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Atherosclerotic Stenosis of the Extramural and Intramural Coronary Arteries of Man

Related Lesions *

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Summary. Atherosclerotic stenosis of the extramural coronary arteries was quantitated for a series of 223 hearts of adults and found to correlate positively with values for stenosis of the intramural coronary arteries of that series. However, minor grades of extramural coronary stenosis may be associated with advanced stenosis of the intramural coronary arteries and myocardial microinfarction, which may explain symptoms of ischemic heart disease in the absence of demonstrable extramural coronary stenosis. Stenosing lesions of extramural and intramural coronary arteries apparently involve the same process, and develop through reorientation, proliferation and migration of pleomorphic smooth muscle cells of the arterial wall, combined with increased formation of mucopolysaccharides, and elastic and collagen fibers. The process corresponds to that by which coronary arterial stenosis appears to develop in swine and other animals.

Zusammenfassung. Bei 223 Herzen adulter Menschen wurden stenosierende atherosklerotische Veränderungen an extra- und intramuralen Arterien quantitativ ausgewertet. Zwischen beiden Arteriensystemen besteht eine positive Korrelation hinsichtlich Grad der stenosierenden Atherosklerose. Einzelne Herzen mit nur geringgradiger Stenose extramuraler Arterien wiesen jedoch eine hochgradige Stenose intramuraler Arterien und gleichzeitig Mikroinfarkte auf. Solche Befunde können Symptome einer ischämischen Herzkrankheit beim Fehlen nachweisbarer extramuraler Coronarstenosen erklären. Stenosierende Veränderungen an extra- und intramuralen Coronararterien haben eine gemeinsame Pathogenese und entwickeln sich durch Reorientierung, Proliferation und Migration von pleomorphen glatten Muskelzellen der Arterienwand, kombiniert mit vermehrter Bildung von Mucopolysacchariden, elastischen und kollagenen Fasern. Diese Genese entspricht derjenigen der stenosierenden Coronarsklerose beim Schwein und anderen Species.

Introduction

Spontaneous myocardial infarction and fibrosis of zoo and of domesticated animals have been attributed to atherosclerotic stenosis of the intramural coronary arteries because advanced stenosis of these arteries always accompanied the myocardial lesions, while pronounced stenosis of the extramural coronary arteries was extremely rare (Ratcliffe *et al.*, 1960; Ratcliffe, 1965, 1968; Luginbühl and Jones, 1965; Luginbühl and Detweiler, 1965; Luginbühl, 1966a, b; Lindsay and Chaikoff, 1966; Detweiler *et al.*, 1968). Myocardial infarction and fibrosis in these animals were usually distributed through the inner third to inner half of the left

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ventricular wall, which in location, at least, corresponded to the more frequent sites of myocardial (post infarction) fibrosis in man (Sayen and Sheldon, 1949; Wartman, 1963; Otsu, 1970). However, post infarction myocardial fibrosis in man usually has been attributed to stenosis or occlusion of one or more of the extramural coronary arteries (Blumgart *et al.*, 1940; Baker *et al.*, 1961; Tjotta, 1963; Otsu, 1970).

Nevertheless, relationship between clinical and anatomical signs of myocardial ischemia and fibrosis, and intramural coronary stenosis in man has been known or suggested, for many years (Sutton and Brandes, 1931; Zinck, 1939). More recent studies provide additional indirect and direct evidence of this relationship (Edwards, 1956; More and Sommer, 1962; Donomae *et al.*, 1965; Baroldi, 1966; Likoff *et al.*, 1967; Bruschke *et al.*, 1971).

The present study was undertaken to determine the frequency and severity of stenosis of the intramural coronary arteries of man as seen at autopsy of adults that had died of myocardial infarction and of a variety of other disease processes. This study also attempts to determine whether or not stenosing lesions of the intramural coronary arteries may be related to atherosclerotic stenosis of the extramural coronary arteries and to myocardial infarction.

Material and Methods

Autopsies at the Underwood Memorial Hospital, Woodbury, New Jersey (U.S.A.) provided 223 hearts from adults for this study, 105 from females aged 25–94 years, mean 65.9, and 118 males aged 30–95 years, mean 66.8. Major causes of death in this series were myocardial infarction and myocardial weakness, 65; neoplasms, 42; pulmonary embolism and pneumonia, 32; cerebral hemorrhage, 23, and renal disease, 15. Lesions suggesting diabetes were found in 4 of the series.

This series provided 89 examples of myocardial infarction, 23 acute, 26 acute recurrent and 40 fibrotic lesions unaccompanied by acute infarction. Twelve each of the acute and acute recurrent lesions were not accompanied by thrombosis of extramural coronary arteries. Coronary arterial thrombosis accompanied 2 of the fibrotic lesions, and in one instance thrombosis was not associated with a recognizable myocardial lesion.

Redfield recorded the severity of extramural coronary stenosis in the unfixed specimens by transecting the arteries at 2–3 mm intervals from origins through segments 3–5 cm in length. Maximum grade of stenosis was recorded for each artery according to an arbitrary scale 0–5. Thus, 0 = no lesion, $1 < 25\%$ stenosis, $2 < 50\%$, $3 < 75\%$, $4 > 75\%$ and 5 occlusion. Values for the right, the anterior descending and the left extramural coronary arteries, as recorded separately, ranged from 1–5, and were totaled for each heart for comparison with heart-score values, which are estimates of the severity of intramural coronary stenosis as will be explained presently.

After values for extramural coronary stenosis had been recorded, Redfield cut a block of myocardium 6–8 mm in thickness through both ventricles perpendicular to their longer axis and approximately midway between apex and base. These blocks were fixed in buffered neutral formalin, and after fixation, a complete sample was cut from the proximal surface of left and right ventricular walls and septum for histological sections.

Ratcliffe recorded heart-scores without knowledge of the grade of extramural coronary stenosis or cause of death. Heart-scores estimate the severity of intramural coronary stenosis and depend upon two factors: 1) number of arterial cross sections greater than 15–20 μ in microscopic sections from hearts and 2) estimated grades of stenosis (luminal reduction) in each of these arteries.

Stenosis is estimated from luminal reduction by cells and intercellular substances between internal elastic membrane and endothelium, in sections stained by the Weigert-Van Gieson-

lightgreen method. And again values for stenosis are arbitrary, 0–5: 0 = no lesion, 1 < 25%, 2 < 50%, 3 < 75%, 4 > 75% and 5 occlusion.

Derivation of a heart-score, illustrated by an example from this series, follows: $(1 \times 202 + 2 \times 126 + 3 \times 44 + 4 \times 15) : 420 = 1.538$, which is rounded to 1.55. Here, 1, 2, 3 and 4 are grades of stenosis: 202, 126, 44 and 15, numbers of arterial cross sections so classified according to grades of stenosis, and 420, total cross sections of arteries in the microscopic preparations from this heart. Values thus derived are increased by 1.0 for convenience in statistical treatment, when for example, values may be 0.95 or less. Thus a value of 1.0 would mean: no lesions found. Values increase with the number of stenotic arteries and the grade of stenosis in each, and for this example the value was 2.55.

Heart-scores are derived from samples of the intramural coronary arterial bed, samples being contained in microscopic sections from each heart and of course, subject to the variations of sampling. This method was developed and validated for quantitating the more rapidly progressive intramural coronary lesions of chickens (Ratcliffe and Snyder, 1967). Later it was used for quantitating intramural coronary stenosis of adult swine with heart weights of more than 1 kg (Ratcliffe *et al.*, 1969). Hence, in terms of sample size the method is considered valid for this study.

Results

Extramural Coronary Arteries

Numerical values for stenosis of the proximal segments of the left, the anterior descending and the right coronary arteries of this series ranged from 3 to 14, the higher value signifying a grade 4 lesion in 1 and thrombosis of 2 arteries. Values for stenosis of the proximal coronary arteries for this entire series divide naturally into 5 groups, which reflects the relative uniformity in size of stenosing lesions in the 3 arteries of a majority of the hearts. For example, 30 hearts have been assigned to group 1 in which all extramural coronary scores were 3, and each artery contained a grade 1 lesion. Similarly, group 2 contained 33 hearts (maximum grade of stenosis for 3 arteries = 6) and in this group only 1 heart contained proximal coronary lesions of unequal size, its formula being $3 + 1 + 1$, with the larger lesion located in the left coronary artery.

In the 57 hearts assigned to group 3 values for stenosis of the proximal coronary arteries ranged from 7–9, but only 4 of this group were graded less than 9 and in them the larger lesion also had formed in the left coronary artery. Of 82 hearts in group 4 of this series extramural coronary stenosis was graded 10–12. And in 47 hearts graded less than 12 the more advanced lesions were distributed as follows: left coronary 16, anterior descending coronary 21, and right coronary 10. Twenty-one hearts contained grade 4 coronary lesions with 1 or more thrombi to give totals for extramural coronary stenosis of more than 12.

Values for extramural coronary stenosis generally tended to increase with age, but did not follow a consistent pattern. Regression analysis of values for extramural coronary stenosis on age found that the association was not statistically significant.

Intramural Coronary Arteries

Stenosis of the intramural coronary arteries was found in all hearts of the series. Values ranged widely, but may be grouped into five classes that correspond to the classes of extramural coronary stenosis. A considerable range of values was expected from earlier experience, but in this study extensive scarring was encountered for the first time, and found to interfere with heart-score determina-

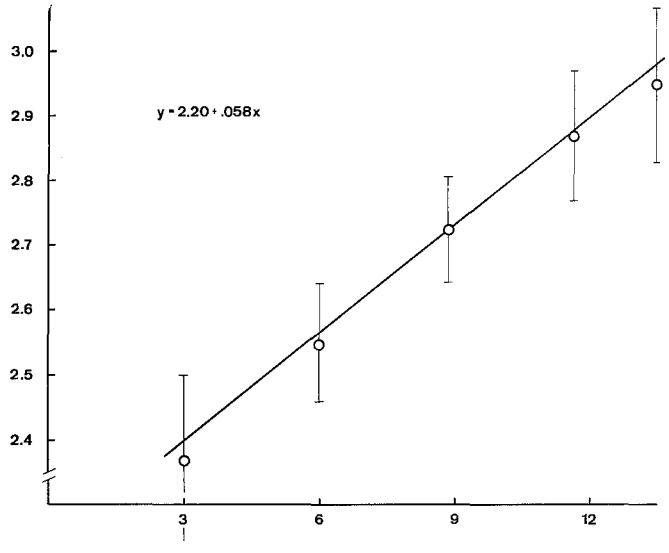

Fig. 1. Regression of values for extramural coronary stenosis (sums of grades 1 to 5×3, horizontal axis) on values for intramural coronary stenosis, heart-scores (vertical axis). Heart-scores grouped according to values for extramural coronary stenosis. Mean heart-scores for each group with 95% confidence limits

tions. Accordingly, 13 hearts of group 4 and 9 hearts of group 5 were omitted in calculating mean heart-score values.

Heart-scores for group 1 extramural coronary stenosis ranged from 140, the lowest values in the series, to 3.50, one of the highest, with a mean value of 2.45 and only 3 of 30 heart-scores greater than 2.95. Heart-scores of 2.95 or larger were accompanied by either or both recent and fibrotic microinfarcts in approximately 75% of the series. Heart-scores for group 2 ranged from 2.15 to 3.40, mean value 2.54 with only 2 of 33 scores greater than 2.95. Values for group 3 ranged from 1.80 to 3.50, mean value 2.68 with 12 of 57 scores greater than 2.95. Group 4 values ranged from 2.45 to 3.40, mean 2.79 with 21 of 69 scores greater than 2.95. Group 5 scores ranged from 2.60 to 3.40, mean 2.91 with 4 of 12 values greater than 2.95. Thus, less than 10% of heart-scores for groups 1 and 2 approximated the maximum, but the frequency of higher values increased to 20% for group 3 and to 30% for groups 4 and 5. Fig. 1 illustrates a regression analysis of values for extramural coronary stenosis (horizontal axis) on intramural coronary stenosis or heart-scores (vertical axis). The t test for the regression equation gave a value of 9.36 with 3 degrees of freedom ($P < 0.01$). The 95% confidence limits for mean heart-score values of this series also are shown on (Fig. 1).

Age and heart weight were not significantly related to heart-score values according to regression analysis.

The functional significance of intramural coronary stenosis in this series cannot be fully estimated, but the increasing severity of this disease process in association with increasing extramural coronary stenosis was accompanied by an

increased frequency of microinfarcts of the myocardium. Thus, in groups 4 and 5, 2 to 3 generations of microinfarcts (indicated by the apparent age of the collagen that had replaced muscle or by the stage of lysis of muscle) were found in approximately 80% of the hearts. Presumably microinfarcts of the myocardium also reflect an effect of ischemia.

Microinfarcts also were seen as irregularly continuous lesions, easily visible macroscopically by inspection of microscopic slides by transmitted light. These foci were rarely peripheral to acute infarcts, when these were found, but had developed at considerable distances from the larger lesions, and in the absence of larger lesions.

Intramural Coronary Stenosis: Location—Histological Appearances

Microscopic sections of myocardia were cut in a plane perpendicular to the longer axis of the heart. Thus, a majority of class A and B intramural arteries (Estes *et al.*, 1966) were seen in transverse section. In addition, sections included many smaller branches of these arteries. Heart-scores were determined from sections stained by Weigert-Van Gieson-lightgreen, which permitted ready identification of arteries no larger than 15 to 20 μ in diameter. Stenosing lesions of the intramural arteries of the left ventricular myocardium tended to be most numerous in the inner half or inner third of the muscle and in some instances were especially numerous in arteries of the papillary muscles. Lesions of arteries in the right ventricular myocardium usually were less advanced and rarely so limited to distinct regions as in the left ventricular myocardium.

Distribution of lesions of the intramural coronary arteries, as they appeared in microscopic sections, suggested that their development had been segmental. The disease process apparently most often involved segments of larger arteries and their branches (Fig. 2a and b). However, lesions apparently progressed irregularly from site to site, and progress in one site probably was independent of progress in another.

Similarly, microscopic features of stenosing lesions ranged widely. The more common lesions were characterized by focal replacement of smooth muscle cells of the media by collagen and elastic fibers to reduce medial thickness. Multiple fractures of the elastica interna accompanied this change, combined with intimal thickening by masses of collagen and elastic fibers between which lay numbers of smooth muscle cells (Fig. 3). Less commonly, the medial smooth muscle had been replaced more or less completely by collagen fibers and the stenosing lesions were formed by relatively coarse elastic fibers and collagen strands between which smooth muscle cells were distributed. And rarely, lesions seemed to have been forming actively by proliferation of smooth muscle cells combined with incomplete replication of the elastica interna.

Common Features of Extramural and Intramural Coronary Lesions

Proximal segments of the extramural arteries of this series usually contained either advanced lesions, or lesions that, although smaller, appeared to be inactive. Microscopic sections of either type contained little to indicate how they may have originated, or progressed. However, the more distal segments of these arteries,

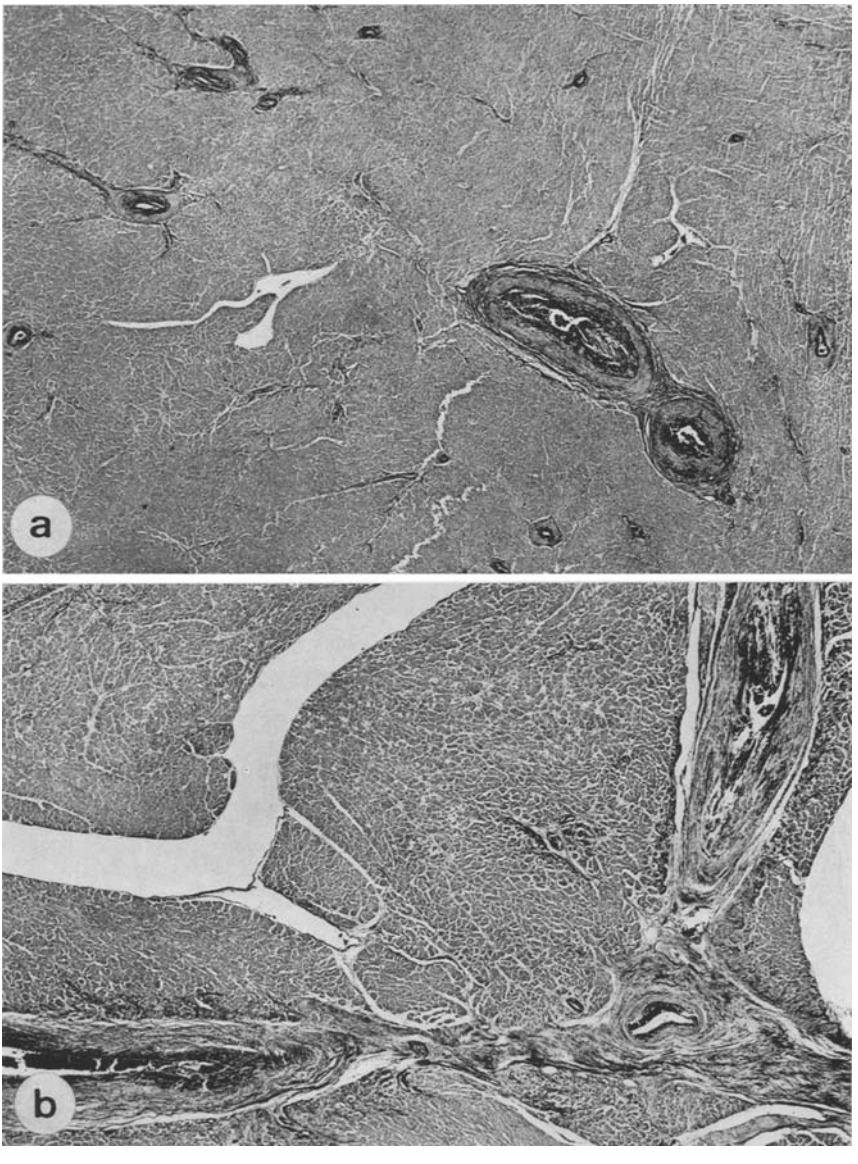

Fig. 2. a Stenosis of intramural arteries near endocardium in a male; death at 46 from myocardial infarction. Grades of stenosis ranged widely, and some arteries do not appear to be affected. (Weigert-Van Gieson-lightgreen ×20). b Stenosis of deep intramural arteries that appeared to be branches from a vessel not shown in this field, from a female, death at age 64 from carcinoma. Again grades of stenosis vary and some of the smallest branches show advanced lesions. (Weigert-Van Giesen-lightgreen ×50)

carried by the myocardial samples, frequently contained more active lesions. Microscopic features of these lesions indicated that they had been produced by the following changes in the medial (and intimal?) smooth muscle cells: pleo-

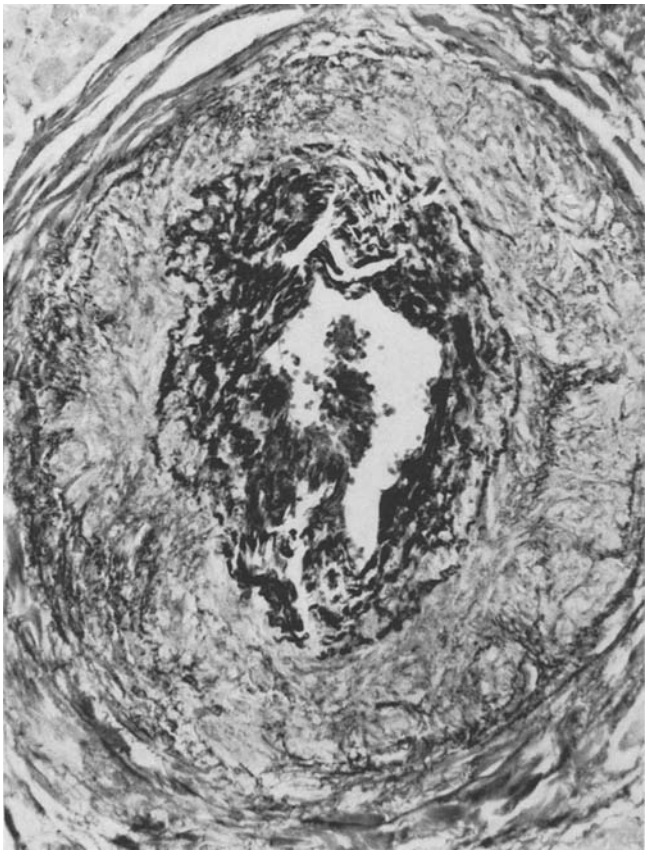

Fig. 3. Grade 3 stenosis of a deep intramural coronary artery from a female, death at age 64, from carcinoma of colon. The media had been irregularly replaced by focal collagen formation. The elastica interna was not clearly defined but apparently had undergone fragmentation, and in part, been fused with the mass of elastic fibers, collagen and smooth muscle cells that reduced the lumen. (Weigert-Van Gieson-lightgreen ×170)

morphism, reorientation, proliferation and migration through the fractured elastica interna to form stenosing lesions. These changes were accompanied by replications of the elastica interna, by the formation of elastic fibers between cells of the lesions and by increased production of mucopolysaccharide in and between the pleomorphic cells. Smooth muscle cells deeper in the lesions were often enlarged and vacuolated to form "foam-cells". Collagen was inconspicuous in the more cellular of these lesions, but was increased when the apparent movement of smooth muscle cells towards the lumen was less conspicuous.

Discussion

The results of this study demonstrate that progressive development of stenosing lesions of the extramural coronary arteries of man usually is accom-

panied by correspondingly severe stenosis of the intramural coronary arteries. Apparently, however, rates of progress of lesions in one sector of this arterial system may be independent of rates of progress in other sectors. Thus, relatively large heart-scores in this series were not invariably associated with corresponding values for stenosis of the proximal coronary arteries. And, examination of a limited series might find a negative correlation between severity of extramural and intramural coronary lesions (Wegelin, 1944). A disproportionate formation of intramural coronary lesions also may explain the development of myocardial ischemia and infarction in the absence of demonstrable extramural coronary stenosis or occlusion (Hale *et al.*, 1966; Likoff *et al.*, 1967; Campeau *et al.*, 1968; Eliot and Bratt, 1968; Bruschke *et al.*, 1971). Lack of complete correspondence between grades of extramural and intramural coronary stenosis also may explain success or failure of attempts to improve myocardial blood supply by surgery (Abrams and Adams, 1969).

Further, fixation under pressure of 150 mm Hg of hearts from several animal species has found that intramural lesions with grade 2, or greater, stenosis were not distended, while histologically unchanged arteries in these hearts were widely distended (Ratcliffe, 1965).

Relatively low values for extramural coronary stenosis (3, 6 or 9) accompanied by high values for heart-scores also may reflect responses to intense stimulation. Experimental animals exposed for approximately 12 months to intense social stimulation have developed stenosing lesions of the intramural coronary arteries much more rapidly than of the extramural coronary arteries (Ratcliffe and Snyder, 1967; Ratcliffe *et al.*, 1969). The extent of lesions at all levels of the coronary system reflects intensity and duration of stimuli.

Microscopic structure of stenosing lesions of the extramural and intramural coronary arteries in this series of hearts suggests that their origin and progress involve the same process, which combines reorientation, proliferation and migration of smooth muscle cells in segments of the arterial media (and intima ?) with pleomorphism of these cells and increased production of mucopolysaccharides, collagen and elastic fibers. In this series, lesions of intramural arteries rarely had progressed to a stage in which medial coats were replaced by collagen and densely staining elastic fibers formed the greater part of the stenosing masses. Many of the less advanced extramural lesions corresponded closely to the microscopic structure of the intramural lesions except that in their deeper parts cells appeared to have been distended with lipid. Expansion of these lesions has not been described and illustrated but apparently continued by the same process, combined with more or less extensive replacement of elastic fibers and smooth muscle cells by collagen, which then underwent focal loss of fibrillar structure and cholesterol deposition to reproduce the classical appearance of atheroma. Thus, evidence from this series of hearts indicates that stenosing lesions of the intramural and extramural coronary lesions follow the histological pattern that has been demonstrated for swine and other animals (Luginbühl and Jones, 1965; Luginbühl, 1966; Ratcliffe and Snyder, 1967; Ratcliffe *et al.*, 1969, 1970). The chief difference between microscopic structure of intramural lesions in this series and corresponding lesions of lower animals appears to be a greater cellularity of the latter. This difference may be attributed to differences in rates of development, the lower

animals having died or having been killed at much less advanced ages. This opinion is supported by comparing differences in the microscopic structure of intramural lesions found in swine killed for study at 1 year and at approximately 10 years of age (Ratcliffe *et al.*, 1969, 1970).

Intramural coronary lesions of man that correspond closely to the intramural lesions of this series have been reported by earlier observers and explained either as hypertrophy (Wolff, 1929) or as normal developments with possible relation to myocardial ischemia (Zinck, 1939). However, Sutton and Brandes (1931) and Donomae *et al.* (1965) established this relationship.

Blumenthal *et al.* (1960) emphasized a relation between these lesions and diabetes. However, evidence of diabetes was recognized in only 4 of the present series and lesions in them did not differ distinctly from others in the series. Further, earlier workers did not offer evidence of diabetes in their series. Moreover, intramural lesions that corresponded to "hereditary medial necrosis" (James, 1967) were not found.

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