

# THE RELATION BETWEEN MYOCARDIAL LESIONS AND CORONARY ARTERY DISEASE

## I. AN UNSELECTED NECROPSY STUDY

BY

C. J. SCHWARTZ AND J. R. A. MITCHELL

*From the Departments of the Regius Professor of Medicine, and of Morbid Anatomy, Radcliffe Infirmary, Oxford*

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The use of words that convey different meanings to different workers is bound to lead to confusion, and this is particularly likely when terms with a precise implication in one discipline are transferred to another. In no field has this been more striking than in the study of cardiac and arterial disease, where terms like thrombosis, occlusion, infarction, and ischæmia have been used loosely in necropsy studies, and have also been used as diagnostic labels in clinical medicine. The problem is serious enough when simple words are used, but all-embracing terms such as "ischæmic", "arteriosclerotic," and "degenerative" heart disease can be interpreted in so many ways as to make them virtually meaningless.

We considered therefore that there was a real need for a detailed study that would define the range of heart lesions found in an unselected necropsy sample, describe them in terms that did not imply or assume causation, and correlate their prevalence with age, sex, heart weight, blood pressure level, and the state of the coronary arteries.

### MATERIAL AND METHODS

During the period of study, every tenth patient and latterly every fifth patient aged 35 years and over on whom a necropsy was performed at the Radcliffe Infirmary, Oxford was included in our series. In all 137 patients (75 men and 62 women) were studied (Tables I and II) forming a random and unselected sample of the hospital necropsies carried out during this period. Although considerable selection must have occurred in respect of hospital admission this is minimized by the fact that any patient requiring hospital admission in this area can only be admitted to one of the United Oxford Hospitals, every type of medical service being catered for within the group. The necropsies on patients dying in the United Oxford Hospitals are all carried out at the Radcliffe Infirmary and during the period of our study the necropsy rate was 90 per cent.

The necropsies on these patients were performed by C.J.S., and the intact heart and unopened aorta,

TABLE I  
AGE AND SEX DISTRIBUTION OF UNSELECTED NECROPSY SAMPLE OF 137 PATIENTS

Age (years)	Number of patients	
	Men	Women
35-54 .. .. .	15	11
55-64 .. .. .	24	19
65-74 .. .. .	20	13
75 or over .. .. .	16	19
Total .. .. .	75	62

TABLE II

AGE AND DIASTOLIC BLOOD PRESSURE DISTRIBUTION IN THE 119 PATIENTS IN WHOM VALID PRESSURE RECORDS WERE AVAILABLE

Age (years)	Number of patients								Total
	Men				Women				
	Diastolic blood pressure (mm. Hg)				Diastolic blood pressure (mm. Hg)				
	<90	90-109	110-129	130-	<90	90-109	110-129	130-	
35-54 .. .. .	6	5	1	1	8	2	0	1	24
55-64 .. .. .	6	10	2	2	7	6	2	1	36
65-74 .. .. .	6	5	5	1	5	3	1	2	28
75 or over .. .. .	8	6	0	0	8	7	2	0	31
Total .. .. .	26	26	8	4	28	18	5	4	119

carotid, and iliac arteries were removed, the other systems being examined in the usual way. Clinical and electrocardiographic data were analysed by J.R.A.M. without knowledge of the necropsy findings, information being abstracted from the patient's hospital case notes, amplified where necessary by discussion with the clinicians in charge of each case and with the patient's general practitioner.

After removing blood clot from the chambers, the hearts were weighed and the condition of the valves assessed. The coronary ostia were then exposed by incising the walls of the aortic arch longitudinally to within 1 cm. of the orifices which were measured with metal knitting needles. The long bevel of the needles was ground down to leave a rounded tip, and the diameter of each size of needle was measured with a micrometer gauge. The range of diameters of the needles used was 2.0 to 7.6 mm., and the diameter of the largest needle which would enter the coronary ostium freely was taken as the ostial size.

*Injection of the Coronary Arteries.* The *injection mass*, which was freshly prepared before each injection, consisted of equal quantities of barium sulphate suspension ("micropaque"—Damancy) and 20 per cent aqueous gelatin solution. Two stock solutions of gelatin were prepared. Distilled water, freed from dissolved gases by boiling for 30 minutes, was allowed to cool to 60°C. and the gelatin added (B.D.H. laboratory quality). If the gelatin is added at higher temperatures it may be denatured and its setting qualities impaired. To the distilled water used for one of the stock solutions of 1 g./100 ml. Berlin Blue (Gurr's No. 10 781) was added, and this coloured solution was used to make up the injection mass for the right coronary artery. A crystal of thymol was added to each stock gelatin solution, and the solutions stored in stoppered flasks in an oven at 37°C. until required; after a month they were discarded and fresh stock solutions prepared. We found that 150 ml. of each injection mass was sufficient to fill the tubing, expel saline from the system, and inject the arteries.

The *injection apparatus* (Fig. 1) consisted of a one-litre Buchner flask containing 0.85 per cent sodium chloride solution made up in gas-free distilled water, and two 250-ml. flasks containing the injection masses were clamped in a water bath at 45°C. and pressure built up in the reservoir with a foot-operated car-tyre pump. The glass cannulae used had a terminal flange (Gross, 1921) which allowed them to be tied in position with a minimum of penetration into the coronary arteries, minimizing the risks of occluding the early branches which are common in the left coronary artery, and of dislodging proximally situated thrombi.

The *injection* was carried out *after* exposing the proximal 2 cm. of each coronary artery by incising the visceral pericardium and pushing aside the epicardial fat. Successful injection depends on completely excluding air bubbles from the system so the cannulae and the connecting tubes were flushed through with saline, and while the cannulae were being inserted into the coronary ostia a slow flow of saline was maintained to prevent entry of bubbles. A strong linen thread was placed round the artery and cannula as near to the ostium as possible using a half-circle non-cutting needle, and the cannula was tied in position. The heart was placed in a bowl of saline at 45°C., suspended by the cannula ligatures, and both coronary arteries were perfused for eight minutes with saline at 45°C. at 80 mm. mercury pressure.

The injection masses were then allowed to fill the tubing and cannulae, the clips on the side arms being opened to allow the masses to expel the saline, thereby avoiding dilution with residual saline. The coronary arteries were then perfused simultaneously with the injection masses for five minutes at 80 mm. mercury pres-

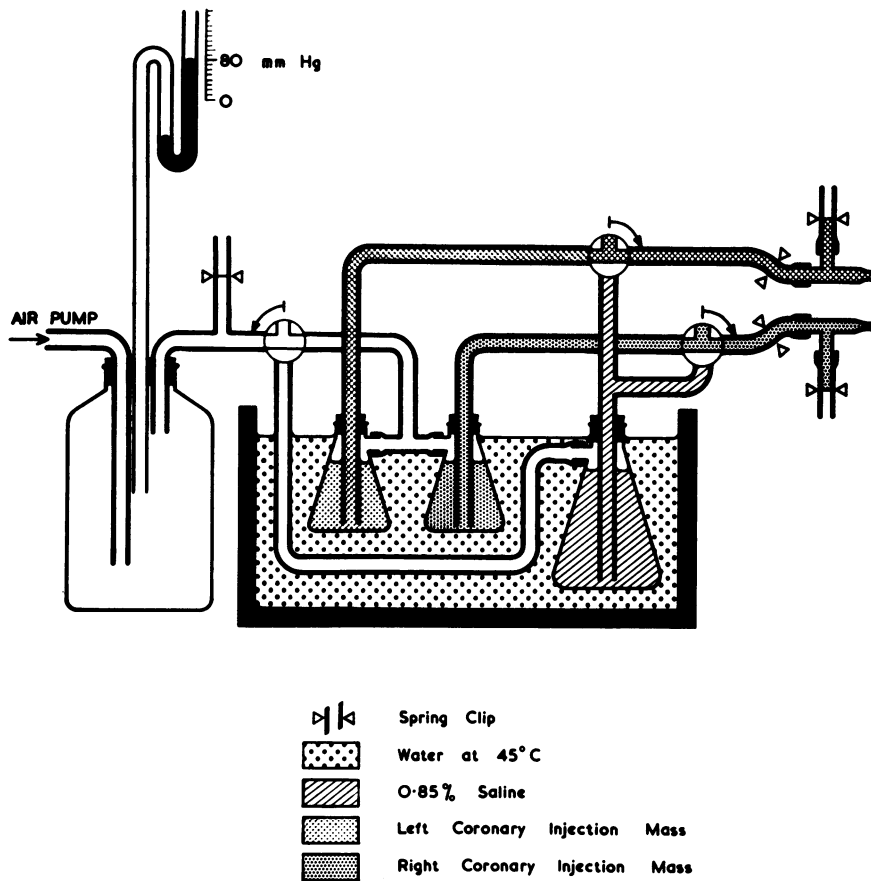


FIG. 1.—Diagram of injection apparatus.

sure, the uncoloured white mass being used for the left, and the blue mass for the right coronary artery. After injection, the tubes leading to the cannulae were clamped, ligatures were passed around the arteries and tied rapidly to prevent reflux of the masses as the original ligatures were cut, and the cannulae withdrawn. The heart was washed to remove free injection mass, care being taken not to deform the still-fluid injection mass by external pressure, and was then immersed in 10 per cent formalin at 4°C. The chambers were filled with formalin, and the heart was suspended in the fixative to avoid pressure artefacts. Fixation was usually complete in four weeks, the injection mass then being solid. Hearts weighing more than 600 g. required a longer period of fixation.

*Stereoradiography of Injected Hearts.* Postero-anterior views were taken on standard Kodak film without intensifying screens, a tube shift of 5 cm. being used to obtain stereoscopic pairs. A tube with a 1-mm.<sup>2</sup> focus was used, and the film focus distance was 110 cm. Exposures were made at 60–70 kV and 320–400 mA.

*Serial Sectioning.* The heart was washed in water and the bulk of the atria removed. The flat heart-base thus obtained was attached to an aluminium alloy chuck (external diameter 14 cm., depth 4 cm., the front surface being grooved: acetone and dry ice chips were placed in the cavity of the chuck, and the heart was attached to the grooved surface by freezing it onto a pad of moistened filter paper). The chuck was then mounted on a hand-operated bacon slicer and sectioned at 4 mm. intervals from apex to base. The sections were retained in sequence, numbered, and examined macroscopically, before being mounted between perforated zinc discs 11.5 cm. in diameter, which were held in order in brass tripods to facilitate handling and processing.

The sections were then processed by a method similar to that described by Spalteholz (1911). (a) Bleaching—24 hours in 10 volumes per cent hydrogen peroxide. (b) Dehydration—four changes of cellosolve (2-ethoxy ethanol B.D.H. laboratory quality) of four days each. (c) Clearing—two changes of methyl salicylate (B.D.H. laboratory quality) of 24 hours or more in each.

*Microradiography of Transverse Sections.* These films provided a permanent record of the vascular pattern of the section. A Machlette A.E.G. 50 beryllium tube was used, with a film focus distance of 38 cm. Fine grain film (Kodaline K.S.3) without intensifying screens was used with an exposure of 40 seconds at 15 mA and 40 kV.

*Examination of Material.* The stereoradiographs were examined jointly by the authors for coronary artery occlusions, stenosis, and calcification. We also recorded whether the radiographic density of the small vessels was normal or whether it was increased or decreased, generally or locally. The uncleared heart sections were examined macroscopically for myocardial lesions, and their site and size were noted. After clearing in methyl salicylate they were examined under the dissecting microscope as follows.

(a) *Coronary Stenosis.* The arteries named in Fig. 2 were examined, vessels running obliquely to the plane of the section being first cut transversely with a sharp blade. Three grades of stenosis were recorded (World Health Organization, 1958): *No stenosis*—no reduction in the diameter of the lumen. *Moderate stenosis*—some narrowing but more than half the diameter of the lumen remains. *Severe stenosis*—less than half the diameter of the lumen remains.

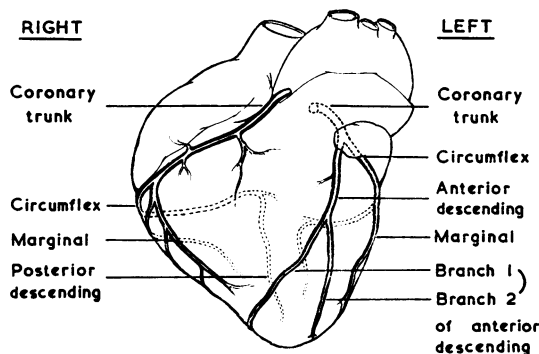


FIG. 2.—Diagram of coronary arteries. The degree of stenosis was assessed in the named arteries. Two major anatomical variations were seen. (1) The left coronary trunk may be extremely short, dividing immediately into its circumflex and anterior descending branches (66% of the hearts examined); (2) The main posterior descending artery may be a branch of the left coronary system (11% of men; 7% of women).

(b) *Coronary Score.* From the stenosis assessment of individual vessels we calculated an overall index of severity for each heart to allow different groups of patients to be more readily compared. The most severe grade of stenosis found in each of the named arteries was recorded. Each grade was given an arbitrary score: 0=no stenosis; 1=moderate stenosis; 2=severe stenosis. The scores for the named arteries were added and expressed as a percentage of the maximum possible for that heart. Thus a score of 0 per cent means that none of the arteries were narrowed, and a score of 100 per cent means that every named coronary branch had severe stenosis at some point along its course.

(c) *Coronary Occlusion.* This was assessed on the cleared transverse sections under the dissecting microscope, and was defined as the complete obliteration of the lumen, no injection mass being present.

(d) *Dye Mixing.* In each cleared transverse section the presence in branches of one coronary artery of the injection mass that had been introduced into the other artery was recorded and graded as slight or extensive.

*Histology.* Areas showing or suggesting myocardial lesions on the examination of the uncleared transverse sections were marked, and removed after the cleared sections had been studied. In addition to these abnormal areas circumferential blocks were removed routinely from all hearts, approximately one-third and two-thirds of the distance along the base-apex axis. These muscle blocks and segments of the coronary arteries were embedded in paraffin, multiple 6  $\mu$  sections prepared, and stained with hæmatoxylin and eosin (H. and E.); Masson's trichrome; periodic acid-Schiff (P.A.S.); Mallory's phosphotungstic-acid-hæmatoxylin (P.T.A.H.); and azure A and orcein-elastic.

## RESULTS

### A: Preliminary Survey

The histological preparations from the 137 hearts were examined by the authors jointly, without knowledge of the clinical background or the grading of the coronary arteries. On this initial

examination an attempt was made to define the extent to which the lesions could be subdivided, using simple criteria, and we consider that the following types can be distinguished.

1. Changes in the heart muscle.
2. Changes in the perivascular and interstitial tissues.
3. Changes in the papillary muscles.
4. Changes in the endocardium.
5. Miscellaneous lesions—fatty change, carcinomatous and leukæmic infiltration, myocarditis, and arteritis.

*Changes in the Heart Muscle.* We observed (a) muscle necrosis with and without cellular reaction, and (b) cellular and fibrous scars (Fig. 3 and 4). We found that these areas of muscle

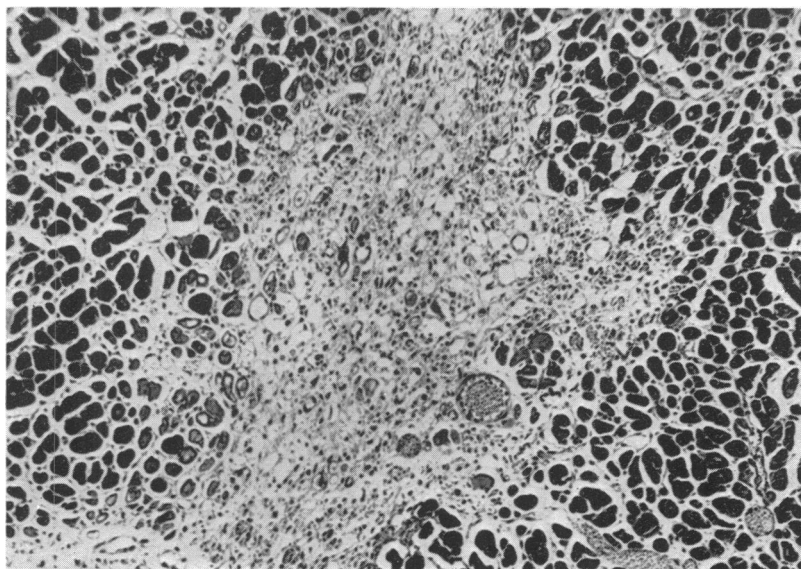


FIG. 3.—Small cellular lesion, consisting of fibroblasts, lymphocytes, and young collagen. (Trichrome:  $\times 90$ ).

necrosis and replacement did not show a continuous size distribution, but fell into two groups, which we have called small and large lesions (Fig. 5). The small lesions had an area of less than  $1 \text{ cm.}^2$ , and usually extended through one or two of the 4-mm. heart slices (the biggest of these small lesions had a volume of  $1.5 \text{ cm.}^3$ : the longest lesion extended for 2 cm. in the long axis of the heart and the biggest area seen was  $1 \text{ cm.}^2$ ). The large lesions extended through 10 to 20 of the 4 mm. slices, the smallest having a volume of  $8 \text{ cm.}^3$ : the shortest lesion extended for 3.6 cm. and the smallest area seen was  $4 \text{ cm.}^2$ . We considered, therefore, that there might be two distinct types of muscle necrosis or muscle replacement by cellular and fibrous scar tissue, resulting in small and large lesions.

A point of some significance is the accuracy with which small lesions can be recognized macroscopically on the transverse heart slices. In this study, pale areas resembling small scars macroscopically were seen in 47 patients: in 29 of these (62%) microscopic examination confirmed the presence of a scar. In the remaining 18 patients no areas of scar tissue were seen histologically, but in 7 (15%) fatty changes were present. Fatty change, therefore, produced an appearance resembling myocardial scarring in 15 per cent of our cases, and the need for histological confirmation of suspected small lesions in the myocardium is emphasized. In three patients in whom no macroscopic evidence of small lesions was found, we saw histological evidence of small scars.

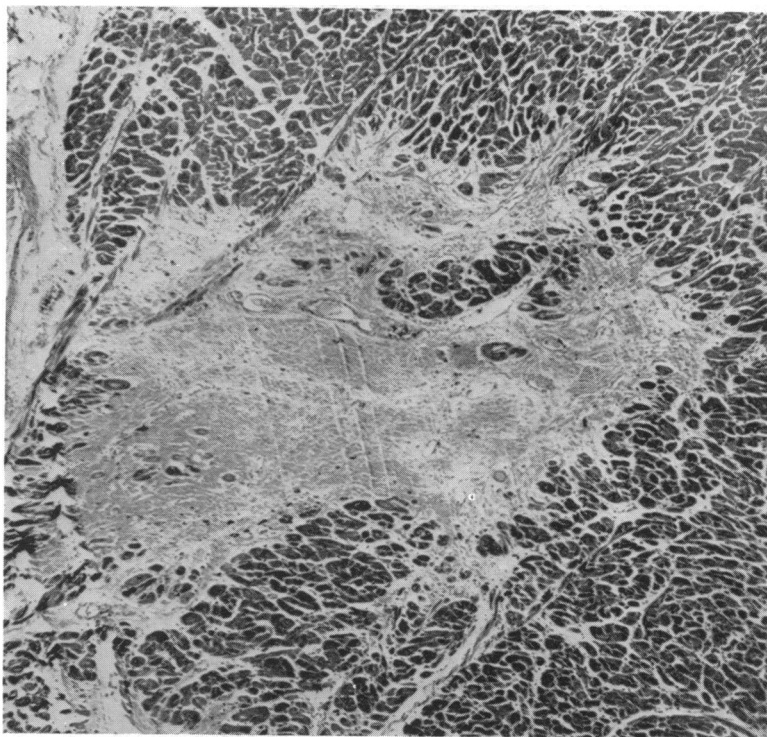


FIG. 4.—Small scar. (Trichrome:  $\times 20$ ).

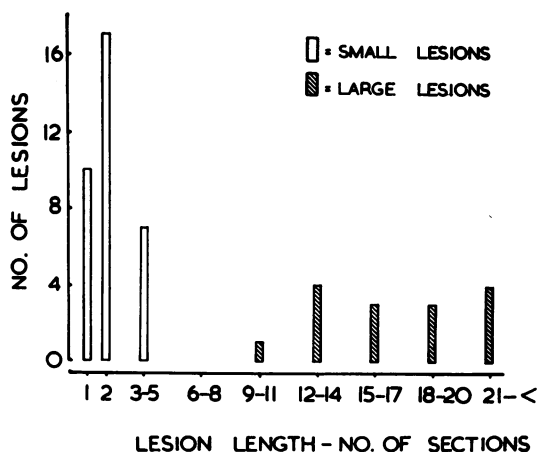


FIG. 5.—Length of replacement lesions, expressed as the number of 4-mm. transverse sections in which lesion was seen.

*Changes in Perivascular and Interstitial Tissues.* In some of the hearts, the heart muscle fibres and the small intracardiac vessels were surrounded by dense fibrous tissue, whereas in other hearts this fibrous stroma was represented by fine strands of collagen only.

a. *Perivascular Fibrosis.* Areas of dense fibrous tissue surrounding the intracardiac branches of the coronary arteries, merging with their adventitial coat, and extending for a variable distance between the adjoining muscle fibres (Fig. 6). These tongues of fibrosis may extend in attenuated bands for a considerable distance and along their course encase groups of fibres from the surrounding myocardium. These areas of perivascular fibrosis often merge imperceptibly with areas of interstitial fibrosis. Perivascular fibrosis is not associated with any recognizable disease of the intracardiac arteries:

the fibrous tissue usually contains a few cells resembling fibroblasts, although small scattered foci of lymphocytes with an occasional plasma cell are occasionally seen. The areas of perivascular fibrosis do not appear to be associated with any loss or replacement of muscle fibres. In some hearts the changes are minimal and localized, while in others the changes are greater and diffusely

scattered throughout the myocardium. We have attempted to express the degree of perivascular fibrosis seen on sections stained by Masson's trichrome method on an arbitrary scale.

1. *Absent*.
2. *Present*: perivascular fibrous tissue present, but amount small and distribution localized.
3. *Marked*: large areas of perivascular fibrous tissue throughout the heart.

b. *Interstitial Fibrosis*. Strands of fibrous tissue may occur between the heart muscle fibres (Fig. 7), often merging with the fibrous tissue around the vessels (Fig. 8). Like the areas of perivascular fibrosis, the interstitial fibrous tissue is relatively acellular, containing only a few fibroblasts.

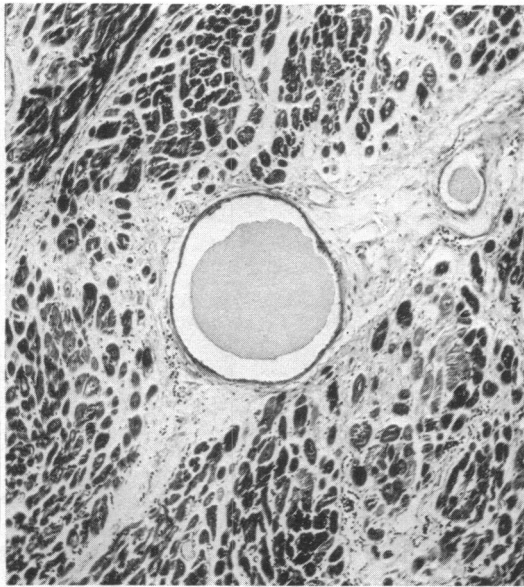


FIG. 6.—Perivascular fibrosis. (Trichrome:  $\times 60$ ).

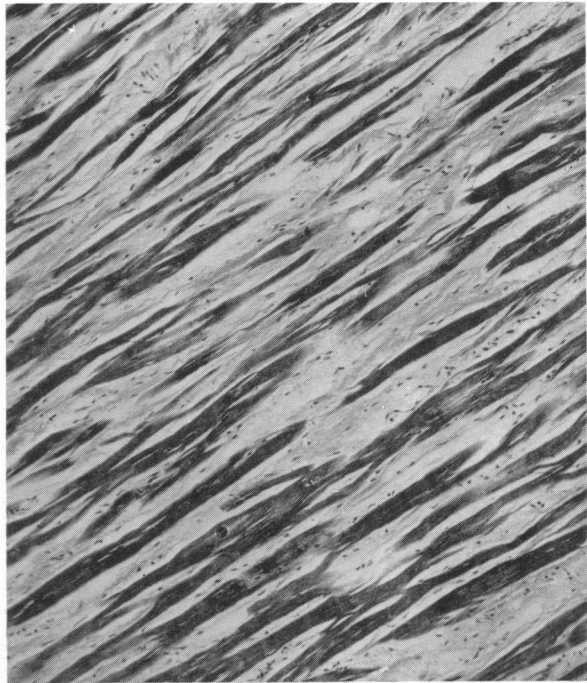


FIG. 7.—Interstitial fibrosis. (Trichrome:  $\times 116$ ).

We have expressed the degree of interstitial fibrosis, as seen on sections stained by Masson's trichrome method, on an arbitrary scale.

1. *Absent*.
2. *Present*: fibrous tissue present, but amount small and distribution localized.
3. *Marked*: conspicuous masses of interstitial fibrous tissue scattered throughout the heart.

*Changes in Papillary Muscles*. Like the main mass of the myocardium, the papillary muscles may show massive or focal necrosis, but the commonest lesion is fibrosis. We consider that there are two distinct types of papillary fibrosis.

(a) In association with large lesions of the main heart muscle mass. Here the papillary fibrosis is separated from the endocardium and the papillary blood vessels by a layer of surviving muscle: in such areas the small arteries in the papillary muscle appear to be completely normal (Fig. 9).

(b) Fibrosis extending right out to the endocardial surface and also investing the papillary vessels. In areas of fibrosis of this type, the small vessels are often abnormal, showing a diffuse thickening of the wall (Fig. 10) with elastic hyperplasia (Fig. 11) and hyaline degeneration (Fig. 12).

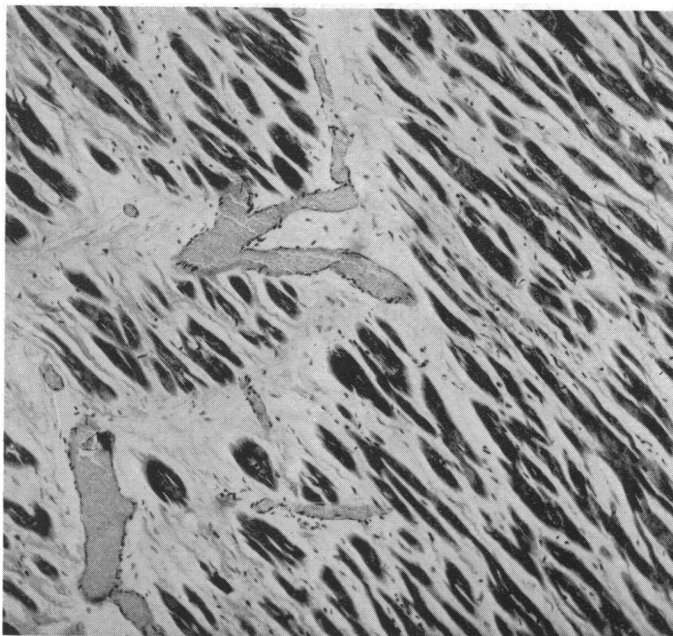


FIG. 8.—Perivascular fibrosis merging with interstitial fibrosis. (Trichrome:  $\times 116$ ).

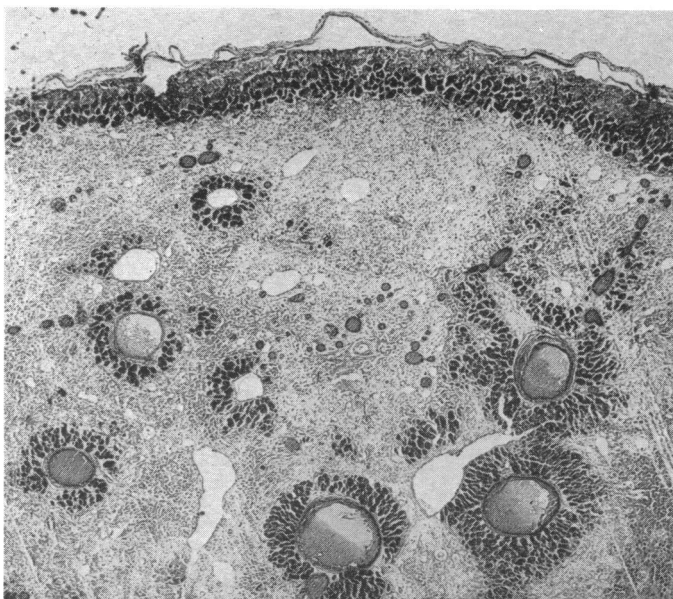


FIG. 9.—Papillary fibrosis in association with large lesion. Note perivascular and endocardial surviving muscle. (Trichrome:  $\times 12$ ).



To assess the prevalence and degree of papillary fibrosis and thickening of small vessels we used an arbitrary scale, similar to that described for perivascular and interstitial fibrosis.

(a) *Papillary fibrosis*

1. *Absent.*
2. *Present*—fibrous tissue in single papillary muscles.
3. *Marked*—large masses of fibrous tissue in more than one muscle.

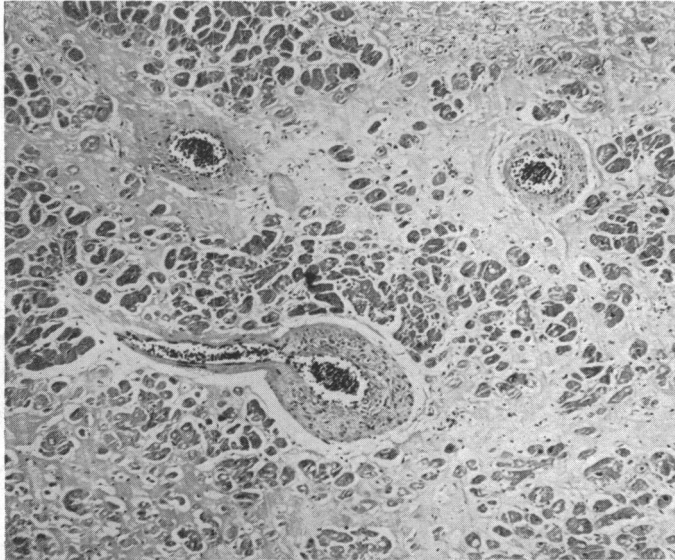


FIG. 10.—Papillary fibrosis. Note that fibrous tissue extends right up to small vessels, and that the latter show wall thickening. (Trichrome:  $\times 77$ ).

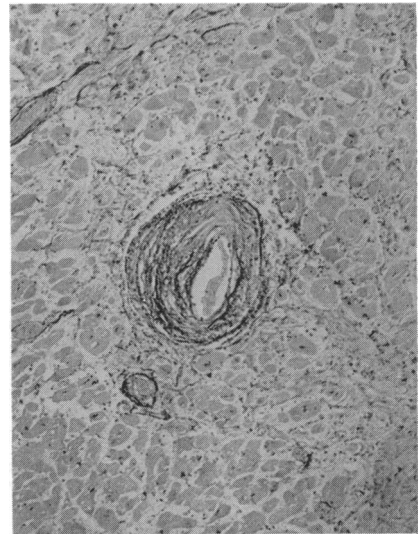


FIG. 11.—Small vessel disease in fibrosed papillary muscle. (Orcein elastic:  $\times 79$ ).

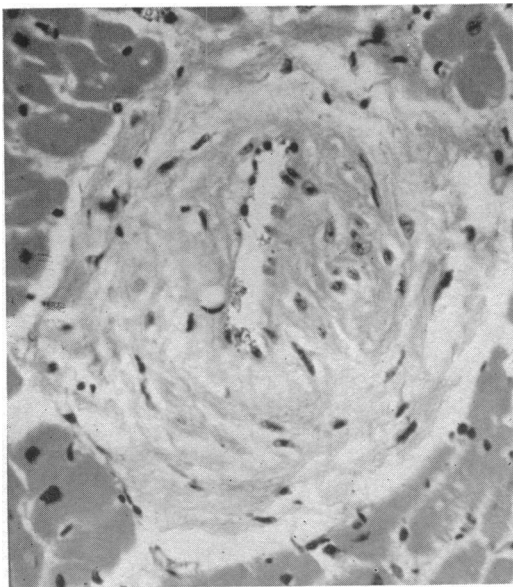


FIG. 12.—Small vessel disease in fibrosed papillary muscle. (H. and E.:  $\times 262$ ).

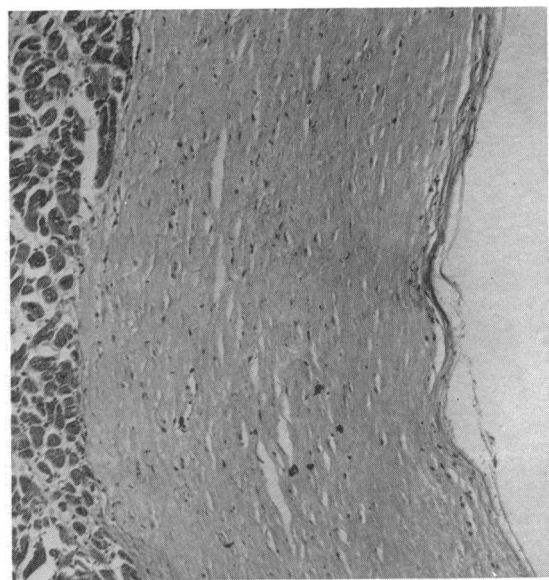


FIG. 13.—Massive endocardial fibrous rind. (Trichrome:  $\times 67$ ).

(b) *Small vessel disease*

1. *Absent.*
2. *Present*—thickening, confined to one papillary muscle.
3. *Marked*—gross thickening in several sites.

*Changes in the Endocardium.* The endocardium is normally closely applied to the inner muscle bundles with only a thin layer of loose connective tissue separating the two layers. Some of the hearts studied have shown various degrees of thickening in the endocardium: Fig. 13 shows an extreme degree of endocardial fibrosis, and as we have found that the presence of a massive rind of this type is closely associated with an underlying large cardiac lesion, we will deal with it in detail in a subsequent paper devoted to large lesions.

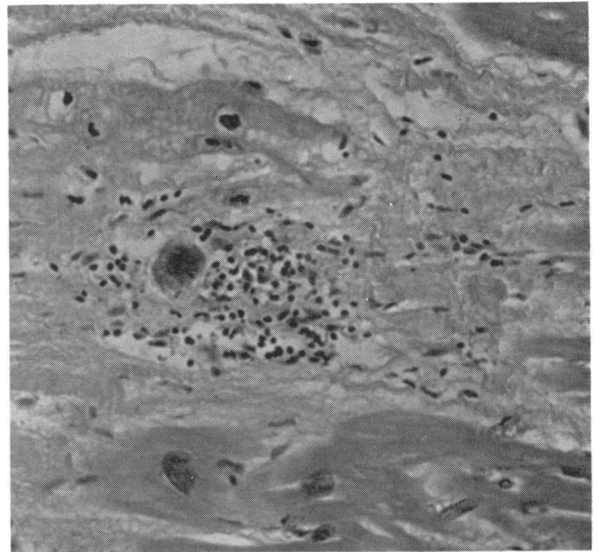


FIG. 14.—Focal myocarditis. (H. and E.:  $\times 166$ ).

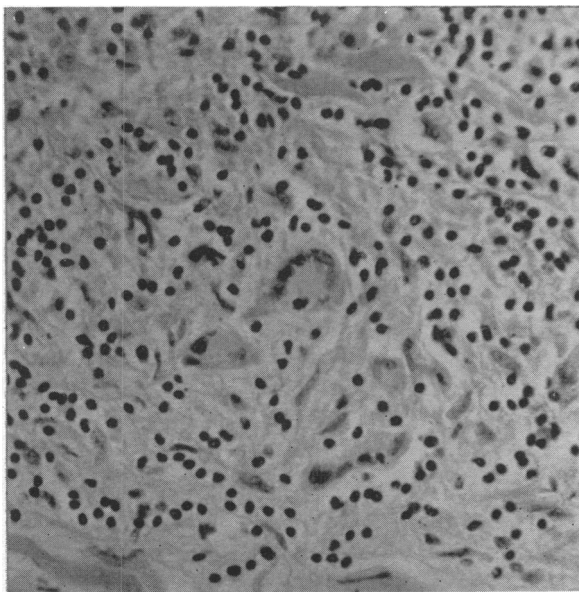


FIG. 15.—Focal granulomatous myocarditis showing giant cell. (H. and E.:  $\times 220$ ).



FIG. 16.—Focal myocarditis. (Trichrome: ×226).

*Miscellaneous Lesions.* These comprised (a) fatty change; (b) secondary carcinomatous deposits; (c) leukæmic infiltration; and (d) focal areas of cellular infiltration, usually consisting of lymphocytes and plasma cells, sometimes accompanied by giant cells (Fig. 14, 15, and 16). These areas of “focal myocarditis” usually lay in the interstitial and perivascular fibrous tissues.

*B: Second Survey*

The histological preparations were re-examined, to determine the prevalence and degree of the various types of lesion defined by the preliminary survey. Table III shows the age prevalence in men and women of large and small lesions and of the different types of fibrosis. Many of the changes are strongly age dependent, and this must be taken into account in correlating the lesions with the

TABLE III  
PERCENTAGE PREVALENCE OF MAIN TYPES OF LESION

Age (years)	Percentage prevalence											
	Men						Women					
	Lesions		Fibrosis				Lesions		Fibrosis			
	Large	Small	Inter- stitial	Peri- vascular	Sub- endo.	Papil- lary	Large	Small	Inter- stitial	Peri- vascular	Sub- endo.	Papil- lary
35-54 .. ..	7	13	13	67	27	40	0	9	18	55	27	73
55-64 .. ..	13	29	8	83	50	54	5	11	21	68	37	53
65-74 .. ..	25	40	30	85	60	80	8	31	15	77	77	62
75 or over ..	13	38	31	75	38	75	11	32	26	74	48	58
Mean .. ..	15	31	20	79	45	63	6	21	21	69	47	60

coronary artery stenosis score, blood pressure level, and heart weight. We have therefore plotted, for each type of lesion, a series of scatter diagrams, comparing on an age basis, those members of the random sample with and without the lesion in question. The diastolic blood-pressure diagrams

do not include patients in whom the pressure was not recorded in the hospital or general practitioner's notes, during the final admission and had not been recorded in the 12 months before death, or patients in whom the pressure had been recorded but the validity of the reading was in doubt due to blood loss, cerebral vascular accident, or "cardiac infarction."

*Changes in the Muscle.* The overall prevalence of *large lesions* in the randomly selected men (15%) was more than twice that of the women (6%). The age distribution also shows a sex difference, for no large lesions were found in women under 55 years, the prevalence rising with age to maximum in the 75 years and over age-group, whereas in men the greatest prevalence was in the 65-74 age-group (Table III). Fig. 17 compares the coronary scores of men with and without large lesions and shows a clear relation within each age-group between the presence of a large lesion and a high coronary score. Fig. 18 shows the randomly selected women on the same basis, and emphasizes the lower prevalence of large lesions in women, the numbers being too small to be informative.

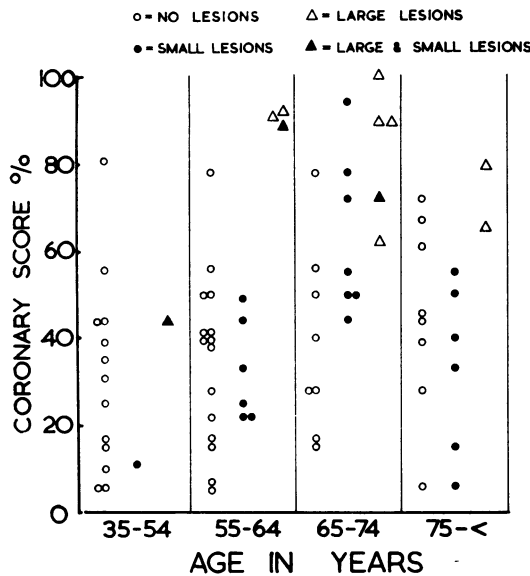


FIG. 17.—Coronary stenosis scores of men with no replacement lesions and with large and small lesions.

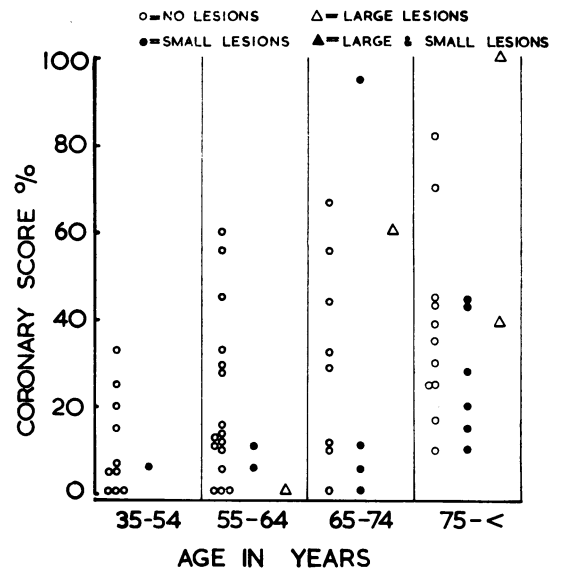


FIG. 18.—Coronary stenosis scores of women with no replacement lesions and with large and small lesions.

In addition to severe coronary narrowing, as shown by a high coronary score, another aspect of coronary disease is of importance in the patients with large lesions. In the 122 randomly selected men and women in whom no large lesions were found, the prevalence of coronary occlusion was 4 per cent; of the 15 patients with large lesions 10 (67%) had occlusions. We propose to deal with this aspect of the problem in more detail when describing a further group of patients with large lesions. Thus large lesions are related to severe coronary stenosis and to coronary occlusion. We consider that they can be called ischæmic, and that the term myocardial infarct can be justifiably applied to them.

Fig. 19-22 show the relationship of large lesions with diastolic blood pressure, and with heart weight. The only clear relation to emerge is that in the younger men and women, large lesions are found in hearts that show weights in excess of the average for the age-group.

*Small lesions* show a marked age trend in prevalence, increasing in both sexes up to the 65-74 age-group, and then remaining steady. The overall prevalence is greater in the men (31%) than the women (21%) but the sex difference is much less than for large lesions (Table III). Fig. 17-22 show the relation between small lesions and the various parameters. Apart from one age-group in the male sample, it is clear that small lesions do not relate to coronary score, and there is

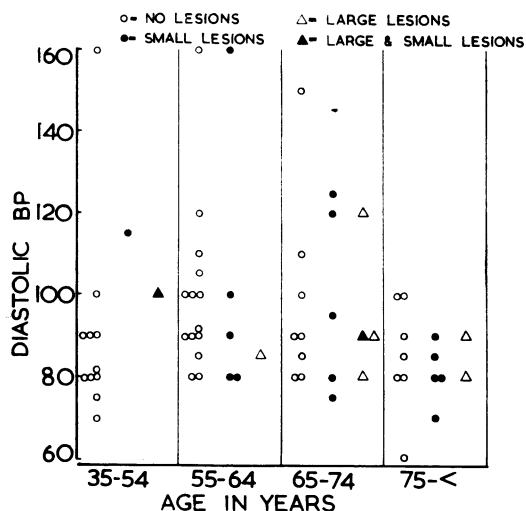


FIG. 19.—Diastolic blood pressure levels (mm. Hg) in men with no replacement lesions and men with large and small lesions.

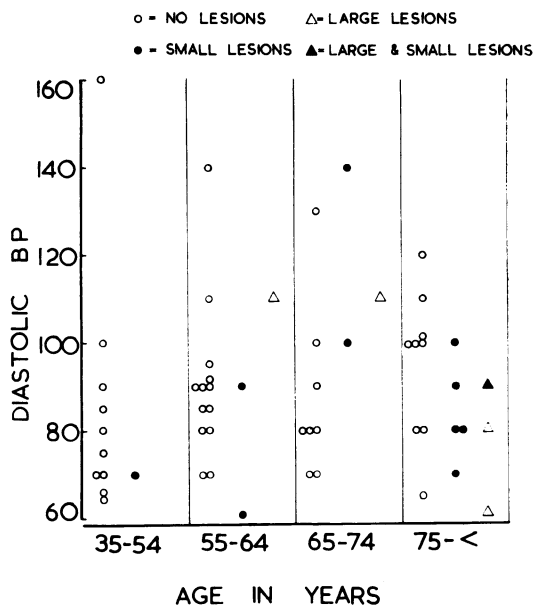


FIG. 20.—Diastolic blood pressure levels (mm. Hg) in women with no replacement lesions and those with large and small lesions.

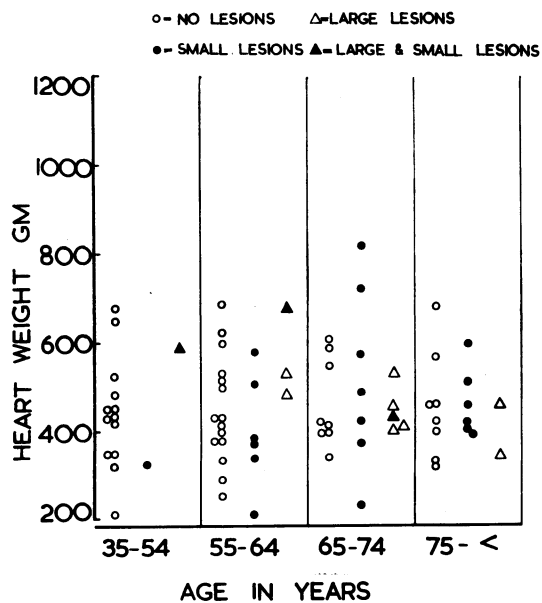


FIG. 21.—Heart weights in men with no replacement lesions and those with large and small lesions.

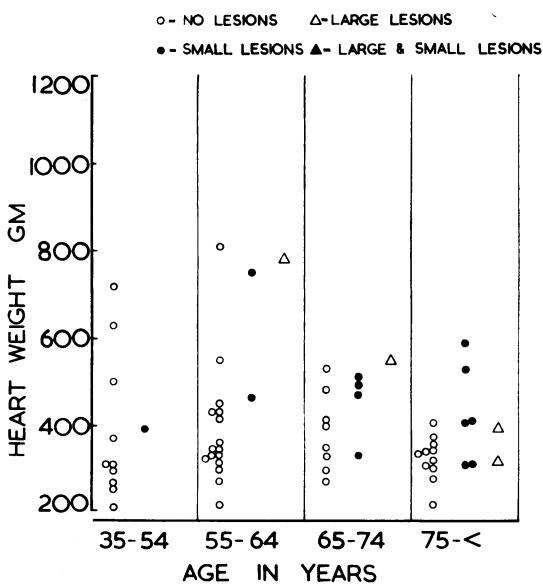


FIG. 22.—Heart weights of women with no replacement lesions and those with large and small lesions.

no apparent relation with diastolic blood pressure or heart weight. Thus the only definite relation of these small lesions is to age. They are not related to the severity of coronary stenosis nor to the presence of coronary occlusion, nor have we found any abnormality in the small intracardiac arteries in the vicinity of small lesions. There is thus no justification for the widely held view that they are a manifestation of "ischæmic heart disease."

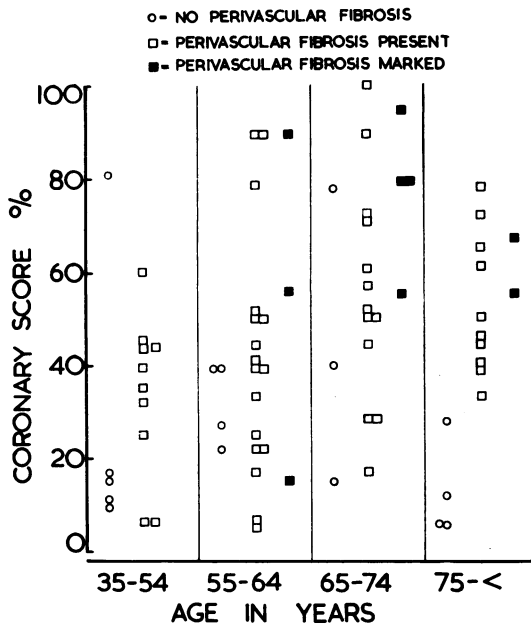


FIG. 23.—Coronary stenosis scores of men without perivascular fibrosis and those with the two grades of perivascular fibrosis.

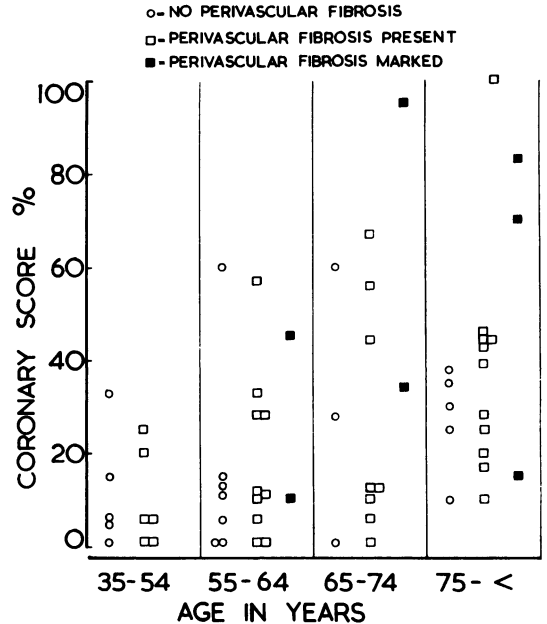


FIG. 24.—Coronary stenosis scores of women without perivascular fibrosis and those with the two grades of perivascular fibrosis.

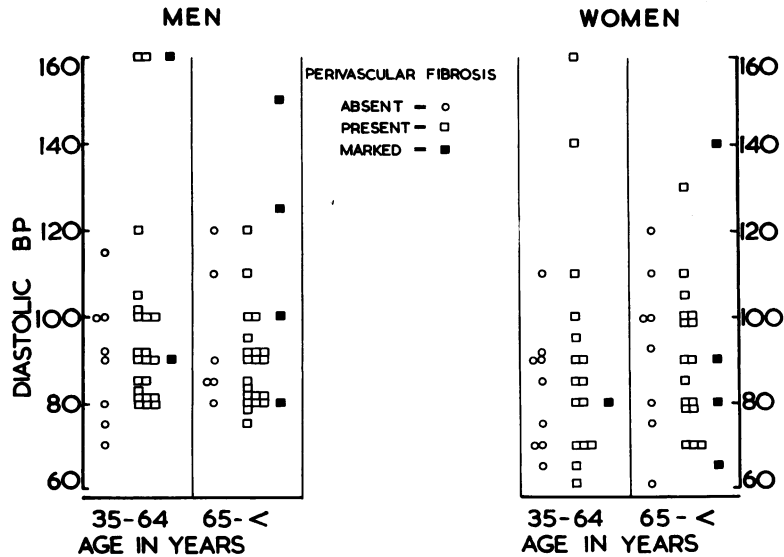


FIG. 25.—Diastolic blood pressure (mm. Hg) in men and women without perivascular fibrosis and those with the two grades of perivascular fibrosis.

*Changes in Interstitial and Perivascular Tissues.* Fibrous tissue around the intracardiac vessels is a very common finding, being present in 79 per cent of the men and 69 per cent of the women in our survey. A structure with such a high prevalence could be an integral part of the normal anatomy of the heart, were it not for the fact that the prevalence of perivascular fibrosis changes with age (Table III). Fig. 23-28 compare the prevalence and degree of perivascular fibrosis with the various parameters studied. There appears to be a slight relation with diastolic blood pressure in men but not in women, and a strong relation with heart weight in both men and women (of the 16 hearts with marked fibrosis, only one weighed less than 400 g. and 7 weighed over 600 g.). Although both men and women show this relation with heart weight, when heart weight and coronary score are plotted together a different pattern of perivascular fibrosis is seen in the two sexes (Fig. 27 and 28). In men, heart size and coronary score are clearly interrelated, and marked perivascular

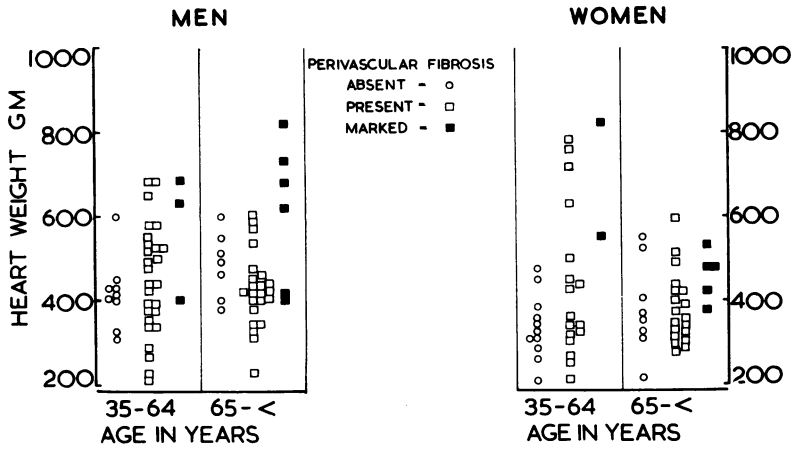


FIG. 26.—Heart weights of men and women without perivascular fibrosis and those with the two grades of perivascular fibrosis.

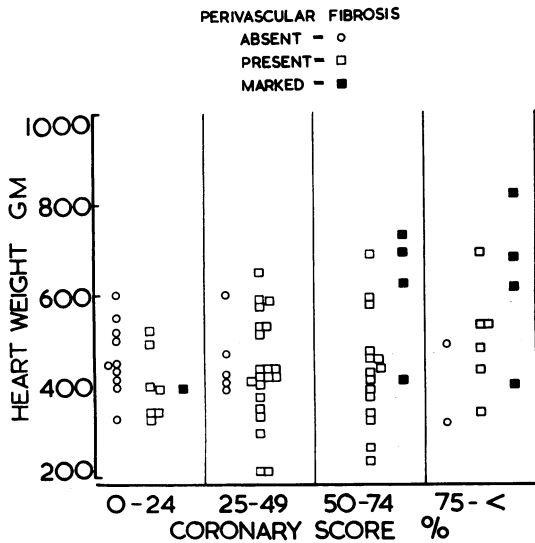


FIG. 27.—The relation between heart weight and coronary stenosis score in men without perivascular fibrosis and in men with the two grades of perivascular fibrosis.

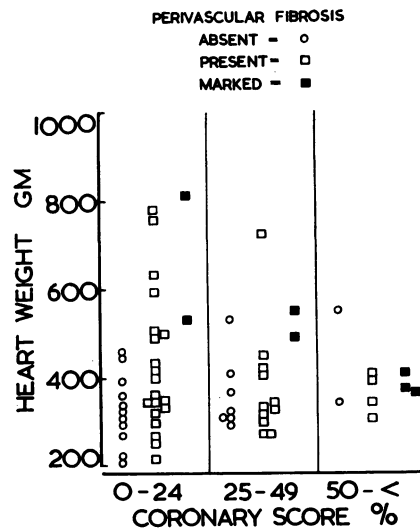


FIG. 28.—The relation between heart weight and coronary stenosis score in women without perivascular fibrosis and with the two grades of perivascular fibrosis.

fibrosis is most common in patients with large hearts and severe coronary disease: in women, it occurs in big hearts with a low coronary score or in hearts of average weight with high coronary scores. It seems likely therefore that an increased amount of perivascular tissue can be related to many factors: there may be a simple age-related increase, but it is clearly also related to increased heart weight, itself a multi-factorial phenomenon. In men, it is, in addition, related to coronary score but in women it occurs mainly in large hearts with minimal coronary disease: in such hearts the concept of "relative ischæmia" has previously been introduced, but our study provides no evidence to support this view.

Fibrous tissue between the muscle bundles is much less common than perivascular fibrosis (20% in men and 21% in women) but the two conditions are clearly related (Table IV). Thus perivascular fibrosis can be found in hearts without interstitial fibrosis, whereas interstitial fibrosis was never found in hearts without perivascular fibrosis. The degree of fibrosis in the two sites shows a clear relation, and we suggest that interstitial fibrosis may arise in response to a more marked or more prolonged stimulus than that which leads to the development of perivascular fibrosis.

TABLE IV  
RELATION BETWEEN PERIVASCULAR AND INTERSTITIAL FIBROSIS IN 137 PATIENTS STUDIED: RESULTS EXPRESSED AS NUMBER OF PATIENTS IN EACH CATEGORY

Interstitial fibrosis grade	Number of patients			Total
	Perivascular fibrosis grade			
	Absent	Present	Marked	
Absent .. .. .	35	70	3	108
Present .. .. .	0	13	7	20
Marked .. .. .	0	3	6	9
Total .. .. .	35	86	16	137

Fig. 29-34 show the coronary scores, diastolic blood pressure levels, heart weights, and the ratio of coronary score to heart weight of patients with and without interstitial fibrosis. The pattern is similar to that for perivascular fibrosis, emphasizing the close relation between the two types of fibrosis. The most important single factor is increased heart weight (of the 9 patients with marked interstitial fibrosis, only 1 had a heart weight of less than 500 g.). In men this is associated with a high coronary score, whereas in women heart weight alone is of importance. It should be noted that although the overall prevalence of interstitial fibrosis is similar in men and women, the marked grade occurred more often in the women (6 cases as opposed to 3). These women had unremarkable coronary scores: only one had a diastolic blood pressure of over 100 mm. Hg, but 5 of the 6 had hearts weighing 500 g. or more.

*Changes in the Papillary Muscles.* The histological features of the two types of *papillary fibrosis* have already been described, and in Table III their combined prevalence is shown. Although the mean prevalence is almost identical in men and women, fibrosis of the papillary muscles has a peak prevalence at different ages in men and women, occurring in the former in the range 65-74 years and in the latter in the range 35-54 years.

*Small Vessel Disease.* Narrowing of small arteries in the papillary muscles, was found in 48 per cent of men and 53 per cent of women. In men the prevalence of small vessel disease increases with age, while in women it is maximal under 65 years of age, and in this group is approximately twice as common as in men of comparable age (Table V). There is no clear correlation between these arterial changes and coronary score (Fig. 35), nor do they show any correlation with heart weight, except perhaps for women in the 35-64 year age-group (Fig. 37). Small vessel disease in



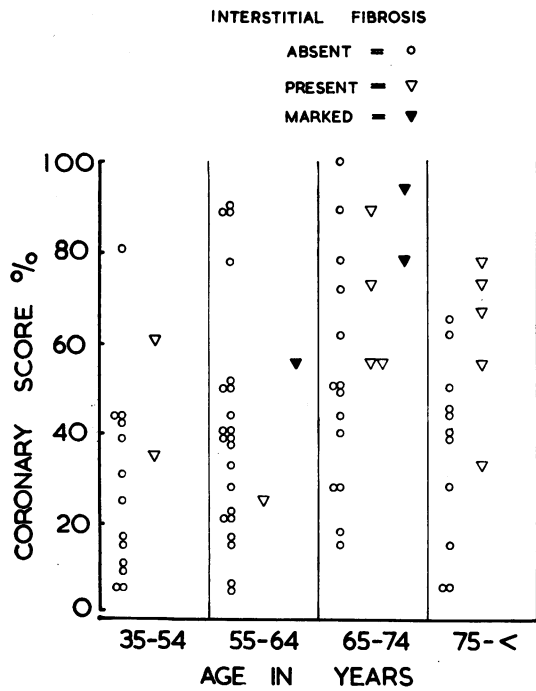


FIG. 29.—Coronary scores of men without interstitial fibrosis and with the two grades of interstitial fibrosis.

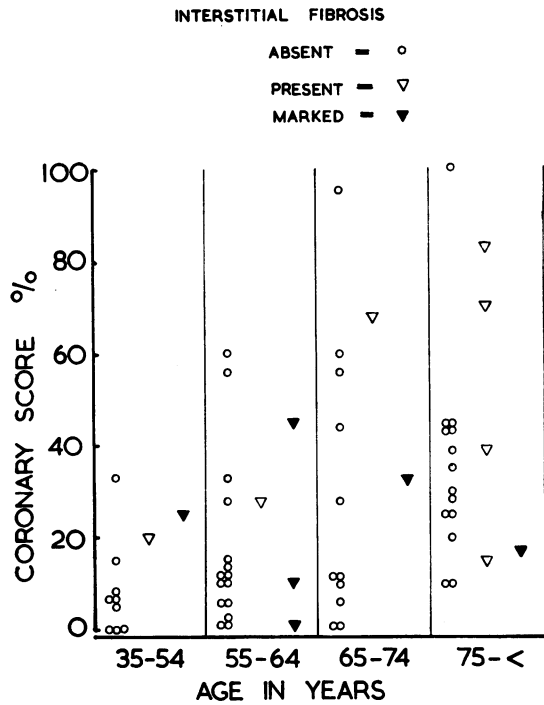


FIG. 30.—Coronary scores of women without interstitial fibrosis and with the two grades of interstitial fibrosis.

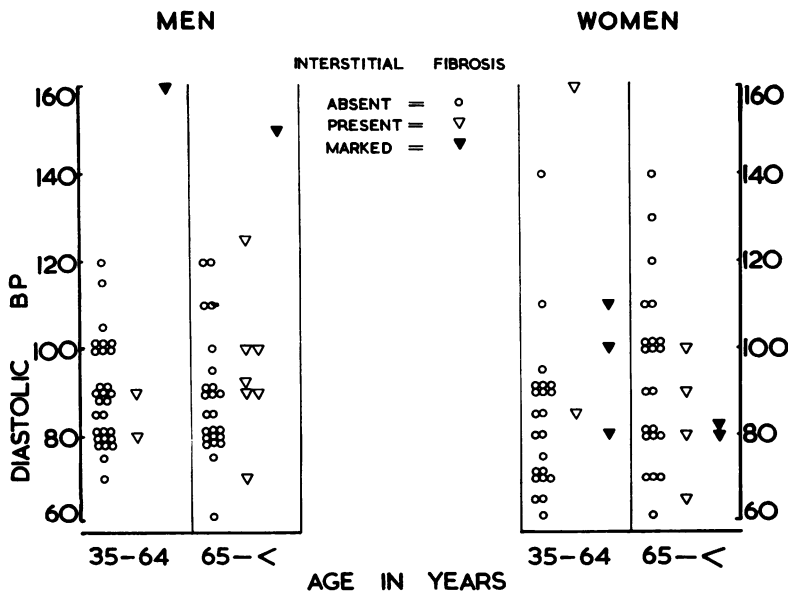


FIG. 31.—Diastolic blood pressure levels (mm. Hg) in men and women without interstitial fibrosis and those with the two grades of interstitial fibrosis.

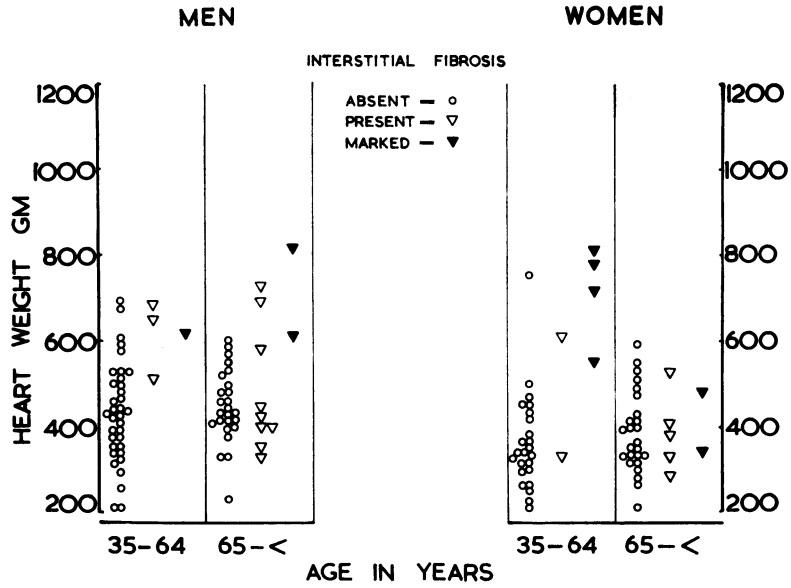


FIG. 32.—Heart weights of men and women without interstitial fibrosis and of those with the two grades of interstitial fibrosis.

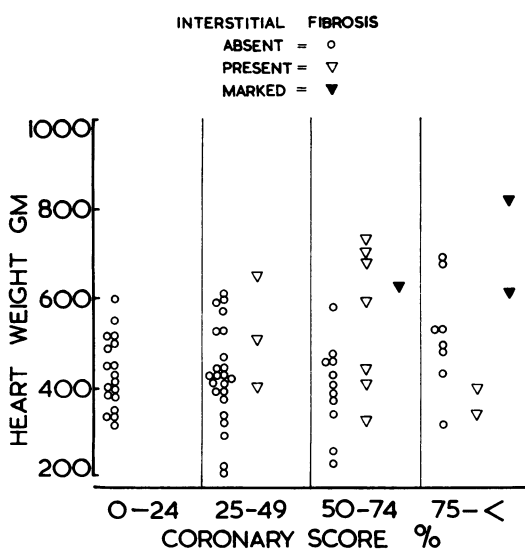


FIG. 33.—The relation between heart weight and coronary stenosis score in men without interstitial fibrosis and in those with the two grades of interstitial fibrosis.

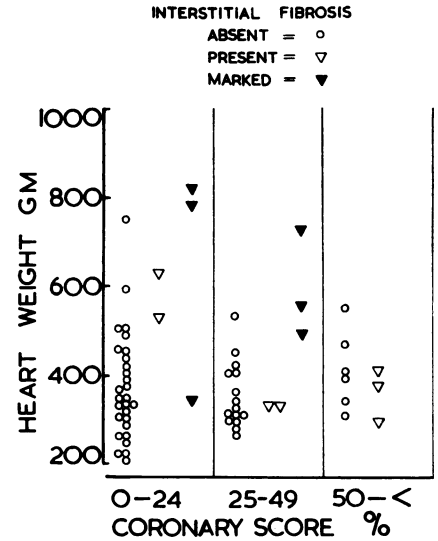


FIG. 34.—The relation between heart weight and coronary stenosis score in women without interstitial fibrosis and with the two grades of interstitial fibrosis.

TABLE V  
 PERCENTAGE PREVALENCE OF SMALL VESSEL THICKENING IN MEN AND WOMEN AGED UNDER 65 YEARS,  
 AND 65 YEARS AND OVER

Age (years)	Percentage prevalence			
	Men		Women	
	Small vessel disease		Small vessel disease	
	Present	Marked	Present	Marked
35-64 .. .. .	23	10	47	14
65 or over .. .. .	39	20	38	9
Mean .. .. .	31	15	42	11

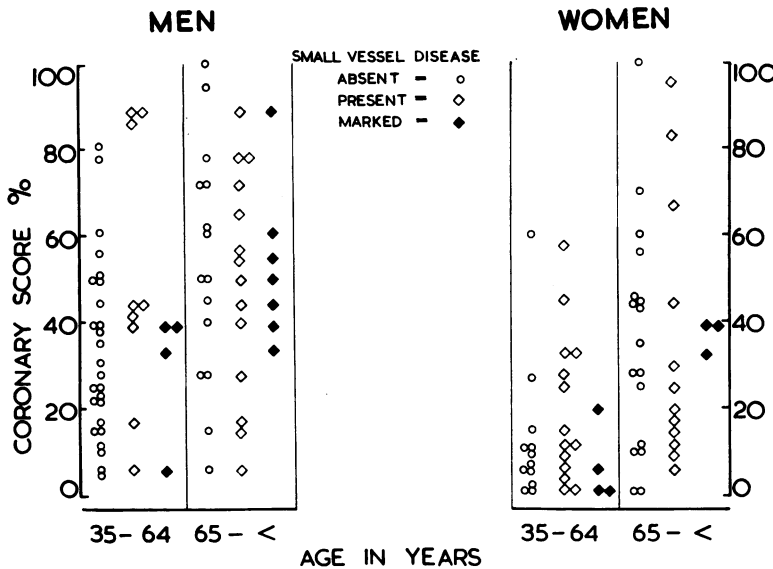


FIG. 35.—Coronary scores of men and women without small vessel disease and of those with the two grades of this disease.

papillary muscles might be a manifestation of high blood pressure, but we have been unable to show any consistent relation with blood-pressure level (Fig. 36). Moreover, of the 69 patients with small vessel thickening, there were 7 in whom the changes were not confined to the endocardial zone, but were present in the main mass of the myocardium. In 5 of these patients, valid blood pressure readings were available, the diastolic levels being 95, 150, 160, 160, and 170 mm. Hg. Thus generalized small vessel disease is related to blood pressure level, whereas the papillary type is not. We have examined the kidneys and adrenals in the 16 patients who had marked small vessel thickening confined to the papillary muscles and in only 2 did we find abnormal small vessels. The papillary vessels, therefore, seem to differ in their behaviour from vessels in the rest of the heart and in other organs. However, small vessel disease is clearly related to the presence and severity of papillary fibrosis (Table VI). Of the 18 patients with a severe grade of small vessel disease 17 (94%) had papillary fibrosis, while of the 68 patients without any histological evidence of small vessel disease,

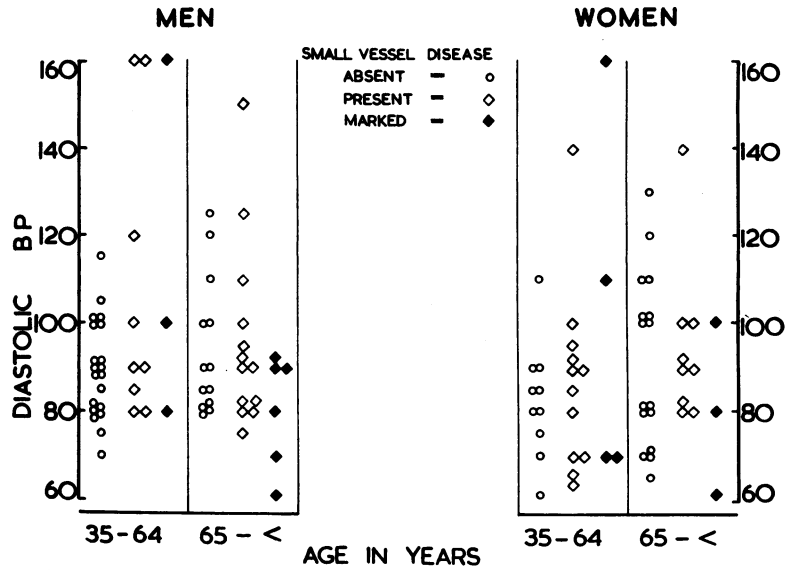


FIG. 36.—Diastolic blood pressure levels (mm. Hg) in men and women without small vessel disease and in those with the two grades of disease.

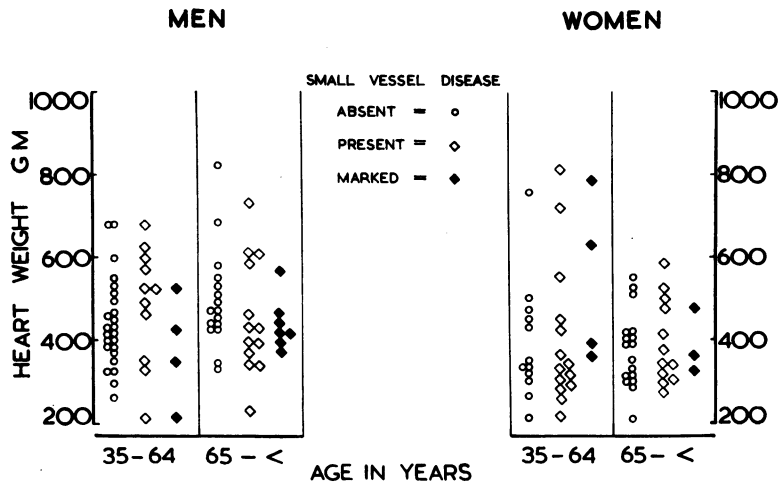


FIG. 37.—Heart weights of men and women without small vessel disease and in those with the two grades of disease.

only 24 (35%) had papillary fibrosis: of all patients with papillary fibrosis, 72 per cent have some degree of small vessel disease. There is thus a strong relation between the presence of small vessel disease and the occurrence of papillary muscle fibrosis.

*Miscellaneous Lesions of the Myocardium.* The prevalence of interstitial fatty change is higher in men (23%) than in women (18%), and in men this change shows only slight age dependence, rising (Table VII), from 27 per cent in the 35-54 year age-group to 38 per cent in the group of 75 years of age and over. In women no fatty changes were seen in the youngest group, and the prevalence rose to a peak of 31 per cent in the group 65-74 years of age. These interstitial fatty changes usually consist of a collection of fat cells, resembling adipose tissue, but we have insufficient information on

TABLE VI

RELATION BETWEEN PAPILLARY FIBROSIS AND SMALL VESSEL THICKENING IN THE 137 PATIENTS STUDIED: RESULTS EXPRESSED AS NUMBER OF PATIENTS IN EACH CATEGORY

Small vessel disease	Number of patients			
	Papillary fibrosis			Total
	Absent	Present	Marked	
Absent .. .. .	44	23	1	68
Present .. .. .	6	37	8	51
Marked .. .. .	1	15	2	18
Total .. .. .	51	75	11	137

TABLE VII

PREVALENCE OF OTHER HEART LESIONS IN MEN AND WOMEN

Nature of lesion	Men		Women		Total	
	No. of cases	Percentage prevalence	No. of cases	Percentage prevalence	No. of cases	Percentage prevalence
Fatty change	21	28	11	18	32	23
Carcinomatous infiltration ..	3	4	2	3	5	4
Leukæmic infiltration ..	2	3	0	0	2	1
Myocarditis ..	2	3	7	11	9	7

the body weight and skin fold thickness of our patients to correlate fatty deposits in the heart with general adiposity.

*Carcinomatous infiltration* was found microscopically in 4 per cent of our sample, and in only 2 of the 5 cases were the malignant metastatic deposits visible macroscopically. *Leukæmic infiltration* was found in 3 per cent of the men, no examples being found in the women. Of the 2 cases found, one showed gross macroscopic evidence of infiltration. The total prevalence of lesions designated as *focal myocarditis* was 7 per cent, and these lesions were three times as common in women (11%) as in men (3%). The focal lesions form a heterogeneous group, some containing lymphocytes and an occasional giant cell (Fig. 14), while others resemble the so-called granulomatous myocarditis (Fig. 15). We also found examples of the so-called isolated myocarditis (Fig. 16) where there is no appreciable abnormality in the myocardial fibres and the cells are restricted to the interstitial spaces.

*Endocardial Fibrosis.* The prevalence of this lesion is shown in Table III. In both sexes there is a clear increase in prevalence with age, reaching a peak in the decade 65-74 years and thereafter declining. Although there is no consistent difference in the prevalence of all degrees of endocardial fibrosis in men and women, a massive endocardial rind is found in 11 per cent of men as opposed to 6 per cent of women: this difference is due to the different prevalence of large lesions in men and women, massive endocardial fibrosis being strongly related to a subjacent large lesion. Endocardial fibrosis will be discussed in detail in a subsequent paper devoted to large lesions.

If one regards the "normal" *pericardium* as a single layer of mesothelial cells overlying a variable amount of acellular loose epicardial areolar tissue, then half the cases in our survey were abnormal, for these criteria were fulfilled in only 49 per cent of men and 52 per cent of women. Cellular infiltration of the pericardium and epicardium (consisting largely of lymphocytes and variable numbers

of plasma cells) in the absence of any appreciable fibrotic thickening, has a mean percentage prevalence of 11 per cent in men and 24 per cent in women, while fibrotic thickening of the pericardium with or without an associated cellularity was found in 37 per cent of men and 21 per cent of women. Cellular pericarditis, predominantly of a chronic type, is therefore more than twice as common in women as in men, while in the latter, fibrotic thickening of the pericardium predominates.

The appearance of dye in the branches of one coronary artery, which at injection had been perfused into the other artery, is evidence of the presence of *intercoronary anastomosis*. Such dye mixing has been found in 82 per cent of men and 76 per cent of women, emphasizing the high prevalence of intercoronary anastomoses in an unselected necropsy sample. The extent and direction of this dye mixing is shown in Table VIII, and it can be seen that the flow in over 60 per cent of

TABLE VIII  
PERCENTAGE PREVALENCE OF PRESENCE OF DYE FROM ONE CORONARY ARTERY IN BRANCHES OF OTHER CORONARY ARTERY

Group	Dye mixing—Percentage prevalence					
	None	Right to left		Left to right		Both ways
		Slight	Marked	Slight	Marked	
Men .. .. .	18	31	32	5	5	9
Women .. .. .	24	31	37	4	4	0

patients occurs in a right-to-left direction, men and women showing no significant differences in this respect. The functional significance of these intercoronary anastomoses is unknown, and one cannot extrapolate from injection studies in a still heart to coronary blood flow in life, but it is important to note that anastomoses occur in hearts showing none or minimal coronary stenosis, a finding which suggests that the presence of such communications is not wholly dependent upon the presence of coronary disease.

*Radiological Small Vessel Pattern.* *Local increase in density* was seen in 4 men and 2 women. All these patients were found to have large lesions and the prominent meshwork of small vessels was situated in the ventricular wall in the area affected by the lesion. We shall discuss this vascular lesion in detail in the paper dealing with large lesions. *General increase in density* in men shows an increasing prevalence with age, whereas in women there is a peak prevalence in the 55–64 year age-group, and a decline thereafter. We are unable to account for this difference, but consider that it may be related to heart weight, in that in the men the mean heart weight increases with age, while the women show a peak heart weight in the 55–64 decade.

*Coronary Artery Disease.* We have so far considered the coronary tree as a whole by using the coronary score as an index of coronary stenosis severity. It is also important to know the distribution, age, and sex prevalence of stenosing lesions in the different parts of the coronary system. Table IX compares the prevalence of the three grades of stenosis in the named branches of the right and left coronary arteries, and confirms that severe stenosis is far more common in branches of the left coronary artery than in the branches of the right coronary artery. Severe stenosis shows an increasing prevalence with age in both men and women (Table X), in the former reaching a peak in the age-group 65–74 years and thereafter showing a decline, while in women the difference between the older age-groups is less striking. There is considerable sex difference in the prevalence of severe stenosis, men being more affected than women at all ages up to 74 years, whereas in the age-group 75 years and over the sex difference is less obvious. It should also be noted from the scatter diagrams correlating coronary score with age, that 9 women (15%) in the random sample had scores of zero with no discernible narrowing at any point in the coronary arteries, whereas no men with completely normal arteries were seen.

TABLE IX

ANATOMICAL LOCALIZATION OF CORONARY STENOSIS, EXPRESSED AS PERCENTAGE OF WHOLE GROUP OF 137 PATIENTS WHO SHOWED THE SPECIFIED GRADE OF STENOSIS IN NAMED BRANCHES OF CORONARY ARTERIES

Stenosis Grade	Percentage prevalence									
	Left coronary artery						Right coronary artery			
	Coronary trunk	Anterior descending	Branch 1	Branch 2	Circumflex	Marginal	Coronary trunk	Circumflex	Marginal	Posterior descending
None ..	56	10	29	45	41	60	46	53	84	67
Moderate ..	28	50	32	28	38	22	42	30	8	23
Severe ..	16	40	39	27	21	18	12	17	8	10

TABLE X

AGE AND SEX DISTRIBUTION OF SEVERE CORONARY STENOSIS IN VARIOUS SITES, EXPRESSED AS PERCENTAGE OF PATIENTS IN EACH AGE AND SEX GROUP WHO WERE FOUND TO HAVE SEVERE NARROWING IN EACH SITE

Group	Age (years)	Percentage prevalence of severe stenosis								
		Left coronary artery					Right coronary artery			
		Anterior descending	Branch 1	Branch 2	Circumflex	Marginal	Coronary trunk	Circumflex	Marginal	Posterior descending
Men .. ..	35-54	38	25	25	25	13	13	6	13	0
	55-64	31	35	38	23	31	8	12	12	12
	65-74	70	78	70	43	39	22	30	22	30
	75-	56	63	13	31	13	25	31	6	13
Women ..	35-54	9	9	0	0	0	0	0	0	0
	55-64	15	35	15	10	5	15	5	0	0
	65-74	40	33	33	27	13	7	13	13	7
	75-	47	32	16	16	21	11	26	5	5

TABLE XI

PREVALENCE AND EXTENT OF RADIOLOGICALLY DETECTABLE CALCIFICATION IN MEN AND WOMEN OF DIFFERENT AGES

Age (years)	Percentage prevalence		Mean number of calcified arteries per patient affected	
	Men	Women	Men	Women
35-54 .. ..	20	9	1	1
55-64 .. ..	58	21	2.1	2.3
65-74 .. ..	90	16	2.5	2.5
75 or over ..	94	84	2.6	2.2

*Coronary Artery Calcification.* The percentage prevalence of radiological calcification on an age and sex basis is presented in Table XI. It is clearly more common in men than in women, except in the age-group 75 years and over, where this difference is less marked. In both men and women the prevalence of calcification shows a large increase with age, but in the latter the greatest increment occurs in the age-group 75 years and over. Although the women show a lower case prevalence than the men, the mean number of calcified arteries per affected patient is almost identical in each sex at all ages. There is therefore a difference in case prevalence in men and women but

no difference in the amount of calcification in an affected person. With increasing age, in both sexes, the number of calcified arteries per affected patient increases.

#### DISCUSSION

We have described the types of lesion that can be seen in the myocardium in an unselected necropsy survey, and have found that replacement lesions, where there is loss of muscle fibres, can be divided into two separate populations on the basis of their size (small lesions which extend for less than 2 cm. in the longitudinal axis of the heart, and large lesions which have a minimum length of 3-6 cm.). *Large lesions* are strongly related to coronary artery narrowing, and patients with these lesions have a high prevalence of coronary artery occlusion. On these criteria we consider that large lesions can be properly included under the generic name "ischæmic heart disease," and the pattern of surviving muscle in a large lesion gives additional evidence of an ischæmic basis, for we have commonly found a rind of spared muscle along the endocardium and around small arteries (Fig. 9).

*Small lesions*, however, show no clear relation to coronary stenosis, but do show a striking increase in prevalence with age. We have no evidence that these lesions are ischæmic: if they were, we might expect their prevalence to be higher in the patients with large lesions than in the rest of the random sample, but this is not so. This difference between large and small lesions is of considerable importance in epidemiological surveys, and serves to emphasize that not all lesions in the myocardium have an ischæmic basis. From the practical viewpoint it appears to be possible to differentiate between ischæmic and non-ischæmic replacement lesions on the basis of size, and a difference in the epidemiological behaviour of lesions of different sizes has already been suggested by Morris and Crawford (1958), who found that there was a strong relation between large cardiac scars and physical activity of work, this relation being less with respect to smaller scars.

Although small lesions show a striking age dependence, we are reluctant to accept that they are an inevitable and natural sequel to ageing, and we suggest that they may be the end result of various types of acute focal lesions (myocarditis associated with infectious diseases, Saphir, 1960; myocardial necrosis of the metabolic type described in animals by Selye, 1958; and the heterogeneous types of myocarditis which we have already described, including that associated with acute rheumatism). All these lesions may ultimately have a common end result of focal fibrosis, losing any specific identifying characteristics in the course of their development. There is some evidence for this hypothesis, for we have found in this random survey that small focal areas of acellular myocardial necrosis occur with a prevalence of 2 per cent, while the heterogeneous group of lesions designated as myocarditis had an overall prevalence of 7 per cent. There is therefore a constant background of small myocardial lesions from which areas of scarring might develop. The increasing prevalence of small lesions with age is compatible with such a hypothesis, reflecting the duration of exposure to the risk of developing such lesions as myocarditis and myocardial necrosis. An additional point in favour of this view is that of the 137 patients studied and in whom the overall prevalence of small lesions was 26 per cent, there were 7 patients with rheumatic valvular lesions of whom 5 (73%) had small scars.

We found focal myocarditis in 3 per cent of men and 11 per cent of women, an overall prevalence of 7 per cent. This is similar to the 4.3 per cent prevalence found by Saphir (1941, 1942a and b) but the large sex difference seen in our series has not been noted in other surveys, and we have no explanation for this finding.

We have found that perivascular and interstitial fibrosis is particularly common in large hearts. It has been suggested that cardiac hypertrophy may lead to "relative ischæmia," and although this could apply to some of our male patients, where marked perivascular and interstitial fibrosis was found in large hearts with severe coronary stenosis, it does not apply to the women where severe fibrosis occurs in patients with large hearts with little or no coronary stenosis. As increased heart weight is of multifactorial origin, being related to congenital and acquired heart lesions, systemic and pulmonary arterial pressure, and non-cardiac disease, it is hardly surprising that our study has



failed to show any clear correlation with any of these individual factors, or to offer any single explanation for the development of the fibrosis. It is clear, however, that using the presence of severe coronary stenosis or occlusion as an arbiter, this type of fibrosis is not primarily ischæmic.

We have also shown a curious relation between thickening of small vessels in the papillary muscles and the type of papillary fibrosis that surrounds the small vessels and spreads out to the endocardium, thus differing from the pattern of fibrosis found in association with large lesions. This finding clearly merits further study, for in other sites, vessel thickening of this type correlates with raised arterial pressure, but this does not seem to apply to these papillary vessels. We do not know whether the papillary fibrosis could produce the vessel thickening, whether the vessel disease produces the fibrosis, or whether they coincide anatomically but are causally unrelated.

Like the neck arteries, aorta, and iliac arteries (Schwartz and Mitchell, 1961, 1962), the coronary arteries have a characteristic distribution of stenosing lesions, in that the left coronary artery and its branches are more severely affected than the right, and that of all the branches of the left artery, the anterior descending is the most severely affected. A clearer understanding of the reasons for this patchy distribution would undoubtedly shed light on the ætiology and pathogenesis of the lesions. There are several major differences between the right and left coronary arteries. First, the right coronary trunk, and its continuation the right circumflex artery, run for considerable distances without giving rise to major branches, whereas the left coronary trunk branches at once into circumflex and anterior descending arteries and the latter soon divides into its two branches. Secondly, the right coronary trunk and circumflex arteries run around the heart in the atrio-ventricular groove while the anterior descending artery runs across the ventricular surface in the long axis of the heart. If the arteries are examined in life by cine-angiography, the vessels in the atrio-ventricular groove do not move appreciably during the cardiac cycle, but as the ventricles shorten during systole the anterior descending artery is pulled up and becomes sharply angulated. Thirdly, the flow pattern in the two coronary arteries is dissimilar (Gregg, 1950) because of the difference in systolic intra-ventricular tension in the two ventricles. In the right coronary artery, supplying mainly right ventricular muscle, coronary flow continues even during systole, whereas in the left coronary artery, flow stops during systole. We consider that these three factors together could produce increased mechanical strain and turbulent blood flow in the left coronary artery and particularly in the anterior descending branch. We have suggested that in other arterial sites these factors may be related to the localization of arterial stenosis (Schwartz and Mitchell, 1962).

The high prevalence of dye mixing in this random sample is of interest, for although injection studies can provide no information about cross-circulation in life, channels linking the right and left coronary branches were present in some 80 per cent of our series. The direction of dye mixing was usually from right to left, and we consider that when the coronary arteries are perfused simultaneously the right, which has a smaller capacity, will fill first, and the injection mass can then flow through the anastomotic channels into the branches of the left artery. Our injection mass penetrated into vessels of approximately  $40\mu$  diameter, so the anastomotic channels are of arteriolar size. It has been suggested (Schlesinger, 1938) that intercoronary anastomoses seldom occur in normal hearts and that they develop as a result of ischæmia. Other workers (Prinzmetal *et al.*, 1947; Baroldi, Mantero, and Scomazzoni, 1956; Laurie and Woods, 1958) have found that anastomotic channels are a common finding in normal hearts. Our results strongly support this view, and the prevalence of dye mixing in our study (80%) agrees closely with the 75 per cent prevalence found by Laurie and Woods (1958).

#### SUMMARY

We report the results of a detailed examination of the hearts of 137 patients, constituting an unselected sample of necropsies performed on patients aged 35 years and over.

A simple descriptive classification of the lesions was used and it was found that areas of muscle necrosis or replacement are of two types, large and small. Large lesions show a clear relation to coronary stenosis severity and to coronary occlusion, and can therefore be attributed to ischæmia.

Small lesions show strong age dependence, and do not appear to be of ischæmic origin: we suggest that they may be the end result of many types of focal necrosis and myocarditis.

Perivascular and interstitial fibrosis are interrelated and show a correlation with heart weight. Two types of papillary fibrosis occur: one is associated with thickening of the walls of small papillary vessels, and the other type is associated with an underlying large lesion.

The distribution of stenosing lesions in the coronary arteries is described and attention is drawn to the lower prevalence of lesions in the right coronary branches and to the high prevalence of lesions in the anterior descending system of the left coronary artery.

Injection mass from one coronary artery has been found in the branches of the other coronary artery in 80 per cent of the hearts examined.

This work was done while C.J.S. was the C. J. Martin Research Fellow of the National Health and Medical Research Council of Australia, and was latterly a member of the External Staff of the Medical Research Council; J.R.A.M. was in receipt of a Clinical Research Fellowship of the Medical Research Council throughout.

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