STRUCTURAL ALTERATIONS WITHIN THE AORTIC INTIMA IN INFANCY AND CHILDHOOD*

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Arteriosclerosis in young persons has been reported with increasing frequency in recent years. The most comprehensive study of juvenile arteriosclerosis is that of Zeek[1] who reviewed the world literature up to 1930. She collected 98 necropsied cases of patients under 20 years of age, but stated a complete survey was impossible since so few examples were listed in the medical indexes under either arteriosclerosis or vascular disease. One-half of the total number of cases in that report occurred during the age period from 10 to 14 years, with 6 cases less than 1 year old and 10 cases between 1 and 4 years of age. The survey included the aorta and peripheral and visceral vessels, but apparently was concerned only with atherosclerotic lesions. While no one condition stood out prominently enough to signify etiologic value, the infectious diseases were the most common cause of death, although Zeek hastened to add that such is also the case without arteriosclerosis.

Willius and Smith[2] studied the incidence and degree of coronary and aortic sclerosis in 5,060 consecutive post-mortem examinations. In the age group from 0 to 9 years of age the coronary arteries revealed grade I sclerosis in 10.2 per cent, and grade II sclerosis in 0.2 per cent. Similarly in the same age group the aorta disclosed grade I in 23.2 per cent, grade II in 0.5 per cent, and grade III in 0.2 per cent. Unfortunately, the histologic criteria for this grading were not stated nor was there any description of the pathologic changes or correlation with the cause of death.

The development of early and often severe arteriosclerosis in diabetic children has long been recognized. Warren,[3] who studied the incidence of arteriosclerosis by decades in diabetic patients, stated that no arteriosclerosis was observed in 9 cases from 0 to 10 years, while there was a 41 per cent incidence in 17 cases between 11 and 20 years of age. Likewise xanthomatosis, another systemic pathologic condition associated with a disturbance in cholesterol metabolism, has been shown to be fatal in very young children by reason of its effects on the vascular system.[4] That juvenile arteriosclerosis, even in the absence of metabolic disorders, may be progressively fatal is attested to by

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French and Dock's[5] analysis of 80 fatal cases of coronary arteriosclerosis in soldiers ranging from 20 to 36 years of age.

While all the instances cited refer to the atherosclerotic variety of arteriosclerosis in children and young adults, there have also been several reported examples of a very unusual type of arterial disease apparently limited to infants.[6-8] The affected vessels, including the aorta, revealed calcium deposition in relation to the internal elastic membrane with an associated intimal fibroblastic proliferation. The etiology of this condition has not been satisfactorily explained and it seems to have no counterpart in adult arterial disease.

Our interest in juvenile arterial disease was stimulated by the accidental finding of microscopic areas of intimal thickening in routine blocks from infants' aortas. Nothing unusual had been noted on gross examination of the aorta so that the location and extent of these changes could not be determined. Dock[9] described similar intimal changes in the coronary arteries of infants, terming them intimal cushions, and stated that the increased severity of the process in the male might be an explanation for the difference in sex incidence of coronary occlusion in later life. Fangman and Hellwig[10] confirmed's Dock's observations but believed that these thickenings represented the earliest stages of intimal atherosclerosis rather than an inherited anatomical peculiarity. Several questions presented themselves concerning this intimal change in the infant's aorta, *i.e.*, relative frequency, location, sex incidence, cause of death, histopathologic changes, progression, and possible relationship of this lesion to atherosclerosis.

Material and Method

In an attempt to clarify these problems, the aortas from 50 consecutive pediatric necropsies were studied. The entire length of the aorta was preserved and fixed in 10 per cent formalin. Serial blocks were taken in a transverse plane at 0.5 cm. intervals and numbered consecutively from the aortic valves to the bifurcation of the iliac arteries. Using this technic, the number of blocks varied from 10 to 57, with an average of 25 per case. A variety of staining procedures was used, including hematoxylin and eosin, Verhoeff's elastic stain, Mallory's phosphotungstic acid hematoxylin stain, Wilder's stain for reticular fibers, Masson's trichrome stain, buffered toluidin blue for evidence of metachromasia, and a periodic acid, silver, methenamine stain.[11] No attempt was made to correlate the findings with the clinical data until the study was completed.

Clinical Data

Twelve cases showing an unusual intimal thickening were encoun-

tered among the 50 aortas studied. Some of the data relevant to these children are collected in Table I. While this represents an incidence of 24 per cent, it must be pointed out that the figure has little significance in view of the peculiar age scatter. Thirty-nine of the total died within the first 2 weeks of life, the majority being either stillborn or premature infants, and in this group only one case was encountered. This was a premature infant of 7½ months' gestation who died on the first

TABLE I

Summary of Cases of Aortic Intimal Hyperplasia

Case no.	Necropsy no.	Age	Sex	Cause of death	No. of plaques	Location of plaques
1	A51-80	1 day	M	Prematurity (7½ months)	1	Low thoracic
2	A51-82	5 weeks	M	Atresia of ileum	1	Low thoracic
3	A51-3	6 weeks	M	Asphyxia from formula aspiration	2	Arch Lumbar
4	A50-104	10 weeks	M	Internal hydrocephalus, meningomyelocele	1	Arch
5	MPA51-40	3 months	M	Biliary duct atresia, biliary cirrhosis	1	Low thoracic
6	MPA51-22	6 months	M	Embryonal hepatoma with metastases	2	Low thoracic Lumbar
7	MPA51-39	6 months	M	Meningo-encephalitis	3	Arch and thoracic Lumbar (2)
8	MPA51-41	8 months	M	Biliary duct atresia, biliary cirrhosis	1	Lumbar
9	A51-17	17 months	M	Bronchopneumonia	1	Low thoracic
10	MPA51-34	8 years	M	Amyotonia congenita, bronchopneumonia	3	Low thoracic (2) Lumbar
11	MPA51-46	8 years	F	Skull fracture, subdural hematoma, contusion of brain	2	Mid thoracic Lumbar
12	MPA51-19	14 years	F	Rheumatic heart disease, subacute bacterial endocarditis	3	Arch Thoracic Lumbar

day of life. Each of the remaining 11 necropsied infants, ranging from 5 weeks to 14 years, showed evidence of intimal change. Although 10 of the 12 cases occurred in males, no conclusions can be drawn regarding sex incidence because so few female children in the older group were studied.

Considerable variation in the cause of death is apparent. Infectious disease accounted for 4 deaths while liver and biliary duct abnormalities were the cause of death in 3 cases. It is unfortunate that blood cholesterol levels were not determined in the latter.

The site of the intimal thickenings was determined and this is of interest because, in general, the distribution tended to correspond with that noted in atherosclerosis of later life. The numbers in parentheses

indicate that more than one focus of thickening was found within the area listed. Although lesions were observed in the arch, the thoracic and lumbar areas were the more frequently affected. It is of interest that these thickenings tended to be located on the posterior aortic surface.

Review of the family history of these infants disclosed no findings judged to be of significance.

Pathologic Findings

The intimal coat of the infant aorta is normally a very simple structure, being composed of a single layer of endothelium which appears to lie directly upon a prominent internal elastic membrane. Early in life there is formed a subendothelial zone consisting of branching elastic tissue, collagenous fibers, smooth muscle, and a few wandering cells. This is such a slowly progressive and uniform change throughout the vessel length that this layer normally has assumed little prominence even at puberty.

Bremer[12] has pointed out that mesenchymal differentiation appears at widely different periods in embryonic life in different arteries and is usually accompanied by a narrowing of the vessels as the circulation becomes more definite. Persistence of this mesenchyma-like structure was invariably noted in our study within the intima and inner media of the innominate, left common carotid and left subclavian arteries at birth, and for a considerable length of time thereafter (Fig. 1). This change is emphasized because similar intimal and medial changes were observed within the aortic arch adjacent to the point of origin of these three vessels (Fig. 2), and could readily be differentiated from the intimal lesion which will be described. Another aortic intimal structure which must be distinguished from pathologic intimal hyperplasia is the small elastic tissue elevations which are located just proximal to the origin of all aortic branches. These structures are well developed at birth, show no evidence of degenerative change in later life, and are recognized by their characteristic shape, location, and abundant elastic tissue (Fig. 3).

The changes with which this paper is concerned are entirely intimal, extending from the endothelial lining to the internal elastic membrane, and were not visible on gross examination. When viewed as a true cross section, these intimal thickenings were conchoidal and occupied one-fourth to one-half of the aortic circumference. Although there was variation in thickness, the plaques were generally between one-half and three-fourths the thickness of the underlying media. It is of interest that there was no correlation between age and degree of intimal

thickening, some of the examples of more marked thickening occurring in the younger infants. Despite the fact that the transition from the plaque to the normal intima was gradual, nothing unusual was noted within the intima adjacent to these thickenings (Figs. 4 and 5). The individual plaques were elongated in the longitudinal axis of the aorta and varied in length from 0.5 to 4.5 cm., with an average of 1.5 cm.

The endothelium over the affected areas revealed an apparent increase in the number of cells with cytoplasmic swelling and prominent vesiculation of their nuclear structure. Many of the cells were arranged tangentially and occasional cells appeared to be in a plane perpendicular to the luminal surface. Necrosis of the endothelium with deposition of a thrombus on the injured surface over the plaque was noted in cases 7, 9, and 12, all of these presumably being associated with bacteremia. Directly beneath the endothelium and comprising the main structure of the plaque was a pale-staining connective tissue matrix in which the only cellular elements appeared to be of fibroblastic origin. With the use of appropriate stains, much of this acellular material was shown to be elastic tissue (Fig. 6), and was distributed generally as a delicate network, although some relatively coarse fibers were present. The elastic tissue appeared to be of maximum density in the mid-portion of the plaque, with decreasing amounts as one approached either the endothelial layer or the internal elastic membrane. The latter structure was thickened in the region of the plaque and consistently showed focal loss of ability to stain a homogeneous black with Verhoeff's technic. In addition, it failed to show the usual undulatory appearance and seemed flattened, with indistinct margins, fragmentation, fraying, and disintegration of structure. At no point was there any evidence to suggest that the intimal elastic fibers described were arising from the internal elastic membrane. The remainder of the non-cellular material comprising this intimal thickening consisted of an extremely delicate meshwork of collagenous fibrillar material and small amounts of metachromatic staining material as demonstrated on formalin-fixed tissue with a buffered toluidin blue stain. The metachromatic substance was noted chiefly beneath the hyperplastic endothelial cells and in that portion of the intima which was in contact with the internal elastic membrane. It is of interest that this mucopolysaccharide substance was not present to a significant degree within the unaffected intima, although large amounts were noted within the interlamellar spaces of the media.

The cellular elements within the plaque, previously mentioned as fibroblastic in origin, were arranged generally in a plane parallel with the endothelial surface. Altschul,[13] who studied these cells, pointed out

that they have been variously interpreted as proliferated endothelial cells, peculiar migratory smooth muscle cells, and fibroblasts. He preferred the term intermediate since he believed dedifferentiation has usually not gone far enough to permit one to recognize their source.

The cells within the intimal thickenings were characterized by stellate eosinophilic cytoplasm with fibroblast-like multipolar processes. The cell nuclei were spindle or oval, vesicular, and although double nuclei were occasionally seen, mitotic figures and well defined nucleoli were not noted. The periodic acid, silver, methenamine stain, with which collagen fibrils and basement membranes stain dark gray to black, demonstrated each cell to be invested with a very thin cuticle of connective tissue substance. Embedded in this were many black fibrils which extended along the cytoplasmic processes and finally branched away to anastomose with fibrils of nearby similar cells (Fig. 7). Fibrils within the cuticle were sometimes seen in cross section so that it took on a beaded appearance. With Verhoeff's elastic stain some of the fibrils appeared to be elastic and were arranged in a loose, irregular network. The Masson trichrome stain showed no evidence of myofibrils within the cytoplasm of these cells. With the phosphotungstic acid hematoxylin stain a delicate blue pericellular cuticle with a few blue-staining, fine fibrils running along these cells was seen. The periodic acid silver stain revealed this cuticle and the fine, blue-staining fibrils seen with phosphotungstic acid hematoxylin were stained black. These blue staining fibrils were called fibroglia by Mallory[14] who stated they were most numerous in young rapidly growing connective tissue and that they differed chemically from collagen and elastic fibrils. It is our opinion that the periodic acid, silver, methenamine stain demonstrates this cuticle and that embedded within it are fine collagen fibrils. Whether a small percentage of these fibrils embedded in the cuticle are fibroglia or not is not known. Elastic tissue as seen in stains for elastica appears as a tangled network but its exact relationship to the cuticle of these cells is incompletely understood. We think that these cells are fibroblasts and that the periodic acid, silver, methenamine stain gives the most precise detail of this intimal cell.

Medial and adventitial abnormalities were not observed in any of the cases herein reported. Very little attention was directed toward other vessels in these children although the iliac arteries were examined in the majority of cases. Plaques similar to those within the aorta were not seen, although one instance of true medial calcification was noted in case 1 (Fig. 8). This was a premature infant of 7½ months' gestation, who expired on the first day of life and both iliac arteries were affected.

Discussion

The sequence of events which occurs in the development of the atherosclerotic plaque is incompletely understood. Much of the present-day investigation has been concentrated upon the rôle and manner of deposition of lipids while the more basic processes such as intimal fibrosis, hyalinization, and calcification have been largely ignored. This attitude has been due chiefly to the experimental production of atherosclerosis by the administration of cholesterol to a variety of animals. Although most investigators caution against drawing too close an analogy between lesions of experimental and human atherosclerosis, the majority admit that there are striking similarities at the so-called fatty stage of the lesions. The technic followed in our study did not permit the use of fat stains but others have noted minute amounts of lipid within similar plaques in young persons. Lev and Sullivan[15] stated that in some foci of aortic endarteriosclerosis, fat is deposited in the ground substance, muscle fibers, and elastic fibers, and that these fat accumulations become larger with age, forming elevated zones. Although we did not see macrophages in any of our cases, Lev and Sullivan noted these secondarily, with a marked increase in collagen fibers even later. Similarly, Fangman and Hellwig,[10] in their study of cushion-like elevations in the coronary intima of newborn infants, found lipid deposits along the elastic fibers, in the stroma of the cushions, and sometimes within large histiocytes.

Although not a part of the present study, we have recently encountered in 2 very young persons fatty and calcific aortic plaques of grossly typical adult type. The first child was 10 years of age and died as a result of chronic glomerulonephritis (Fig. 9), and the other was 16 years old and died from chronic rheumatic heart disease (Fig. 10). Microscopic examination revealed plaque-like elevations which were strikingly similar to those herein described. There was, however, in these 2 cases, focal necrosis of the fibro-elastic tissue, and the appearance of lipid-containing macrophages was a conspicuous feature. Karsner[16] accepted the opinion that the first change in arteriosclerosis is damage in the lower intima with splitting of elastic fibers, some destruction of fibrous connective tissue and even of muscle, and deposit of lipids. In response to this injury connective tissue then is formed in excess to produce intimal plaques. Since it is our impression that the lesions we have described in these 12 children may be an early phase in the development of the adult atherosclerotic plaque, a few comments on the possible genesis of this lesion in children may be warranted. The first stage is undoubtedly concerned with the action

of some injurious agent, as yet unknown, upon the subendothelial fibroblasts and adjacent internal elastic membrane. The latter structure manifests this by fraying, fragmentation, and the loss of ability to take a deep elastic stain. This injurious effect results in an excessive reparative process by the occasional subendothelial fibroblasts which proliferate and deposit successive layers of elastic tissue and loose collagen fibers. Subsequently the connective tissue cells apparently degenerate, disappear, and at the same time hyalinization of the connective tissue fibrils occurs. Concurrently, lipidic substances accumulate and excite the migration of macrophages into the area to phagocytize this foreign material. Dystrophic calcification is prone to occur in any such necrotic fatty area.

While the relationship of elastic tissue to the formation and development of the atherosclerotic plaque is not clear, certain observations may be pertinent. Blumenthal, Lansing, and Gray[17] pointed out that elastic tissue breakdown and its subsequent calcification may predispose the vessel to intimal plaque formation. Using the micro-incineration technic, they showed that in the aorta and in renal, iliac, and hepatic arteries, calcification is intimately associated with alterations in the physical character and pattern of distribution of elastic tissue. Furthermore, they stated that the intensity and rate of calcium deposition are directly proportional to the intensity and rate of elastic tissue changes. The data of Blumenthal, Lansing, and Wheeler[18] regarding the age incidence of aortic medial calcification show an incidence of medial calcification prior to 20 years of age of only 4 per cent, with an increase to 58 per cent in the group between 20 and 30 years of age. Quantitative analysis of the medial elastic content of the human aorta by these same investigators revealed average elastin content of over 48 per cent in the first 2 decades of life, while in the third decade and thereafter decrease to values between 41.1 and 44.1 per cent was observed.[19] Our observations regarding intimal elastic tissue in children cause one to speculate that, had this elastic content study been extended to include the aortic intima, equal or even more marked changes of a similar trend might have been noted.

Summary

The entire length of the aorta from 50 routine necropsies on infants and children was studied in an effort to determine the frequency, age incidence, location, and histologic pattern of intimal fibrous thickenings which were not visible on gross inspection of the aorta. Fibroelastic plaques were found in one of 39 infants less than 2 weeks of age and in each of the remaining 11 children ranging from 5 weeks to

14 years of age. Because the contours and the anatomical location of these plaques corresponded so closely to the lesions of adult atherosclerosis, it is postulated that these intimal thickenings may represent the earliest phase in the development of the adult lesion.

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[*Illustrations follow*]

DESCRIPTION OF PLATES

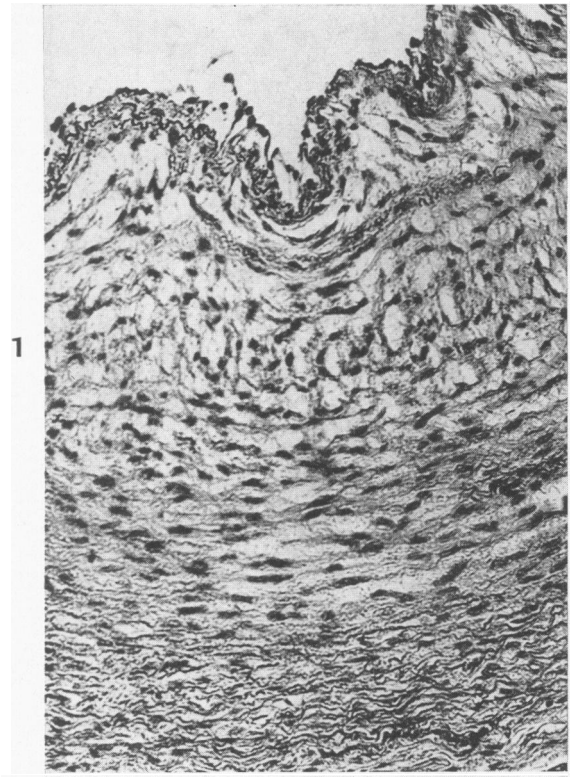
PLATE 146

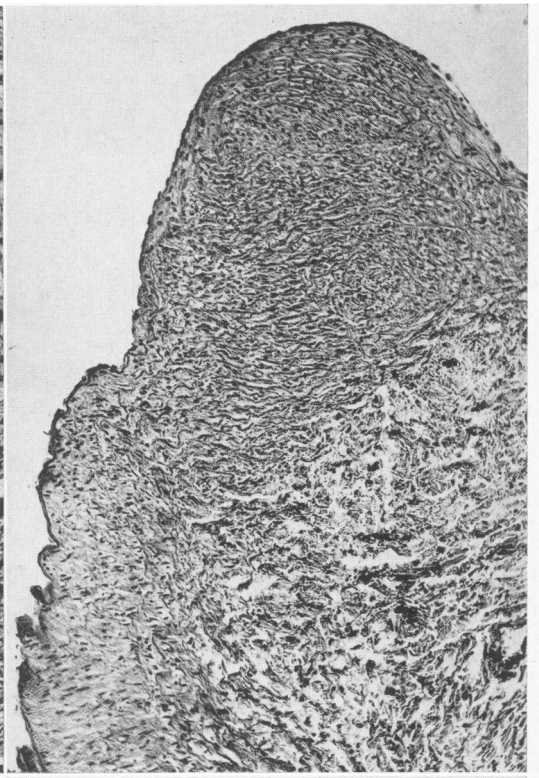
FIG. 1. Innominate artery from a 2-day-old child. The loose mesenchymal structure of the intima and inner media is apparent. × 175.

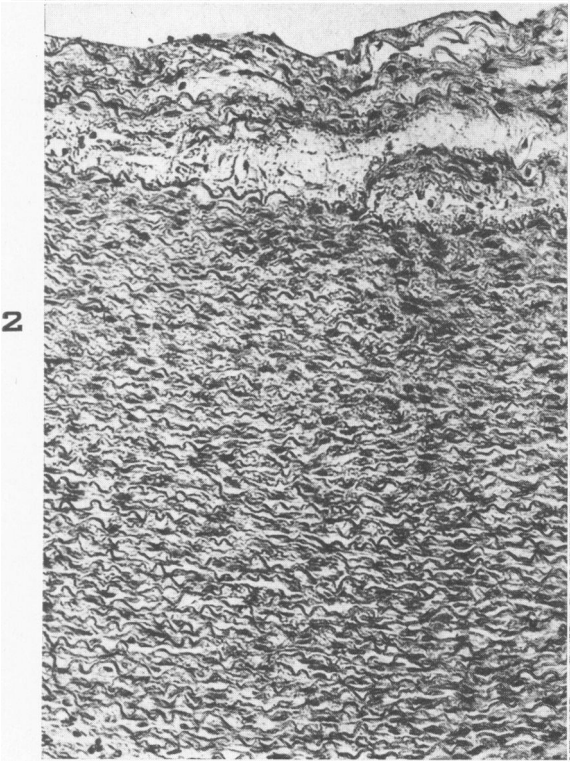
FIG. 2. Aorta at a point adjacent to the origin of the innominate artery of the same infant used for Figure 1. Intima of this character was present constantly in the aortic arch and can be differentiated from true fibro-elastic hypertrophy. × 175.

FIG. 3. Normal elastic intimal hillock noted just proximal to all aortic branches. × 100.

FIG. 4. Case 7. Normal aortic intima at a point opposite thickening shown in Figure 5. × 175.







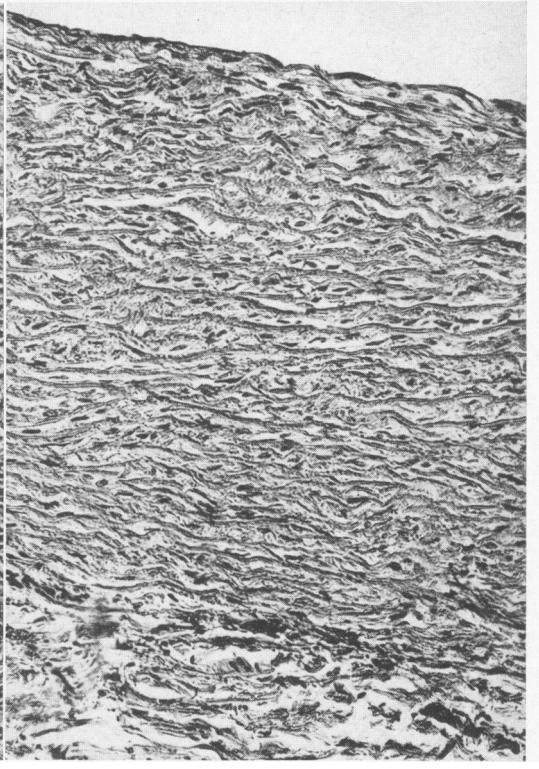


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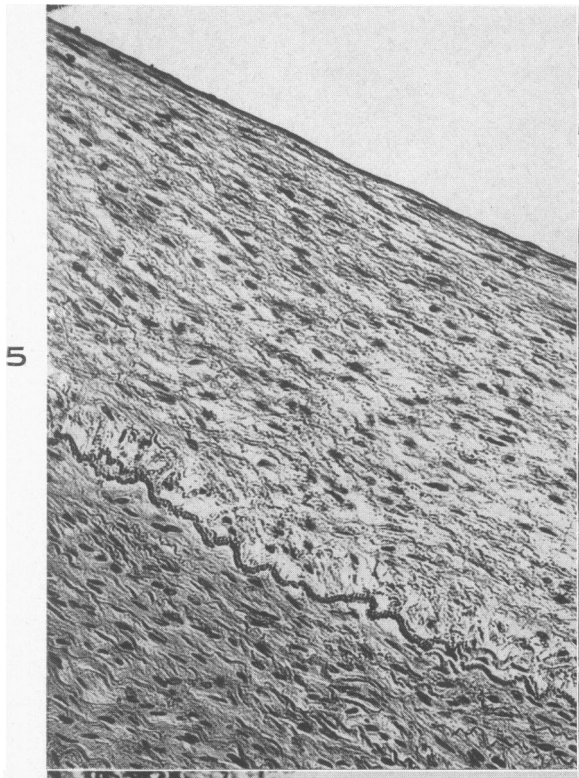
PLATE 147

FIG. 5. Case 7. Intimal fibro-elastic plaque at a point opposite normal intima of Figure 4. Fraying and splitting of the internal elastic membrane is apparent. × 175.

FIG. 6. Case 10. Elastic stain of an intimal plaque. Changes within the internal elastic membrane are particularly prominent. × 175.

FIG. 7. Case 11. Silver-positive filamentous processes radiating from an intimal fibroblast within a plaque. × 1725.

FIG. 8. Case 1. Calcification within the media of a common iliac artery. × 175.



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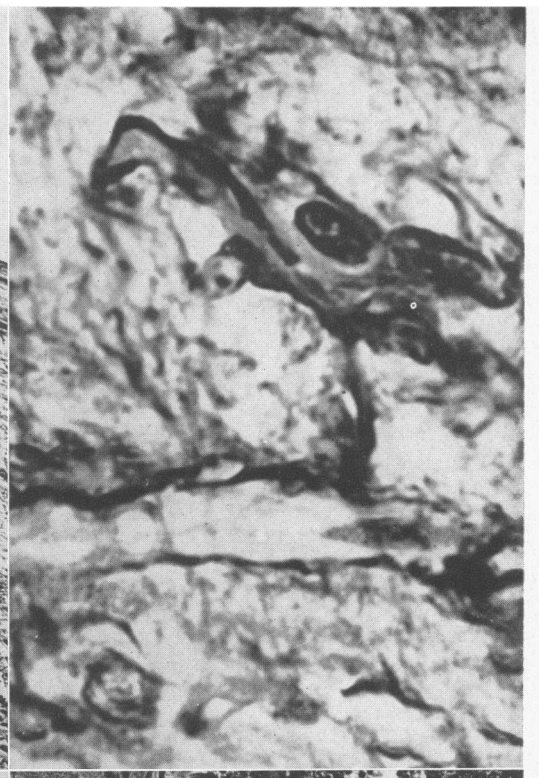

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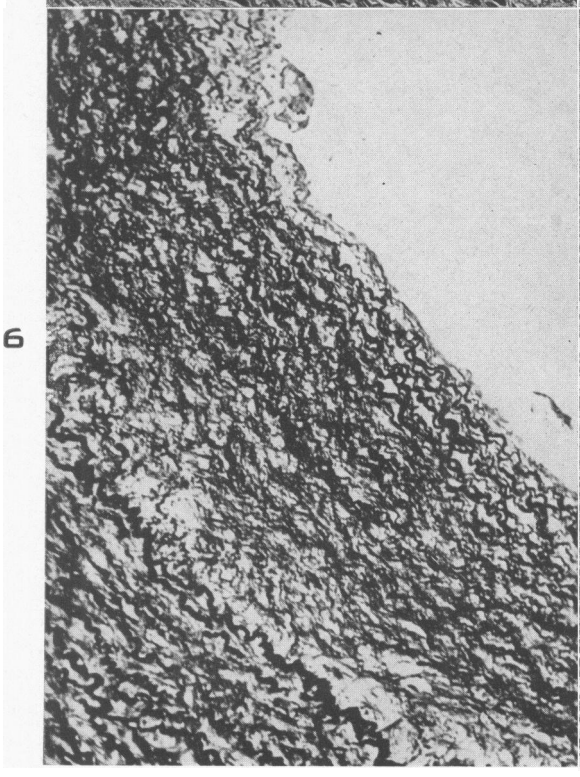

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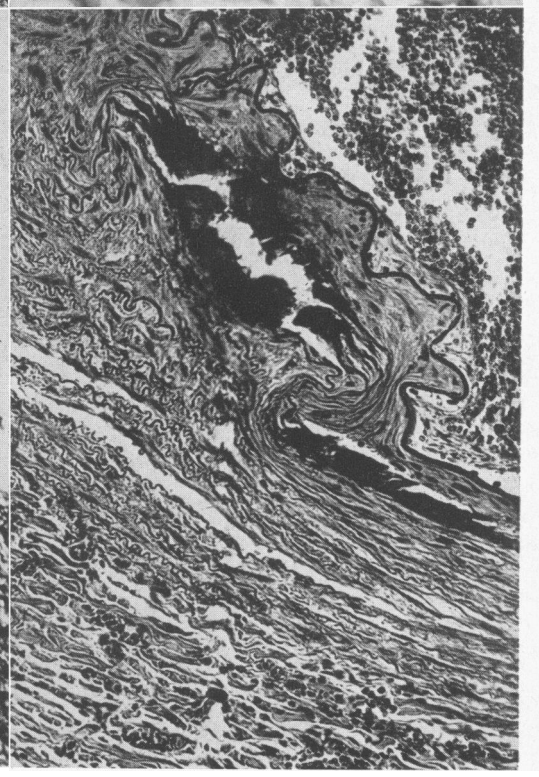

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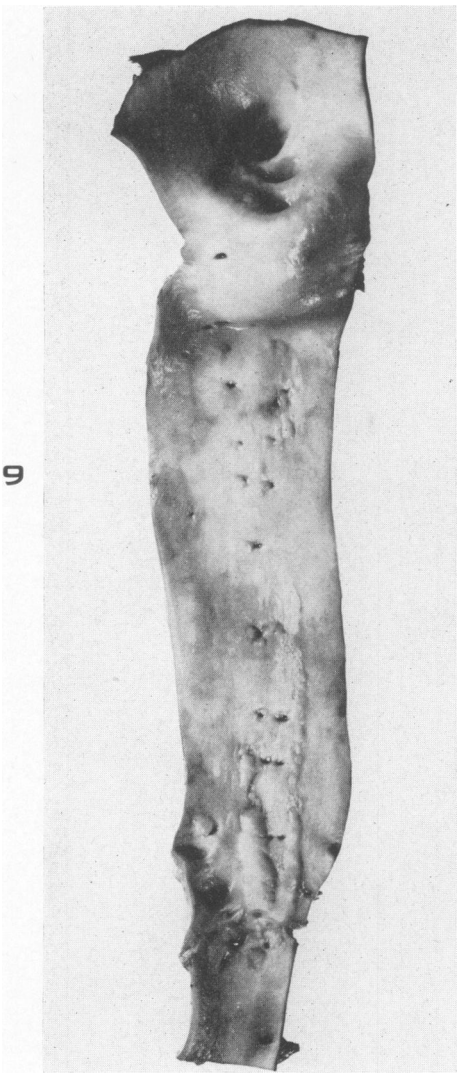
PLATE 148

FIG. 9. Entire length of aorta from a 10-year-old male dying from chronic glomerulonephritis.

FIG. 10. Aorta from a 16-year-old-male dying from chronic rheumatic heart disease. The arch is above.



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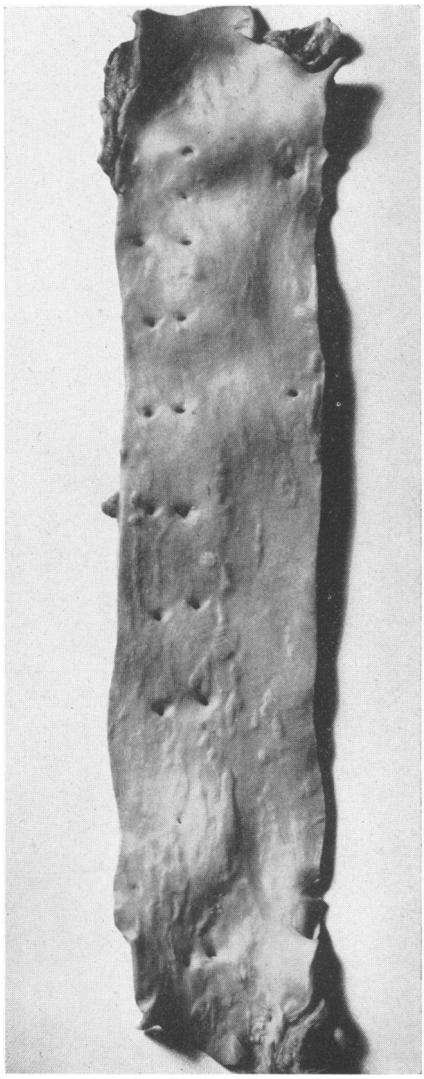

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