Thickenings in the Coronary Arteries in Infancy as an Indication of Genetic Factors in Coronary Heart Disease

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SUMMARY
In Finland, mortality from coronary heart disease is high, and much higher in the eastern than in the western counties. Both left and right coronary arteries of 141 children who died under one year of age at the Children’s Hospital, University of Helsinki, were investigated. Thirty-two of these children formed a western and 41 an eastern group according to the birthplaces of their grandparents in Finland. Correlations were tested between this geographical distribution and some dimensions of the coronary arteries, as well as other clinical variables.

The inner vascular layers of the left coronary arteries were found to be thicker in the eastern group (P < 0.05 in analysis of variance and P < 0.01 in regression analysis). No other significant correlations were observed.

This association of infants having thick inner vascular layers in the coronary artery with a population group where mortality from coronary heart disease (CHD) is very high supports the hypothesis that the thickenings are prearteriosclerotic. The difference found between the arteries of the western and eastern groups might be due to a difference in the vulnerability of the inner vascular wall to extrinsic deleterious factors. The association substantiates the existence of a genetic component in the etiology of CHD and supports the theory that two separate groups of settlers originally colonized Finland.

Additional Indexing Words:
Measuring of coronary arteries Etiology of coronary heart disease Population structure in Finland

The occurrence of coronary heart disease (CHD) varies greatly from one country to another. Finland has one of the worst records in this respect. Compared with the other Scandinavian countries, the standardized death rates for men aged 45–74 years from ischemic heart disease in 1966–1968 were 1,077 for Finland, and 677, 630, and 585 for Denmark, Norway, and Sweden, respectively. But great regional differences also exist within Finland; two eastern counties have the highest incidence of CHD, whereas in the southwestern part the mortality rates are less high (fig. 1).

It has been suggested that thickenings of the inner vascular layers (IVL) occurring in infancy and childhood may bear some relation to later development of coronary artery disease. Thus, Vlodaver et al. have shown in ethnic groups in Israel that the areas of intima plus musculoelastico layer (inner vascular layers) in arterial cross-sections are larger in infants belonging to an ethnic group in which the prevalence of CHD is high. Furthermore, the inner vascular layers are thicker in boys than in girls and thicker in the left than in the right coronary artery. Some findings in animals may also be interpreted as supporting evidence. On the other hand, specific factors, e.g., infections, influence the thickness of the coronary arterial wall even in infancy.

The causes of regional differences in CHD may be both genetic and environmental. The role of genetic factors in CHD is poorly understood and their existence is often disregarded, at least from the practical standpoint, in treatment and prevention. If the preliminary stages of CHD can be detected in very young persons, the weight of genetic etiologic factors relative to environmental ones is likely to be greater in them than in adults. This hypothesis motivated a study of the differences in the coronary arteries of infants from eastern and western Finland.

If the environment, the actual home locality, were the same for all the children whose coronary arteries
were studied, the genetic effect of geographic origin could be separated to a large extent from environmental factors. In fact, this is possible in Finland, where recent internal migration has brought many people of fertile age from all parts of the country to the south, especially to the capital, Helsinki. By studying infants who died in Helsinki, it is possible to obtain subjects whose actual home locality (environment) was in most cases in or near Helsinki, but whose ancestors (genes) originated from all parts of Finland.

Thus, to investigate the influence of genetic factors on the coronary arteries in infants and perhaps on the occurrence of CHD, we analyzed the correlations between the dimensions of the coronary arteries of Finnish infants and the distribution of the birthplaces of their grandparents.

Material and Methods

Samples of coronary arteries were obtained at 141 autopsies performed on infants who had died when under one year of age at the Children's Hospital and Women's Hospital, University of Helsinki. The Children's Hospital in Helsinki takes most of the cases from the southern part of the country needing treatment at specialized hospital level. Almost all children dying in the hospital are autopsied. The main reasons for death are immaturity, infections and congenital anomalies. The only selection made, in addition to the age of the patient, was that the autopsy was made personally by one of the authors (E.P.) not more than 48 hours after death.

Both coronary arteries were sectioned semiserially at intervals of 200 μm. The section from each coronary artery with the greatest area of the inner vascular layers (IVL = musculoelastic layer plus intima) was chosen by visual estimation for morphometric studies. The radii of the left and right coronary arteries and the thickness of the IVL and media were measured. The total technical error of the method can be calculated to be about 5%. The methods of preparing the specimen and making the measurements have been described elsewhere. The birthplaces of the infants and their parents and grandparents were traced from the population registers; the mothers were asked for data on the fathers of the ten illegitimate children. If the grandparents were born in a town, the inquiry was extended one or two generations back whenever possible to make sure of the real origin of the ancestors.

Finland was divided into three areas according to the CHD mortality rates described in figure 1; these areas were numbered 1, 2 and 3 from west to east (fig. 2). The children were coded according to the birthplaces of their four grandparents, into western, intermediate and eastern groups.

Figure 1

Mortality from ischemic heart disease in 1969 by counties in Finland. The figures are expressed in relation to the mean for the whole country = 100.

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Figure 2

The division of the country into areas 1, 2 and 3 according to figure 1 for dividing the children of the series into western and eastern groups. The easternmost boundary in this and subsequent maps marks the eastern frontier of Finland before World War II.
Those with codes 1111 and 1112 formed the western, those with codes without the figure 1 the eastern, and the others (1122, 1123, etc.) the intermediate groups.

The western and eastern groups were compared regarding sex, presence of infarction, presence of congenital heart defect, and the following continuous parameters: gestational age, postnatal age, Apgar score, body weight, blood hemoglobin concentration, heart weight, logarithm of the thickness of the media divided by the arterial radius, logarithm of the thickness of the IVL divided by the radius of the artery, and logarithm of the arterial radius. Logarithmic transformations were used for technical reasons, because they give linear representations for those variables which grow exponentially.

Differences in these factors between the western and eastern groups were tested by analysis of variance. The zero hypothesis was that there is no difference. The alternative hypothesis was that this difference deviates from zero. With the aid of stepwise regression analysis the logarithm of the thickness of the vascular layers of the right and left coronary arteries was explained in turn with the factors mentioned above. The logarithm of the radius of the artery in question was used as an explaining factor. The data were processed with a Burroughs 6700 computer.

The children of the western and eastern groups were also arranged and divided into quintiles according to the thickness of the IVL of the coronary arteries; the birthplaces of the grandparents in the first (thinnest IVL), third, and fifth (thickest IVL) quintiles were marked on maps.

The results were also compared with those obtained by dividing the children into western and eastern groups according to the birthplaces of their parents and of the children themselves.

Of the 141 autopsied infants five were excluded from the present series, one because her weight was less than 600 g, and four because at least one of the parents was not born in Finland.

**Results**

For the 136 families included in the series the birthplaces of all the children and parents were traced. Of the grandparents 11 grandfathers remained unknown because of illegitimacy; in these cases it was assumed that the missing grandfather was from the same area as his partner. The birthplaces of the children, parents, and grandparents are shown in figure 3; as could be predicted, the majority of the children were born in the south near Helsinki, whereas the distribution of the grandparents roughly corresponded to the distribution of the population in Finland.

According to geographical scoring by grandparents, 32 children were western, 41 eastern, and 63 intermediate. By parental division 62 children were western, 33 eastern, and 41 intermediate. Of the children themselves the vast majority, 120, were born in the west, and only 16 in the east. The relations between the three different west-east groupings are shown in figure 4.

In comparisons between the western and eastern groups (according to grandparents) with respect to the mean values of the twelve factors tested (tables 1 and 2), the only significant difference found was for the logarithm of the thickness of the IVL of the left coronary artery divided by the radius (P < 0.05). The

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**Figure 3**

Birthplaces of the 136 children (A), their parents (B), and grandparents (C), marked by one dot per person. The number of persons born in Helsinki is shown by a figure instead of dots.
The numbers of children in the western, intermediate, and eastern groups, grouped according to the birthplaces of the children (left column), parents (middle column), and grandparents (right column), and the relationships between these different groupings.

IVL were thus thicker in the eastern group. Examples of the variation in the thickness of the IVL are shown in figure 5. The corresponding layers of the right coronary artery showed the same trend, but not significantly so. No other significant differences were found.

In the regression model the intercorrelations between the different factors were taken into account. When the most important factors explaining the thickness of IVL were included in the model in the stepwise regression analysis, the regression coefficient of the factor of geographic distribution was significant ($P < 0.01$). Thus, the thickness of IVL is explained significantly by whether the child belonged to the western or the eastern group. Table 3 shows the most important factors and their probabilities explaining the layers in both the left and right coronary arteries. After three or four factors in every model the explanation rate did not increase significantly.

![Figure 4](http://circ.ahajournals.org/)

The birthplaces of the grandparents of the 15 children with the thinnest coronary IVL, those of the 15 children with the thickest IVL, and those of the middle quintile are shown in figure 6. In the quintile with thin IVL the western preponderance of birthplaces is evident. In the middle quintile the birthplaces are quite evenly scattered. In the quintile with thick IVL there are also many points in the west, but a distinct cluster can be seen in the east, especially in area 3, the area with the highest mortality from CHD. In the quintile with thin IVL there were 11 western and four eastern children, in the quintile with thick IVL there were six western and nine eastern children, according to the birthplaces of the grandparents. All the children with thin IVL had been born in the west; of the quintile with thick IVL 12 were born in the west and three in the east.

If the children were divided into western and eastern groups according to the birthplaces of their parents, a corresponding difference ($P < 0.05$) was also found (in respect to the logarithm of the thickness of the IVL of the left coronary artery divided by the radius).

If the children were grouped according to their own birthplaces, statistical comparisons were impossible because the eastern group was too small (16 out of 136).

### Table 1

**Group Means and t Values for Nonlogarithmic Variables in the Western and Eastern Groups According to the Birthplaces of the Grandparents**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean values</th>
<th>t value</th>
<th>P value (df = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (proportion of males)</td>
<td>0.72</td>
<td>1.80</td>
<td>NS</td>
</tr>
<tr>
<td>Infection*</td>
<td>0.44</td>
<td>0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Heart defects*</td>
<td>0.47</td>
<td>1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>250</td>
<td>-0.75</td>
<td>NS</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>38.7</td>
<td>-0.79</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar points</td>
<td>5.6</td>
<td>0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>3100</td>
<td>-0.38</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin†</td>
<td>2.52</td>
<td>-0.72</td>
<td>NS</td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>31.3</td>
<td>1.60</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Proportion of positive cases.
†Age-adjusted scores 1–6 were used.2

### Table 2

**Significance of Differences between Group Means of Logarithmic Thickness of Inner Vascular Layers and Media Divided by the Arterial Radius and Logarithmic Radius of the Left Coronary Artery (df = 71)**

<table>
<thead>
<tr>
<th>Grouping by birthplaces of</th>
<th>Inner layers</th>
<th>Media</th>
<th>Radius</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t value</td>
<td>P value</td>
<td>t value</td>
</tr>
<tr>
<td>Grandparents</td>
<td>2.04</td>
<td>&lt;0.05</td>
<td>-0.38</td>
</tr>
<tr>
<td>Parents</td>
<td>2.01</td>
<td>&lt;0.05</td>
<td>-0.17</td>
</tr>
</tbody>
</table>
Figure 5
Examples of thin IVL (A) and thick IVL (B) in coronary arteries of about the same size (X 40).

Discussion
The results of this investigation show a significant positive correlation between the thickness of the inner layers of the left coronary artery of 136 autopsied infants and the eastern distribution of the birthplaces of their grandparents in Finland. Before we can evaluate the implication of this finding for the importance of genetic factors in the etiology of the thickenings described, and of CHD at a later age, some facts have to be discussed which concern the methods, the exclusion of environmental factors, and the reasonableness of the result in relation to the genetic etiologic hypothesis.

In measuring the thicknesses of arterial layers, allowance has to be made for variations in the state of contraction of the artery, and topographic criteria for the site of the sample must be specified. These and other technical details have been discussed elsewhere. In our opinion the measuring method is reliable.

Do the birthplaces of the grandparents indicate the real geographic origin of the ancestors? The children

Table 3
The Most Important Factors in a Stepwise Regression Model Explaining the Measures of the Left and Right Coronary Arteries. All Continuous Variables Are on a Logarithmic Scale in the Regression Model

<table>
<thead>
<tr>
<th>Explained variable</th>
<th>Explaining variables</th>
<th>Standardized regression coefficient</th>
<th>t value</th>
<th>P value</th>
<th>R²*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left IVL*</td>
<td>Radius</td>
<td>0.58</td>
<td>4.34</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Geographic origin</td>
<td>0.25</td>
<td>3.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or grandparents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gestational age</td>
<td>0.32</td>
<td>2.74</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postnatal age</td>
<td>−0.18</td>
<td>−1.53</td>
<td>NS</td>
<td>0.53</td>
</tr>
<tr>
<td>Left media</td>
<td>Radius</td>
<td>0.39</td>
<td>3.39</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Body weight</td>
<td>0.36</td>
<td>3.35</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postnatal age</td>
<td>0.24</td>
<td>2.25</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apgar points</td>
<td>−0.13</td>
<td>−1.55</td>
<td>NS</td>
<td>0.73</td>
</tr>
<tr>
<td>Right IVL</td>
<td>Body weight</td>
<td>0.63</td>
<td>6.65</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Geographic origin</td>
<td>0.14</td>
<td>1.65</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of grandparents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apgar points</td>
<td>0.12</td>
<td>1.28</td>
<td>NS</td>
<td>0.49</td>
</tr>
<tr>
<td>Right media</td>
<td>Body weight</td>
<td>0.50</td>
<td>4.21</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radius</td>
<td>0.22</td>
<td>1.77</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postnatal age</td>
<td>0.12</td>
<td>1.10</td>
<td>NS</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*R² = explanation rate.
†Inner vascular layers.
were born early in 1970; most of their grandparents had been born around 1920. If the grandparents were born in the country rather than a town, this gives quite a reliable picture of the true origin of the ancestry. In the 1920s internal migration in rural Finland was slight, at least between areas as large as the divisions used in this study. In cases when the grandparents were born in towns, the tracing of ancestors was continued backward to their rural origin, if possible. In a few cases the birthplace of a grandparent may not correspond to the exact origin of his or her ancestors, but this will have hardly any influence on the result of the study.

The population density in Finland is very uneven, greatest in the south and southwest, smallest in the north and northeast. In 1920, at about the time of birth of the grandparents, the number of inhabitants per km² of land area was about 40 in the southernmost province, 10-20 in the middle parts, 10 in area 3 in the east and only 2 in the great northernmost province. Thus the clustering of the grandparents of children with thick IVL in the sparsely populated eastern and northern regions gains further significance.

Several environmental factors — really extrinsic or more or less physiological co-characters — are known to affect the thickness of the IVL in children. The analysis showed that the western and eastern groups did not differ significantly in any of the factors tested. Heart weight, occurrence of infections, etc., which are known to be positively correlated with the thickness of the IVL, were slightly greater in the western group, and weighed against the result obtained rather than in favor of it. Thus the possibility is excluded that the various factors mentioned above caused the thicker IVL in the eastern group.

Some environmental factors, e.g. trace elements of the soil or dietary habits of the family, might have their influence particularly through the mothers. In this study, however, the thickness of the IVL correlated better with the birthplaces of the fathers than with those of the mothers ($r = 0.225, P < 0.05$ for the fathers, $r = 0.142, P > 0.05$ for the mothers).

The possibility that some environmental factors have not been recognized always has to be kept in mind. Because our study subjects were infants, the effects of many such factors were eliminated. What environmental factors could vary parallel to the birthplaces of grandparents or parents? The thickness of IVL correlated with the “easternness” equally well, whether the children were grouped according to the birthplaces of the parents or the grandparents. In fact, the birthplaces of the parents depicted the living environment of the grandparents.

The environmental origin of the children was fairly

Figure 6

Birthplaces of grandparents of children belonging to the western and eastern groups of A) the 15 children with the thinnest IVL (first quintile); B) the 15 children of the third (middle) quintile; and C) the 15 children with the thickest IVL (fifth quintile). Note the western preponderance of dots in the first quintile with thin IVL (A), whereas a cluster of dots can be seen in area 3, with high CHD mortality, in the fifth quintile (C).
homogeneous, even if not fully so. None of the children of the western group was born or had parents who were born in the east, but of the 41 children of the eastern group 16 had themselves been born in the east, and 33 had parents born in that area. Thus the majority of the children of the series had a "western environment," whereas about 2% of the eastern children also had an "eastern environment." Whether these circumstances weaken the argument in favor of the importance of genetic etiologic factors is difficult to judge. Anyway, they do not invalidate the hypothesis that easterness, either genetically or environmentally, is positively correlated with the thickness of the IVL of the left coronary artery.

For an explanation of a genetic, "racial" difference between the inhabitants of western and eastern Finland, we must know something about the early settlement of this country. According to the classic unitarian theory, the population of Finland originated mainly from a single group of immigrants who came from the south during the first centuries A.D. If this were true, then genetic differences in the population would hardly be credible. Recently, however, a dualistic theory has gained support among archeologists and historians. According to this theory, the western part of the population originated from immigrants from the south, whereas the population of the southeastern parts of the country came from the east, by way of the Lake Ladoga region. Before the arrival of these immigrants there may have been a sparse but not insignificant basic population in Finland; in the western parts it consisted partly of German and Scandinavian elements. This theory provides a reasonable explanation for a genetic difference between the "western" and "eastern" people in Finland. It is further supported by the anthropologic studies of Kajanoja (fig. 7A), and by the boundary between the western and eastern groups of dialects (fig. 7B), both of which bear a remarkable resemblance to the boundary between lower and higher mortality from CHD shown in figures 1 and 2.

In any case, the greater part of Finland shown in figure 7C was only settled after 1500, mainly by immigrants from the province of Savo in southeastern Finland. If those immigrants were of eastern origin (which is difficult to decide as yet), then the middle and northern parts of the country would belong to the "eastern" group, and thus the "eastern" area would be very accurately consistent with areas 2 and 3 of great CHD mortality in figure 2. Some marker studies on blood groups by Nevanlinna and distribution of rare recessive diseases in Finland can also be interpreted as support for the dualistic theory.

The results of the present study are in good accordance with the dualistic theory of settlement and give support to that theory. They also support the
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hypothesis that the morphological alterations seen in the coronary arteries of infants may be preliminary stages of the CHD appearing in later life. Thus, the degree of alteration correlates with regional mortality rates in CHD. Secondly, this alteration especially concerns the inner vascular layers, in which the stenosing lesions of CHD occur.

Like many earlier studies concerning the genetics of CHD, this one gives little idea of what is inherited and in what manner. The genetic differences in proneness to CHD may depend on differences in the vulnerability of the IVL when subjected to extrinsic deleterious factors rather than on primary structural differences in the IVL. The small number of patients does not allow definite conclusions. The validity of our findings will have to be tested by further, more extensive studies.

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