Coronary Arteries in Fetuses, Infants, and Juveniles

By Henry D. Moon, M.D.

The coronary arteries of young individuals ranging from fetuses to young adults were studied. Sclerotic lesions were not demonstrated in the coronary arteries of fetuses. In infants the early stages of arteriosclerosis were frequently present and consisted of rupture, degeneration and regeneration of the internal elastic membrane, deposition of mucopolysaccharide, and proliferation of endothelial cells and fibroblasts. These alterations were most prominent in infants of 3 to 4 months. In older individuals there was an apparent decrease in the rate of intimal fibrosis. The lesions of the coronary arteries of young individuals were identical with the early phases of arteriosclerosis in adults.

In a previous study of the coronary arteries it was observed that many different pathologic processes participated in the development of arteriosclerosis and that these processes had an orderly sequence of evolution. The earliest pathologic lesions were deposition of mucopolysaccharide in the intima, rupture, and degeneration of elastic tissue, and proliferation of subendothelial fibroblasts; these were followed by regeneration of elastic tissue and formation of collagen fibers in plaques; the later stages were characterized by deposition of lipid and cholesterol, hyaline degeneration of fibrous connective tissue, calcification, intimal hemorrhage, and thrombosis. The purpose of the present study is to determine the nature and frequency of pathologic processes in the coronary arteries of young individuals.

Materials and Methods

The hearts of 105 individuals were examined. The ages varied from fetuses of 3 1/2 months' gestation to young adults in their early twenties. The ages and sexes are shown in table 1. In all of the individuals death had occurred suddenly, without prior clinical evidence of illness, and usually from a violent physical injury. The proximal segments of the left anterior, left circumflex, and right coronary arteries were removed and fixed in formalin, and paraffin sections were prepared. The sections were stained with hematoxylin and cosin, Weigert's elastic-tissue stain, colloidal iron-prussian blue stain for acid mucopolysaccharide, and a modification of the aldehyde-fuchsin reaction for elastic tissue. In many cases, frozen sections of coronary arteries were stained with oil-red O and hematoxylin and contiguous sections were stained by the procedures used for paraffin sections.

Results

Fetuses. The coronary arteries of fetuses were the only ones in which no pathologic processes were observed (fig. 1A). The intima consisted of a single layer of endothelial cells lying directly on the internal elastic membrane. The internal elastic membrane was a prominent band of homogeneous refractile material lying between the endothelium and smooth muscle and was essentially a continuous tube with longitudinal corrugations. The medial coat of smooth muscle cells was relatively delicate; within it very fine elastic fibrillae were present. The tunica adventitia was an indistinctly defined layer of collagenous connective tissue and some elastic fibers.

In the coronary arteries of 2 individuals, 4 to 6 weeks premature, rupture of the internal elastic membrane was observed. However, there was no reduplication or fraying of the internal elastic membrane; nor was there proliferation of endothelial cells or fibroblasts adjacent to the site of rupture of the elastic tissue.

Infants. Lesions of the proximal segments of the coronary arteries could be demonstrated in most individuals. The earliest alteration was rupture and degeneration of the internal elastic membrane. The altered segment of elastic tissue was characterized by beading, fraying, or complete disruption (fig. 2A, 2B). Small bundles of smooth muscle and fragmented elastic fibrillae were closely associated in the formation of the musculoelastic layer occup-

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ing the zone between the intima and media. Deposits of mucopolysaccharide were observed in these areas. In some individuals there were fibroblastic proliferation, deposition of mucopolysaccharide, and regeneration of the internal elastic membrane. Proliferation of endothelial cells overlying these areas was observed in some instances (fig. 2E).

In infants several months old there had been definite progression of the intimal lesions as compared with newborn infants. Diffuse intimal fibrosis extending around the entire lumen as well as localized fibrous plaques were frequently present in all of the major coronary arteries. These alterations were very pronounced in infants 3 to 4 months of age (fig. 2C). The intima was commonly thicker than the media. Sclerosis was more frequent and more advanced in the left anterior descending coronary artery. Mucopolysaccharide was present in varying amounts (fig. 2F); collagenization was minimal. In some instances the sequence of rupture and subsequent regeneration of the internal elastic membrane had apparently occurred on multiple occasions. It was not uncommon to find several layers of degenerating elastic tissue

Table 1.—Distribution of Age and Sex of Cases

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
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<tbody>
<tr>
<td></td>
<td>Male</td>
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<tr>
<td>Fetuses:</td>
<td></td>
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<tr>
<td>3½ months to 9 months</td>
<td>—</td>
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<tr>
<td>Postnatal:</td>
<td></td>
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<td>0 to 2 years</td>
<td>36</td>
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<tr>
<td>3 to 10 years</td>
<td>13</td>
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<tr>
<td>11 to 22 years</td>
<td>5</td>
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FIG. 1A (Top). Coronary artery, 5-month-old fetus. The internal elastic membrane is intact. A few delicate elastic fibrillae are present in the tunica media and adventitia. Aldehyde-fuchsin. X55. B (Bottom). Coronary artery, 5-month-old male. There are occasionally macrophages with cytoplasmic lipid in the intima. The intima is greater in thickness than the media, which lies in the lower portion of the photomicrograph. Oil-red O-hematoxylin. X180.

on the endothelial side of the reconstituted internal elastic membrane. Frequently very fine droplets of lipid were present in the cytoplasm of fibroblasts as well as in macrophages

Fig. 2. A. Coronary artery, 4-day-old female infant. There is fraying of the internal elastic membrane and increase in thickness of the intima of the lower right portion. Aldehyde-fuchsin. X50. B. Higher magnification of figure 2A to show the area of elastic tissue undergoing alterations. Aldehyde-fuchsin. X200. C. Coronary artery, 4-month-old male infant. The larger artery is eccentrically thickened by intimal reaction. The pale areas in the thickened intima represent areas of unidentified, nonlipid material. The branch to the right shows beginning alteration of the intimal layer. Weigert. X29. D. Coronary artery, 2-month-old male infant. At the left there are bands of lipid in the position of the internal elastic membrane and having the configuration of this layer. The musculoelastic layer contains no demonstrable lipid. Oil-red O-hematoxylin. X200. E. Coronary artery, 6-month-old male. The intima shows a plaque at the lower center. In the upper portion of the artery there is early diffuse thickening of the intima. Aldehyde-fuchsin. X90. F. Higher magnification of plaque in figure 2E. Note rich deposit of mucopolysaccharide in the plaque. Colloidal iron. X360. G. Coronary artery, 3-year-old female. There is generalized thickening of the intima. The process is accentuated adjacent to the opening of the branch. Weigert. X21. H. Coronary artery, 11-year-old male. The intima is greatly thickened by fibroblastic proliferation and deposits of mucopolysaccharide. The media beneath the plaque is undergoing alterations in structure; increased amounts of mucopolysaccharide are present in the media. Colloidal iron. X50.
FIG. 2
No correlation was observed between the lipid droplets and the degree of intimal fibrosis. However, in some instances segments of degenerating elastic tissue were stained by oil-red O (fig. 2D).

In children 2 to 10 years of age the abnormalities noted in the intima were essentially similar to those observed in infants (fig. 2G). There were fibrous plaques as well as diffuse thickening of the intima. The internal elastic membrane was frequently ruptured and reduplicated, and mucopolysaccharide was present in varying amounts. Lipid droplets were occasionally present in these areas. Small amounts of collagen were present. However, in these individuals the sclerotic changes of the intima were relatively less than those in the young infants; the intima was usually thinner than the media.

In the older group, namely 10 to 22 years of age, there was evidence of continued disruption, degeneration and regeneration of elastic tissue, intimal fibrosis, and deposition of mucopolysaccharide (fig. 2H). Collagen was present in small amounts, and lipid was noted occasionally and in a few instances in larger amounts than seen in infants. Sex differences were observed at all ages after birth, the males exhibiting a greater degree of intimal thickening. Our observations in this regard are in essential agreement with the previous reports by Dock, Fangman and Hellwig, and Minkowski.

**DISCUSSION**

The association of lesions of the internal elastic membrane with deposition of mucopolysaccharide and subendothelial fibroblastic activity was a constant finding in the proximal segments of the coronary arteries of infants and children; this association was noted also in previous studies on the histogenesis of coronary arteriosclerosis in adults. Previous studies of arteriosclerosis by many investigators clearly demonstrate the importance of elastic tissue degeneration in the development of arteriosclerosis.

Our observations indicate that rupture and degeneration of the internal elastic membrane are the earliest demonstrable morphologic alterations. This is followed by deposition of acid mucopolysaccharide, fibroblastic proliferation, and regeneration of elastic tissue. It seems reasonable to assume that these morphologic alterations represent essentially a reaction of the vessel to an injury, e.g., intravascular tension greater than the tensile strength of the vessel wall. The proliferation of endothelial cells over early lesions may be interpreted as a part of this phenomenon. The deposition of acid mucopolysaccharide is considered to be a manifestation of fibroblastic activity. Support for this view is provided by the work of Grossfeld, Meyer, and Godman, who have shown that fibroblasts in tissue culture produce hyaluronic acid. Thus, it seems reasonable to regard the early phases of the arteriosclerotic process that are already established at birth as actually a manifestation of a generalized and basic mechanism of tissue reaction to injury. This concept necessarily implicates in the development of arteriosclerosis the many factors that may influence the reaction of connective tissues to injury. The absence of the later phases of hyalinization of plaques, accumulation of large amounts of lipid, and calcification is noteworthy in young individuals. These later stages may well be a function of the aging process. The presence of lipid in some degenerating segments of elastic tissue suggests that the appearance of lipid and degeneration of elastic tissue are closely interrelated.

The absence of lesions of the internal elastic membrane and of the intima in fetuses up to the age of 8 months is noteworthy; alterations in cardiovascular function immediately preceding and following birth may, at least in part, be responsible.

It should be noted that sclerotic thickening of the intima progresses at a rapid rate for several months following birth, so that if the same rate were maintained, coronary insufficiency would occur within a matter of a few years. To some extent, the encroachment of thickened intima on the lumen is counteracted by the increase in total caliber of the vessel that occurs as a normal component of the growth process; nevertheless, there is an apparent decrease in the rate of intimal fibrosis. Although the mechanisms involved are
unknown, this decrease may be effected by a
decreased rate of fibroblastic proliferation or
by intermittent regression of the sclerotic
process.

**Summary**

No lesions of the internal elastic membrane
or intima were demonstrated in the coronary
arteries of fetuses $3\frac{1}{2}$ to 9 months of age.
The early stages of the arteriosclerotic lesion
were frequently present in infants. Rupture
and fragmentation of the internal elastic mem-
brane were observed in newborn infants. This
was associated with deposition of acid muco-
polysaccharide, fibroblastic proliferation and,
ocasionally, endothelial proliferation. These
processes were followed by regeneration of the
internal elastic membrane. In many instances,
these processes had apparently occurred
repeatedly. The degree of intimal fibrosis in
infants several months old was marked and
indicated that this process had occurred at a
rapid rate, whereas in older children and in
young adults there was an apparent decrease
in the rate of intimal fibrosis.

These processes of degeneration and regen-
eration of the internal elastic membrane,
of deposition of mucopolysaccharide, and of
intimal fibrosis in the coronary arteries of
infants and young individuals are identical
with the early nonlipid phases of arterio-
sclerosis in adults.

**Summario in Interlingua**

Nulle lesiones del interne membrana elastic
o intima esseva demonstrate in le arterias
coronari de fetos de inter $3\frac{1}{2}$ e 9 menses de
etate.

Le prime stadios de lesion arteriosclerotic
esseva frequentemente presente in infants.
Ruptura e fragmentation del interne mem-
brana elastic esseva observate in neonatos.
Isto esseva associate con depositos de muco-
polysaccharido acide, proliferation fibroblastic,
e (in certe casos) proliferation endothelial. Iste
processos esseva sequite per regeneration del
interne membrana elastic. In multe casos iste
processos pareva haber ocorritte repetitemente.
Le grado de fibrosis intimal in infants de plure
menses de etate esseva marcate e indicava que
iste processo habeva ocorritte rapidemente
durante que in juveniles e juvne adultos le
processo intimo-fibrotic pareva esser deceleerate.

Iste processos de degeneration e regeneration
del interne membrana elastic, de deposition de
mucopolysaccharido, e di fibrosis intimal in le
arterias coronari de infantes e juveniles es
identic con le nonlipidic phases initial de ar-
teriosclerosis in adultos.

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