td>
<td>8</td>
<td>4</td>
<td>0.2911</td>
<td>1.1644</td>
<td>2</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
<td>0.6324</td>
<td>1.2648</td>
<td>1</td>
<td>5</td>
<td>0.6123</td>
<td>1.8369</td>
<td>3</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>0.9267</td>
<td>1.8534</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>6.6068</td>
<td>19</td>
<td></td>
<td>52</td>
<td>7.5918</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

*At the 0 to 9 age level the expected death rates included neonatal deaths about which no information was contained in the records of the 11 families. On the other hand, there were no deaths among the family members who were alive and aged 0 to 9 years in 1943. This group therefore was not included in the tables.

†The number of members in each sex and age bracket living in 1943.

‡The number of deaths expected per person in each sex and age bracket during 1943 to 1964. This figure is derived from rates expressed per 10,000 persons in Danmarks Statistik.

§The death rate multiplied by the number of persons in each sex and age bracket.

**The actual number of deaths which occurred in each group, all others are known to have survived.

Circulation, Volume XXXVI, July 1967
Table 5
Mortality Experience with Family Members Who Did Not Carry the Hypercholesterolemic Trait*

| Age (yr) | Men | | | | | | Women | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | Death rate | Expected deaths | Actual deaths | No. | Death rate | Expected deaths | Actual deaths |
| 10-19 | 9 | 0.0345 | 0.3105 | 1 | 6 | 0.0273 | 0.1638 | 1 |
| 20-29 | 10 | 0.0431 | 0.4310 | | 6 | 0.0678 | 0.4068 | | |
| 30-39 | 6 | 0.0709 | 0.3545 | 1 | 4 | 0.1314 | 0.3256 | | |
| 40-49 | 3 | 0.1450 | 0.5350 | 1 | 6 | 0.2910 | 1.7466 | 1 | |
| 50-59 | 6 | 0.3157 | 1.5785 | 4 | 5 | 0.6123 | 3.0615 | 2 | |
| 60-69 | 1 | 0.6324 | 0.6324 | | | | | | |
| 70-79 | | 3.4109 | 7 | | | | | | |
| Total | 23 | | | 7 | | | | | 37 | 6.3353 | 4 |

*For comments on age, number, death rate, expected and actual deaths, see footnotes for table 4.

\[
\frac{19}{6.6068} = 288\% \text{ and for the women } \frac{13}{7.5918} = 171\%. \text{ For men and women together it was } \frac{32}{14.199} = 225\%.
\]

In the case of the normocholesterolemic members, the corresponding figures were: for the men \(\frac{7}{3.4109} = 205\%\) and for the women \(\frac{3}{6.3353} = 47\%,\) but they were not statistically significant. For men and women together, the actual to expected mortalities were \(\frac{10}{9.7540} = 103\%\). The death rate among the hypercholesterolemic members was \(\frac{225}{103} = 2.18\) times the death rate among the normocholesterolemic members.

**Cause of Death in Hypercholesterolemia**

Information regarding the cause of death was too partial and incomplete for exact statistics, especially on the normocholesterolemic members, but such data as were available indicate clearly that coronary disease was a frequent cause of death in the hypercholesterolemic members of these families. Of 62 members with hypercholesterolemia in whom the cause of death was known, 32 (51.6%) had died from manifest coronary disease. In addition, coronary disease may have been a factor in some of the 10 (16.1%) who died suddenly without previous evidence of heart disease (table 6).

**Table 6**
Sixty-two Members with Hypercholesterolemic Trait Listed According to Cause of Death and Sex

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriosclerotic heart disease</td>
<td>21</td>
<td>11</td>
<td>32</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Apoplexy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cancer</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Misc. infections</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other causes stated</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Cause not ascertainable</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>26</td>
<td>62</td>
</tr>
</tbody>
</table>

**Age at Death from Coronary Disease**

The average age at death from coronary disease in 41 hypercholesterolemic men in these families concerning whom information was obtained was 56 years. In comparison, Mosbech and Dreyer\(^9\) found that in the 700 men who died in Denmark during March to April 1963, from coronary disease, the average age was 70 years. In 16 women with hypercholesterolemia who had died from coronary disease, the average age at death was 58 years. Mosbech and Dreyer's comparable figure for 430 women who had died from coronary disease during March to April 1963 was 74 years. There is thus some evidence that in cases of familial hypercholesterolemia death from coronary disease occurs...
FAMILIAL HYPERCHOLESTEROLEMIA

Table 7
Family Members with Triglyceride Levels in Excess of 200 mg%  

<table>
<thead>
<tr>
<th>Hypercholesteremic trait</th>
<th>Sex</th>
<th>Identification*</th>
<th>Date of birth</th>
<th>Triglyceride level</th>
<th>Coronary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>M</td>
<td>III-10</td>
<td>11-1-17</td>
<td>210</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>M</td>
<td>VII-20</td>
<td>12-2-11</td>
<td>244</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>M</td>
<td>XI-57</td>
<td>10-19-26</td>
<td>320</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>F</td>
<td>I-25</td>
<td>11-22-04</td>
<td>286</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>F</td>
<td>IX-10</td>
<td>9-3-97</td>
<td>232</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>F</td>
<td>X-6</td>
<td>10-21-96</td>
<td>316</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>F</td>
<td>XI-52</td>
<td>5-10-25</td>
<td>220</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>M</td>
<td>VIII-21</td>
<td>3-8-11</td>
<td>300</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>I-16</td>
<td>12-4-98</td>
<td>240</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>VII-22</td>
<td>7-30-14</td>
<td>202</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>VIII-7</td>
<td>11-15-87</td>
<td>392</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>VIII-20</td>
<td>7-30-08</td>
<td>238</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>XI-19</td>
<td>4-19-04</td>
<td>220</td>
<td>No</td>
</tr>
<tr>
<td>No</td>
<td>F</td>
<td>XI-45</td>
<td>10-21-15</td>
<td>206</td>
<td>No</td>
</tr>
</tbody>
</table>

*Identification numbers are according to Kornerup5 and Orrild.6

Table 8
Average Triglyceride Levels in Men and Women with and without the Hypercholesterolemic Trait*

<table>
<thead>
<tr>
<th>Sex</th>
<th>With hypercholesterolemic trait</th>
<th>Without hypercholesterolemic trait</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Av</td>
<td>SD</td>
</tr>
<tr>
<td>Men</td>
<td>40</td>
<td>124</td>
</tr>
<tr>
<td>Women</td>
<td>63</td>
<td>119</td>
</tr>
</tbody>
</table>

*Differences between men and women with or without the hypercholesterolemic trait are not significant at the 10% level. Differences between men with or without the hypercholesterolemic trait are not significant at the 10% level. Differences between women with or without the hypercholesterolemic trait also are not significant at the 10% level.

earlier than it does in the population at large.

Triglyceride Levels

Triglyceride levels were determined in 208 members of the 11 families and all were found to be below 200 mg% except as listed in table 7. Because the upper limit of triglyceride level has not been established beyond doubt, the entire group of 208 was considered and no significant differences were found in the average triglyceride levels between men and women and within each sex between those with and those without the hypercholesterolemic trait (table 8). The average triglyceride levels in seven men and six women with coronary disease was compared with those of 33 men and 57 women without coronary disease (table 9). All were hypercholesterolemic and average cholesterol levels for each group are given. Average triglyceride levels in all groups are well below 200 mg%. Men and women with coronary disease had higher average triglyceride levels than those without coronary disease, but this difference is within the range of normal and is less than the difference in cholesterol levels.

Discussion

This is a report of 20 years' experience with coronary disease in 11 Danish families with hypercholesterolemia and normal serum triglycerides. Juvenile coronary disease was seen only once, or possibly twice, and some family members with hypercholesterolemia lived to a ripe old age. However, a significantly higher death rate was found in the

Circulation, Volume XXXVI, July 1967
Table 9
Average Triglyceride and Cholesterol Levels in Seven Men and Six Women with Coronary Disease and in Thirty-three Men and Fifty-seven Women without Coronary Disease*

<table>
<thead>
<tr>
<th>Heart disease</th>
<th>Triglyceride† (mg%)</th>
<th>Cholesterol‡ (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with hypercholesterolemic trait</td>
<td>No.</td>
<td>Av</td>
</tr>
<tr>
<td>With coronary disease</td>
<td>7</td>
<td>159</td>
</tr>
<tr>
<td>Without coronary disease</td>
<td>33</td>
<td>115</td>
</tr>
<tr>
<td>Women with hypercholesterolemic trait</td>
<td>No.</td>
<td>Av</td>
</tr>
<tr>
<td>With coronary disease</td>
<td>6</td>
<td>175</td>
</tr>
<tr>
<td>Without coronary disease</td>
<td>57</td>
<td>114</td>
</tr>
</tbody>
</table>

*All were considered as having the hypercholesterolemic trait.
†Triglycerides: Men—difference is significant at 0.002% level; women—difference is significant at 0.01% level.
‡Cholesterol: Men—difference is significant at 0.01% level; women—difference is significant at 0.05% level.

family members with hypercholesterolemia than in those with normal cholesterol levels. No environmental factor was found which could account for the higher death rate in the hypercholesteroleics. The death rate of the hypercholesteroleics was significantly higher than that found for persons of their age and sex, living from 1943 to 1964 in Denmark; that of the normocholesteroleics was not. Most of the members of these families with hypercholesterolemia died from coronary disease at an earlier age than is usual with coronary disease in Denmark. The triglyceride levels in these families were within the range considered normal in Denmark, and there was no significant difference between the hypercholesteroleics and the normocholesteroleics. The members with hypercholesterolemia and coronary disease had triglyceride levels higher than did the members with hypercholesterolemia without coronary disease; the former group also had higher cholesterol levels. There was nothing to indicate that increase in triglyceride rather than increase in cholesterol is related to coronary disease.

Conclusions
The mortality from coronary disease was significantly increased among the members with hypercholesterolemia in 11 Danish families with familial hypercholesterolemia and normal triglyceride levels, but not among the unaffected members of the same families, living in the same environment in Denmark. The latter had the same death rate as was found in the Danish population in general.

Acknowledgment
Mr. Tim Giles of the Actuarial Department of the Occidental Life Insurance Co. was helpful in designing the tables.

References