The Coronary Arteries in Early Life
in Three Different Ethnic Groups

By Zeev Vlodaver, M.D., Harold A. Kahn, M.A., and Henry N. Neufeld, M.D.

SUMMARY
The histologic changes in the coronary arteries in full-term fetuses, infants, and children of 211 consecutive necropsy specimens from Ashkenazy, Yemenite, and Bedouin groups were studied, excluding cardiac deaths.

The developmental structural pattern of the coronary arteries is similar in the three ethnic groups.

Differences in the intensity and quantity of the structural findings between the sexes and among various ethnic groups are found in early life. The intimal tissue in the Ashkenazy male develops in an eccentric form, has more collagen tissue components, and is more highly developed than in the Ashkenazy female. Structural findings in the internal elastic membrane and the elastic fibers of the intima are less apparent in the Bedouin group, particularly in the female, than in the Ashkenazy and Yemenite groups.

Statistical analysis of the quantitative data showed the intima and musculo-elastic layers to be more developed in the Ashkenazy male than in the Yemenite and Bedouin males. However, Ashkenazy males clearly have more intima and musculo-elastic tissue than do the Ashkenazy females. This was not true for Yemenites and was found in only one of three age groups among Bedouins.

The relationship between the structural findings in coronary arteries of children under 10 years and the reported prevalence of coronary heart disease in the corresponding adult population in these three different ethnic groups has been pointed out.

Additional Indexing Words:
Necropsy study of coronary arteries
Fibroblastic proliferation
Developmental patterns
Ashkenazy Jews
Yemenite Jews
Bedouins

Coronary heart disease
Histologic changes

There is a low prevalence of coronary atherosclerosis and coronary heart disease among Yemenite Jews and among Bedouins, both absolutely and in relation to other ethnic groups in Israel.\textsuperscript{1-5} This has usually been related to the habitual intake of saturated fatty acids which is the predominant external influence on serum cholesterol.\textsuperscript{6-8} The histologic changes appearing in the human coronary arteries during the different stages of development from fetal life to childhood, characterized by changes of the internal elastic membrane, proliferation of fibroblasts, and thickening of the intima have been described.\textsuperscript{9, 10} They are present in all human populations\textsuperscript{11} and represent a naturally occurring process.\textsuperscript{12}

The aim of the present investigation was to study the histologic changes in the coronary arteries in full-term fetuses, infants, and children of various ethnic groups in Israel. It was felt that a comparison of the structural changes in early life among ethnic groups having different adult prevalences of coronary atherosclerosis might provide further information on the etiology and pathogenesis of this condition.

Methods
Our observations are based on histologic examination of 211 consecutive necropsy specimens (excluding those related to the cardiac

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demt Hospital, the University of Tel-Aviv Medical
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Bethesda, Maryland, U. S. A. (Dr. Kahn).
Table 1
Ashkenazim, Yemenites, Bedouins: Sex, Age and Ethnic Distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Ashkenazim</th>
<th>Yemenites</th>
<th>Bedouins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;sup&gt;♂&lt;/sup&gt;</td>
<td>&lt;sup&gt;♀&lt;/sup&gt;</td>
<td>&lt;sup&gt;♂&lt;/sup&gt;</td>
</tr>
<tr>
<td>Stillborn—6 days</td>
<td>12</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>1 Week—2 Months</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>3–12 Months</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>1–10 Years</td>
<td>11</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>27</td>
<td>59</td>
</tr>
</tbody>
</table>

Deaths) of Ashkenazy Jews, Yemenite Jews, and Bedouins from fetuses and children up to 10 years of age, during the period 1963-1966 from two medical centers (table 1). All investigations were made blind without knowledge of the type of case under study. The cause of death in most of the cases was an accident or infection. Transverse cross sections were taken from the right and left coronary arteries within 1 cm of their ostia and from the proximal portion of the left anterior descending branch.

Two sections were prepared from each site; one was stained with hematoxylin and eosin and the other with an elastic tissue stain and counterstained with van Gieson's connective tissue stain. For quantitative study of the transverse sections of the coronary arteries, the Visopan planimetric method was employed. The Visopan microscope projects the whole area of the artery on a matt screen. A planimeter, which measures the area as it passes over the walls of the artery, also provides an immediate reading.

Calculations of the ratio of intimal plus musculo-elastic tissue area to total area, for each individual, were based on weighted averages of the three arteries measured. Because of the small sample sizes, in many of the comparisons between differing sex or ethnic groups it was decided to use a nonparametric test of significance not requiring assumptions about normality of the data that seemed unlikely to be met. The test used was the Wilcoxon rank-sum test. The method of conducting the test requires taking data from two samples, for example, Yemenite males 1 to 10 years of age (n = 13) and Yemenite females 1 to 10 years of age (n = 6) and assigning ranks 1 to 19 to these 19 cases without regard to which sample they belonged. The test statistic is the sum of the ranks assigned to the smaller of the two samples, in this case, the Yemenite females
aged 1 to 10 years. By referring the test statistics to a table, it was possible to determine how unusual the particular data at hand were, if in fact both samples were random selections from the same population. The tables were calculated on the basis of the proportion of all possible permutations \( n_1 \times n_2 \) of elements, where \( n_2 < n_1 \) will have rank sums for the \( n_2 \) elements greater or lesser than some stated values.

All of the qualifications generally applicable to necropsy studies are applicable to this one as well. They arise from the potential for differential bias among different groups, as to which of the total deaths reach the autopsy table. Obviously, an autopsy study never can be based on a random sample of the populations being studied, but by restricting our analysis to consecutive autopsies after noncardiac deaths, we hope to have minimized the problem. We do not know of any factor operating to lead to differentially biased samples in the different groups. However, we cannot rule out this possibility.

Results

Quantitative Study

The results of this quantitative study may be summarized as follows:

Ashkenazy males had more intima and musculo-elastic tissue than Bedouin or Yemenite males (fig. 1). This was not true for females (fig. 2). The differences between Ashkenazy males and Yemenite males are significant in two of the four age groups and between Ashkenazy males and Bedouin males in the three age groups that were tested (table 2).

Ashkenazy males clearly had more intima and musculo-elastic tissue than females (fig. 3), the difference being significant in three of the four age groups (table 2). There is no definite relationship in the male-female comparisons in the Bedouin group. No differences were found between males and females in the Yemenite group (table 2).

Analyzing the average proportion of the total area represented by the intimal and musculo-elastic layers (each artery weighted by its total area) produces results very similar to those shown in table 2, which shows the findings obtained by analyzing the area of intimal and musculo-elastic tissue.

Because table 2 refers to many comparisons between various groups, a comment about the

<table>
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<th>Table 2</th>
<th>Intimal and Musculo-Elastic Layers (Quantitative Measurement): Results of Wilcoxon Rank-Sum Test Between Groups</th>
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<tr>
<td>Ethnic groups</td>
<td>Stillborn to 2 days</td>
</tr>
<tr>
<td>Male</td>
<td>Ashkenazy vs. Bedouin</td>
</tr>
<tr>
<td>Female</td>
<td>Ashkenazy vs. Bedouin</td>
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<tr>
<td>Ashkenazy vs. Yemenite</td>
<td>NS</td>
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<tr>
<td>Bedouin vs. Yemenite</td>
<td>NS</td>
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*NS = not significant (P > 0.05).

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Mean values of measurement of intima and musculo-elastic layer in coronary arteries in females of three ethnic groups.

Figure 2

Mean values of measurements of intima and musculo-elastic layer in coronary arteries in three ethnic groups. Comparison between males and females in 211 cases.

First, and perhaps most important, we have not selected any pair for comparison simply because the difference seemed large. The different groups: age (4), sex (2), and population (3) produced 276 possible pairwise comparisons. Significance tests were made and reported on the 36 pairs that we intended to report on before the data were collected. Then, although each test has a 0.05 (or 0.01) probability of incorrectly identifying a difference as real, the chance that at least
coronary arteries of the fetuses, infants, and children were characterized by fragmentation, splitting, and reduplication of the arterial elastic membrane, proliferation of the subendothelial fibroblasts with subsequent thickening of the intima and the formation of collagen tissue, and hyaline degeneration. The thickness of the media diminishes with the development of the intima, and between the intima and media the musculo-elastic layer develops. The adventitia, rich in connective tissue, is separated from the media by the external elastic membrane. Differences in the intensity of these structural findings were found in the three population groups in the first year of life.

Changes in Internal Elastic Membrane

The early fragmentation, splitting, and reduplication of the internal elastic membrane

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Figure 4

Pronounced changes in the internal elastic membrane. Left coronary artery of a 2-month-old male, Ashkenazy group. Elastic tissue stain counterstained with van Gieson’s connective tissue stain; ×70.

one of our 33* tests will incorrectly identify a real difference is very much greater than this. As a matter of fact, there is a non-negligible possibility of having one or two such false positive significance tests among our 33. However, since 12 of the pairs tested were found to differ significantly, the possible inclusion among the 12 of one or two false positive results would not materially affect our pattern of findings.

No differences were found in these figures between the right and left coronary arteries in each of the three groups.

Histologic Study

Examination of the material from 211 cases showed that the structural findings in the

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Figure 5

Moderate changes in the internal elastic membrane. Left descending coronary artery of a 2-month-old male, Yemenite group. Elastic tissue stain counterstained with van Gieson’s connective tissue stain; ×70.

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*Three pairs lacked an adequate number of cases for testing.
occupied almost the whole of the media, was well developed in the Ashkenazy and Yemenite groups, particularly in the former. This layer was also well developed in male Bedouin infants, but was poorly developed in the female Bedouin. The adventitia was well developed in all the groups studied and could be delineated from the media by the external elastic membrane.

In addition to the differences in the intensity of the findings between the various groups studied, there were also certain definite morphologic differences which were more obvious after the first year of life. In seven of the 11 cases in the 1 to 10-year-old male Ashkenazy group, changes in the intima were intense and eccentric. In some cases the intima occupied one third of the lumen of the vessel with predominance of collagen tissue.

**Figure 6**

Minimal changes in the internal elastic membrane. Right coronary artery in a 2-month-old female, Bedouin group. Elastic tissue stain counterstained with van Gieson's connective tissue stain; ×80.

were pronounced to be moderate in the Ashkenazy and Yemenite groups (figs. 4 and 5), minimal in the Bedouin female group (fig. 6) and minimal to moderate in the Bedouin male group (fig. 7).

**Fibroblastic Proliferation**

The subendothelial fibroblastic proliferation was more pronounced in the Ashkenazy male group and showed a tendency to eccentric development in six out of nine cases in the 1 week to 12 months age group (fig. 8). In six of the eight cases in the Ashkenazy females, in 36 of the 42 cases in the Yemenite, and in 38 of the 42 cases in the Bedouin 1 week to 12 months group, the proliferation of the fibroblasts was moderate in degree and arranged concentrically.

**Musculo-elastic Layer Development**

A thick musculo-elastic layer, which often
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somewhat more pronounced than in the female. None of the eight cases in the 1 to 10-year-old female Bedouin group showed changes of the type seen in the Ashkenazy group. In only four of the 14 cases in the 1- to 10-year Bedouin male group were collagen and elastic fibers found in the intima with predominance of the elastic tissue, but in most of these cases fibroblast proliferation persisted in the intima, even in this group.

The histologic findings in this study confirm our previous observations that in the normal heart the developmental and structural pattern of the coronary arteries is similar in the three ethnic groups.\textsuperscript{11, 12} The following phases were recognized in all the subjects studied and represent normal stages in the development of the coronary arteries in man:

\textbf{Figure 8}

\textit{Eccentric development of the intima, with fibroblastic proliferation, and pronounced changes in the internal elastic membrane. Left coronary artery of a 7-month-old male, Ashkenazy group. Elastic tissue stain counterstained with van Gieson's connective tissue stain; \times{}50.}

and reduced proliferation of fibroblasts in the intimal layer (fig. 9). Hyaline changes were also found in the intima during the first year of life.

In the Yemenite groups, the intima contained elastic fibers and collagen tissue in equal amounts; this so-called fibroelastic layer developed concentrically and did not affect the vessel lumen (fig. 10). There were no differences in male and female Yemenites.

In the female Bedouin group minimal changes were found in the intimal layer, even in later childhood, and the internal elastic membrane was intact or showed only localized splitting. The media was well developed, with rich elastic fibers interspersed between the rows of smooth muscle cells. In the Bedouin males, the intimal changes were moderate but

\textbf{Figure 9}

\textit{Asymmetrical thickening of the whole arterial wall. The intima occupies half of the lumen with collagen, elastic tissue changes, and vacuoles. Left descending coronary artery of a 7-year-old male, Ashkenazy group. Elastic tissue stain; \times{}32.}
Concentric development of the intima with predominating elastic fiber, in the left coronary artery of an 8-year-old male, Yemenite group. Elastic tissue stain counterstained with van Gieson's connective tissue stain; ×32.

(1) the reactive phase with degenerative and proliferative changes; (2) the adaptive phase with the development of the musculo-elastic layer; and (3) the maturity phase with the formation of collagen tissue and the elastic tissue changes in the intima. Differences in the quantity and intensity of these structural changes between the sexes and various ethnic groups are found even in early life.

Statistical analysis of the quantitative study showed the intima and musculo-elastic layer in the Ashkenazy males to be more developed than in the Yemenite and Bedouin males. These differences are apparent soon after birth, but are more obvious at the end of the first year of life. The intimal tissue in the Ashkenazy males is more developed than in Ashkenazy females. This was not true for Yemenites. Among the Bedouins, only one of the three groups tested showed such a difference.

These differences between the sexes and the ethnic groups in children up to 10 years of age are consistent with the known differences in the prevalence of coronary atherosclerosis, coronary heart disease, and myocardial infarction in the corresponding adult population.1-4

There is a significant difference in the prevalence and severity of atherosclerosis between the Ashkenazy and the non-Ashkenazy ethnic groups above the age of 50.1

In a long-term epidemiologic study of ischemic heart disease in Israel,2 the results of the age-adjusted rates for the diagnostic categories of angina pectoris and history of heart attack by areas of birth show the Central and East European groups with the highest rates of the disease, the Southeast European and Israeli groups in-between and the Middle East and North African groups with the lowest rates.

Other Israeli studies3, 7, 8 also indicated higher rates of myocardial infarction in males of European origin compared to those from Asia and Africa. Higher rates in males than females have also been shown in European-born, but not in the Asian-born group.5

The male predominance of intimal development in the Ashkenazy group in early life is similar to that found among American15 and European16 infants. The lack of sex differences in the intimal development in the Yemenite and Bedouin groups is similar to the findings in other ethnic groups that have a low incidence of coronary heart disease.17

In our study, interesting qualitative differences were found among the various groups. Changes in the internal elastic membrane and the elastic fibers of the intima were less apparent in the Bedouin group than in the Ashkenazy and Yemenite groups. In the Bedouins, in the 1- to 10-year age group—particularly in the females—an intact internal elastic membrane was a common finding, and the elastic fiber changes in the intima were moderate.

According to Lansing's theory18 changes of the elastic tissue of the intima in the

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arteries preceded the development of atherosclerosis, so that the low incidence of coronary atherosclerosis in the Bedouin adult life may be related to the lack of elastic changes in infancy. Studies based on elastic tissue staining and micro-incineration techniques show that the elastic elements of the arteries of Negroes manifest a lesser tendency to fragment than do the corresponding elements of the coronary arteries of white persons, a finding which correlates with the lower prevalence of coronary heart disease in the Negroes.19

The changes in the internal elastic membrane which occur in the Bedouin group after birth are similar to, but less intense than, those in the other ethnic groups. In the Bedouin, these initial elastic changes due to physiologic hemodynamic processes do not become more pronounced with age, as occurs in the other ethnic groups.

The intima of the Ashkenazy male develops in an eccentric form and has a rich collagenous tissue component. The collagen content of the intima reflects prior fibroblastic activity,20 and in sites where collagen is found the fibroblasts are few. This fact may explain the persistence of fibroblasts at later periods in the 1- to 10-year Bedouin age groups, and in some cases in the Yemenite groups.

The rate of cholesterol synthesis appears to be related to the collagen concentration of the tissues.20 The active avidity of collagen for cholesterol appears to be maximum in young connective tissues. It may, therefore, be possible to relate the rich concentration of collagen in the intima of the young Ashkenazy males with the high incidence of coronary atherosclerosis in the adult population.

The importance of fibrous plaques and the incidence of coronary heart disease have been emphasized in other studies.21

The possibility that the degree of collagen formation in early life is related to external factors, such as nutritional deficiency, which can influence the synthesis of collagen, has been considered. This, however, would not explain the difference in the amount of collagen tissue in the intima of males and females in the Ashkenazy group. Therefore, it seems more appropriate to assume that an intrinsic factor, most probably inherited, determines the maturity stage of the fibroblast and collagen synthesis, thus explaining the difference of collagen tissue formation in the coronary arteries in the males and females of the Ashkenazy group.

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