Histogenesis of Coronary Arteriosclerosis

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The coronary arteries of 250 individuals dying suddenly from traumatic or natural causes were studied. Many different histopathologic processes were found to participate in the development of coronary arteriosclerosis. The earliest changes which occurred, even in infants, were increased fibroblastic activity, deposits of mucopolysaccharide and degeneration of elastic tissue. These changes were not related to lipid deposition. Moderately advanced lesions were characterized by regeneration of elastic tissue, formation of collagen and lipid deposition. The far-advanced lesions showed hyalinization, abundant lipid deposition, calcification, intramural hemorrhage and thrombosis. The possible mechanisms involved in the development of coronary arteriosclerosis are discussed.

The purpose of this study, initiated several years ago, was to determine the sequence of histologic changes in the development of coronary arteriosclerosis in man. As a result of this study it has become apparent to us that multiple histologic processes participate in the development of coronary arteriosclerosis. These processes have a definite sequence in their appearance. The primary or earliest changes have already developed in most individuals by the second decade and in all individuals by the third decade.

Materials and Methods

The data for this study were obtained from autopsies on 250 individuals, nearly all of whom died suddenly without a preceding debilitating illness. The ages of these individuals ranged from 4 months to 90 years.

The hearts were weighed to the nearest gram. The major coronary arteries were sectioned at intervals of 0.3 to 0.4 cm., and multiple blocks of tissue were removed for histologic study from the left anterior, the left circumflex and the right coronary arteries from the proximal segments in areas of maximum sclerotic thickening. Sections of myocardium, endocardium and small coronary arteries were taken. The pieces of tissue were fixed in formalin and embedded in paraffin or carbowax. Multiple sections 7 microns thick were taken from the paraffin blocks and stained with hematoxylin and eosin. Contiguous sections of coronary arteries were stained for elastic tissue and frequently for mucoid ground substance. In 120 cases contiguous sections of the coronary arteries embedded in carbowax were stained for both lipid and mucopolysaccharide. (Both toluidin blue and colloidal iron techniques for mucopolysaccharide were used in many cases.) An unstained section processed in carbowax was used for examination under crossed polarizing lenses.

Observations

A general survey of the material indicated that there were multiple pathologic processes occurring in coronary arteriosclerosis. These processes were: (1) subendothelial fibroblastic proliferation of the intima; (2) appearance of increased amounts of mucoid ground substance in the intima and occasionally in the media; (3) fragmentation and degeneration of elastic tissue; (4) formation of collagen fibers in the intimal plaques; (5) regeneration of elastic tissue; (6) deposition of lipid and cholesterol; (7) "hyaline degeneration" of fibrous connective tissue; (8) deposition of calcium; (9) intramural hemorrhage and thrombosis.

Although there was marked individual variation there was a greater degree of sclerosis...
in the older age groups (fig. 1). The sclerotic changes were less severe in the smaller arteries. These findings were essentially similar to those reported by White and his co-workers.\(^3\)

### Nonsclerotic Coronary Arteries

Nonsclerotic major coronary arteries were not present except in very young individuals. The intima consisted of an endothelial layer beneath which were occasional fibroblasts (fig. 2A). In cross sections of arteries the internal elastic membrane was a delicate wavy layer. In longitudinal sections this layer appeared as a slender band separating the intima from the media. Thus, this layer was essentially a continuous tube (except for the ostia of branches) with longitudinal corrugations. A few delicate elastic fibrillae were present in the medial coat of smooth muscle. Mucoid ground substance was present in small amounts in the media. The adventitia consisted of a small amount of collagenous connective tissue and a few delicate elastic tissue fibrillae.

**Early Coronary Arteriosclerosis.** The early changes were present frequently even in apparently healthy young individuals in the first or second decade of life, who died suddenly of traumatic injuries and could be consistently demonstrated in the proximal segments of the coronary arteries of all individuals after the second decade.

The early lesions, which were best demonstrated in the coronary arteries of young individuals, were characterized by a slight diffuse increase in thickness of the intima. Occasionally this process was localized and involved only a small part of the circumference. Several histologic changes seemed to occur simultaneously. These were: (1) appearance of increased amounts of mucoid ground substance in the intima and media; (2) proliferation of

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**Fig. 1.** The average degrees of fibrosis of the intima and degeneration of the internal elastic membrane in the proximal segments of the coronary arteries by decades.

**Fig. 2A.** Nonsclerotic coronary artery; age 1 year 3 months; Weigert elastic tissue stain. \(\times 275.\)

**B.** Early coronary arteriosclerosis; age 4 months; Verhoeff elastic tissue stain. The intima shows fibrous thickening; degeneration and regeneration of the internal elastic membrane are present. \(\times 150.\)

**C.** Early coronary arteriosclerosis; age 56 years. Colloidal iron impregnation. The intima shows a mild diffuse thickening and increased mucopolysaccharide. The media shows deposits of mucopolysaccharide. \(\times 12.5.\)

**D.** Early coronary arteriosclerosis; age 16 years. Colloidal iron impregnation. There is diffuse thickening of the intima. \(\times 150.\)

**E.** Early sclerosis of coronary artery; age 24 years. Sudan III and hematoxylin. There is diffuse fibrosis of the intima. The lower segment of the thickened intima is filled with lipid; the upper segment contains none. \(\times 12.5.\)

**F.** Moderate advanced coronary arteriosclerosis; age 50 years. Colloidal iron impregnation. Large amounts of mucopolysaccharide are present in the intima and are greatest along the advancing intimal border of the fibrous plaque. There is some collagenization at the base of the plaque. \(\times 150.\)

**G.** Early coronary arteriosclerosis; age 35 years. Verhoeff elastic tissue. Several layers of fragmented elastic tissue appear in the intima adjacent to the media. The part of the intima closest to the lumen shows no elastic fibers and contains increased amounts of mucopolysaccharide. There is an increased amount of elastic tissue in the media.

**H.** Far advanced coronary sclerosis; age 43 years. Colloidal iron impregnation. Small deposits of mucoid ground substance are present in some "hyalinized" areas of the plaque in the large artery. Vacuoles due to lipid are present at the base and in the center of this plaque. Small areas of calcification (pale blue) are present. A branch of this artery at the right shows moderately advanced sclerosis; large amounts of mucopolysaccharides are present in the intima. \(\times 150.\)

*(The use of color in this illustration is made possible by a grant from Winthrop-Stearns, Inc., to the publication fund of the American Heart Association.)*
subendothelial fibroblasts; and (3) small areas of degeneration of the internal elastic membrane.

Fibroblastic proliferation of the intima was seen in all individuals past the age of 20. In most of the early lesions the fibroblasts were dispersed in mucoid ground substance (figs. 2B, 2C and 2D). Collagen was present in small amounts or not at all. Generally the mucoid ground substance was greatest in the areas of maximal fibroblastic proliferation. Increased amounts of mucoid ground substance were also present in some areas of the media.

Concomitant with the increase in mucoid ground substance and fibroblastic proliferation there were focal areas of degeneration of the internal elastic membrane. These areas of degeneration were most commonly seen beneath fibrous plaques. In some instances segments of degenerating internal elastic membrane were carried inward by herniations of smooth muscle (fig. 3A). There was subsequent fibrous replacement of the smooth muscle. In some areas there were successive layers of degenerating and regenerating elastic tissue (fig. 2B). The continuity of the internal elastic membrane was completely reestablished in some of these areas.

No direct or consistent relationship of lipid to the early lesions could be demonstrated. In arteries showing early sclerosis, lipid was frequently absent. In other arteries with early lesions fine droplets of lipid in the intima and occasionally in the media could be demonstrated with specific stains. The lipid appeared within the cytoplasm of elongated cells (fibroblasts) or in the intercellular ground substance. The presence and distribution of such droplets was unpredictable from the sections with hema-

![Fig. 3A](http://circ.ahajournals.org/)

**Fig. 3.** A. Early coronary arteriosclerosis; age 16 years. Verhoeff elastic tissue stain. A short segment of ruptured internal elastic membrane is being carried in by herniation of the media. X 150.

B. Early coronary arteriosclerosis; age 16 years. Verhoeff elastic tissue stain. The internal elastic membrane shows small areas of rupture and reduplication at the left where sclerosis is slight. At the base of a fibrous plaque to the right the elastic tissue is almost completely disrupted. Increased amounts of elastic tissue appear in the media. X 150.

Toxylin and eosin, elastic tissue or colloidal iron stains. Lipid droplets, when present, were in the thickened intima, media or in both layers. In some arteries showing early fibrotic intimal changes and lipid deposition, the fat was present only in some segments of the thickened intima and not necessarily related to a fibrous plaque (fig. 2E). Macrophages containing lipid were almost never observed in any of the early lesions.

**Moderately Advanced Coronary Arteriosclerosis.** With progression of the arteriosclerotic process, fibrous plaques, as well as a greater
degree of diffuse fibrous thickening of the intima, were consistently present. The base and centers of the plaques contained moderate amounts of collagen; the advancing intimal borders of the plaques were composed of loosely arranged fibroblasts and mucoid ground substance quite similar in appearance to the early lesions (fig. 2F). Mucopolysaccharide was more evident in the developing plaques than elsewhere; however, this was not a universal finding.

The internal elastic membrane showed more fragmentation and reduplication than in the early lesions (figs. 2G and 3B). The continuity of this membrane had been re-established in some areas of previous rupture.

Lipid was always present and appeared as both fine and coarse droplets. The distribution of the lipid was noteworthy in that the lipid was almost always greatest at the bases or in the centers of the plaque and least along the endothelial border (figs. 4A, 4B). The media showed more mucoid ground substance and greater collagenization than in most of the early lesions. Beginning encroachment of intimal plaques on the media was also noted.

**Far Advanced Coronary Arteriosclerosis.** Far advanced lesions presented changes not encountered in the earlier stages. Hyaline changes and calcification became apparent at this stage of development. The bases and centers of intimal plaques were hyalinized, and in these areas the lipid content (including crystalline cholesterol) was greatest. The hyaline material frequently was positive for mucopolysaccharide although the staining reaction was not as intense (fig. 2H). Lipid was often present in large globules; lipid-filled macrophages were encountered frequently. The advancing intimal borders of hyalinized plaques were cellular and contained little or no lipid; these areas resembled the early lesions. Calcification first became apparent at the junction of the thickened intima and media (frequently along the internal elastic membrane). Some areas of hyalinized plaques also were calcified. The elastic tissue was markedly degenerated and occasionally completely gone. Lymphocytic infiltration of the adventitia was a frequent finding.

Severe stenosis of the lumina or thrombosis occurred in arteries showing far advanced
changes (figs. 5A and 5B). In some of the hyalinized and fatty plaques there were focal to large areas containing hemosiderin and lipid-laden macrophages as well as lymphocytes. In considerable numbers of thrombosed arteries, hemorrhage into an intimal plaque had occurred with extrusion of hemorrhagic material, hyalinized and calcified tissue and lipid into the lumen.

In some individuals showing advanced thickening and hyalinization of the intima, the coronary arteries were not stenotic but had dilated lumens. These were encountered more frequently in the 70 to 90 year old group.

**DISCUSSION**

There is a remarkably close association of fibroblastic proliferation, increased amounts of mucoid ground substance and degeneration of elastic tissue in the earliest sclerotic changes of coronary arteries. These findings are essentially similar to the careful observations of earlier workers, notably Virchow, Aschoff, Schultz, and Wolkoff. The second stage is characterized by maturation of the "scar" (deposition of collagen) and regeneration of elastic tissue from the mucoid substrate. The third stage is one of degeneration or senescence characterized by the appearance of large amounts of lipid, hyalinization of connective tissue fibrillae and calcification. The affinity of hyaline material for colloid iron suggests that this material is related to the mucoid ground substance of the earlier lesions. It would seem likely that hyaline material repre-

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**Fig. 5.**

**A.** Far advanced coronary arteriosclerosis; age 75. Verhoeff elastic tissue stain. There is complete loss of elastic tissue at the base of the large plaque. In the center and at the base of the plaque there are acicular clefts and vacuoles due to lipid. Calcification is present at the base of the plaque. × 12.5.

**B.** Far advanced coronary arteriosclerosis with thrombosis; age 69. Verhoeff elastic tissue stain. × 12.5.
sis of the intima, increased mucoid ground substance and fragmentation of the internal elastic membrane occurs even in young individuals logically raises the question as to whether or not these changes may be regarded as "normal" or nonpathologic. Although we do not intend to discuss this question at present it should be pointed out that processes which predispose to or cause eventual dysfunction of an organ should by definition be regarded as pathologic.

The lack of correlation between lipid and early arteriosclerotic changes leads us to believe that the deposition of lipid is not the initiating factor in the development of coronary arteriosclerosis. Dock and Moschcowitz have more recently pointed out that intimal fibrosis and lipid deposition are separate pathologic entities. Wilens likewise observed fibrous plaques with little or no lipid in the aorta; however, he suggests that these plaques may be related to previous lipid deposition in infancy. While it is true that individuals with certain derangements in lipid metabolism may develop severe coronary arteriosclerosis and equally true that experimentally induced hypercholesterolemia may evoke profound "cholesterol arteriosclerosis," the histogenesis of such lesions bears little resemblance to histogenesis of coronary arteriosclerosis of the type that is commonly encountered in man. Indeed, if alterations in lipid metabolism play a role in the development of coronary arteriosclerosis, such derangements are localized to pre-existing fibrous plaques. A possible mechanism for deposition of cholesterol in areas rich in mucoid ground substance has recently been suggested by Faber.

On the other hand, in the moderately advanced and far advanced lesions of coronary arteriosclerosis, lipids, including cholesterol are consistently present. This may be the result of one or more of the following factors: (1) increased affinity of an abnormal intercellular ground substance for lipids; (2) abnormal lipid metabolism localized to focal areas; (3) liberation of lipids as a result of cellular degeneration; (4) a superimposed systemic defect in lipid metabolism which is manifested by deposition of lipid only in areas of preexisting damage. The distribution of lipid was noteworthy in that the largest amounts as well as the earliest appearance were generally in the central areas or at the bases of sclerotic plaques. This indicates that the vasa vasorum are more likely the source of any exogenous lipid in sclerotic plaques than the transintimal imbibition of lipid from the lumen of the vessel. Transintimal migration of lipid-laden macrophages was practically never observed in early lesions.

Fragmentation of the internal elastic membrane as a result of intra-arterial tension greater than the tensile strength of elastic tissue must be considered as a possible initiating mechanism in coronary arteriosclerosis. It is likely that the maintenance of elastic tissue and collagen by metabolic processes mediated through the intercellular ground substance are involved in the process of arteriosclerosis. Alterations in this mechanism secondary to nutritional or hormonal imbalance would produce quantitative or qualitative changes in intercellular ground substance, collagen and elastic tissue. The similarity between the arteriosclerotic lesions of monkeys in experimental pyridoxine deficiency and the early lesions of coronary arteriosclerosis found in man has been mentioned in a previous publication from this laboratory. Although the significance of pyridoxine deficiency in human arteriosclerosis is not known, its role through the enzyme systems concerned with protein metabolism and thus involved in the normal maintenance of connective tissue and ground substance bears further investigation.

All of the various histogenetic changes from early to late may occur not only in the same individual but are frequently observed in the same plaque. The earliest changes are always observed on the endothelial side of the plaque, superimposed on the layers with moderately advanced and late changes.

Conclusions

A study of the major coronary arteries of 250 individuals, most of whom died suddenly from traumatic or natural causes, indicates that multiple pathologic processes participate in the development of coronary arteriosclero-
sis and have an orderly sequence in their development. These processes bear certain similarities to the formation of scar tissue.

The earliest sclerotic lesion is characterized by the apparently simultaneous appearance of proliferation of subendothelial fibroblasts, increased amounts of mucoid ground substance and fragmentation of the internal elastic membrane. No relationship between these changes and the occasional presence of fine droplets of lipid could be demonstrated. The moderately advanced and far advanced lesions differed from the early lesions in that lipid was always present. In these lesions there was greater fibrosis of the intima and degeneration of the internal elastic membrane. The earlier stages of fibroblastic proliferation and increased mucoid ground substance, when superimposed on the later stages, were always present on the endothelial side of the plaque. "Hyaline" degeneration of the fibrous tissue and calcification occurred in the far advanced lesions. The possibility of "hyaline" degeneration resulting from abnormal polymerization of mucoid ground substance is suggested.

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REFERENCES

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