THE RELATION BETWEEN MYOCARDIAL LESIONS AND CORONARY ARTERY DISEASE

II. A SELECTED GROUP OF PATIENTS WITH MASSIVE CARDIAC NECROSIS OR SCARRING

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Our survey of the relation between cardiac lesions and coronary disease in an unselected necropsy sample (Schwartz and Mitchell, 1962) showed that large areas of necrosis or scarring were associated with severe coronary narrowing and with coronary occlusion. To study these lesions in more detail we have collected a further 64 patients with large lesions. The findings in these selected patients together with the 15 patients with large lesions from the random survey are reported here.

MATERIAL AND METHODS

During the period of study, when every tenth necropsy carried out on patients aged 35 and over at the Radcliffe Infirmary, Oxford, was being included in our unselected survey, we also collected the heart and great vessels from every patient who fulfilled one or more of the following criteria: a clinical history of (a) severe retrosternal chest pain lasting for more than an hour; (b) a sudden reduction in blood pressure, or the onset of cardiac failure or the development of an arrhythmia, for which no adequate clinical explanation could be found; or (c) sudden death in patients from whom no history was elicited and at necropsy, the organs, other than the heart, provided no explanation for the patient's death.

In addition any patient with the following electrocardiographic findings was included: (a) patients with pathological Q waves, and (b) patients without pathological Q waves in whom serial records had shown changing ST-T patterns.

If the external appearance of the heart of patients at necropsy demonstrated an area of ventricular discoloration and softening, often with an overlying pericarditis, or in the case of older lesions, an area of ventricular thinning, usually with an overlying pericarditis, they were included.

By selecting for study all the cases in which a large lesion might be present, we hoped to collect a consecutive series of large lesions concurrently with the unselected, random sample.

The hearts were injected, radiographed, fixed, serially sectioned on the bacon slicer, cleared, and finally examined histologically in exactly the same way as described for the unselected series. As in the unselected sample, the uncleared heart sections, the cleared sections, and the histological preparations were examined by the authors jointly, and the lesions were described and measured without any knowledge of the clinical, electrocardiographic, or arterial status of the patient: indeed they were examined concurrently with the random sample and, as all hearts were identified only by an experiment number, we had no knowledge of the mode of selection of the heart under examination. Where a large lesion was found, we assigned a histological age to it, on this preliminary "blind" examination, using the criteria described by Mallory, White, and Salcedo-Salgar (1939).

RESULTS

A. Composition of Series

Of 70 hearts selected on the above criteria, 64 were found on examination to have large lesions, and it is these 64 together with the 15 patients with large lesions from the random survey, that we propose to discuss here.

The age and sex distribution of the whole group of 79 patients with large lesions is shown in Table I, and corresponds closely to that of the patients with large lesions in the unselected survey. Men outnumber women by more than 2 to 1, and the age-group 55-74 years contains the majority of men, whereas the women show their highest prevalence in the group 75 years of age and over, no large lesions being found in women under 54 years. Table II shows the diastolic blood pressure levels in the 57 patients in whom valid readings were available.

TABLE I
AGE- AND SEX-DISTRIBUTION OF 79 PATIENTS WITH MASSIVE LESIONS

Age (years)	Number of patients	
	Men with massive lesions	Women with massive lesions
35-54.. ..	9	0
55-64.. ..	21	3
65-74.. ..	19	8
75 or over	8	11
Total	57	22

TABLE II
DIASTOLIC BLOOD PRESSURE IN PATIENTS WITH MASSIVE LESIONS IN WHOM VALID READINGS WERE AVAILABLE

Age (years)	Number of patients								Total
	Men with massive lesions				Women with massive lesions				
	Diastolic B.P. (mm. Hg)				Diastolic B.P. (mm. Hg)				
	<90	90-109	110-129	130-	<90	90-109	110-129	130-	
35-54 ..	3	3	1	1	0	0	0	0	8
55-64 ..	4	6	4	0	0	0	2	1	17
65-74 ..	4	5	5	0	0	2	3	0	19
75 or over ..	3	2	1	0	3	1	2	1	13
Total ..	14	16	11	1	3	3	7	2	57

TABLE III
CLINICAL AND ELECTROCARDIOGRAPHIC ASSESSMENT OF 71 PATIENTS WITH MASSIVE LESIONS, ADMITTED TO HOSPITAL

Clinical assessment					Number of patients				Total
					Electrocardiographic assessment				
					Positive	Negative	Doubtful	Not recorded	
Positive	..	..	..	42	0	5	7	54	
Negative	..	..	..	3	0	2	4	9	
Doubtful	..	..	..	2	0	2	4	8	
Total	..	..	..	47	0	9	15	71	

Table III shows the initial clinical and electrocardiographic assessment, made by J.R.A.M. before the heart had been examined. The Table does not include eight patients with large lesions who died before admission to hospital, for whom no information was available.

The criteria used were the following.

Clinically positive. Severe retrosternal chest pain lasting longer than one hour.

Clinically doubtful. Retrosternal chest pain of shorter duration; pain in other sites; falling blood pressure, arrhythmia, and cardiac failure.

Clinically negative. None of the above features.

Electrocardiogram positive. Pathological Q waves.

Electrocardiogram doubtful. Q waves borderline or normal but ST-T changes present; bundle-branch block.

Electrocardiogram negative. Tracing completely normal.

Although this aspect of the study will be described more fully in a subsequent report, it should be noted that of the 56 patients with large lesions in whom a cardiogram had been recorded, abnormal Q waves were present in 47 (84%), and none of the 56 patients had a normal record. Of the remaining 9 patients with doubtful records, 4 were so classified because only ST-T changes were present (all these patients had posterior large lesions); and in the other 5 patients, left bundle-branch block was the reason for the "doubtful" grading.

Table IV shows the age, heart weight, and coronary ostial size of men and women with massive lesions compared with men and women in the unselected necropsy sample. The higher mean age of the women with massive lesions reflects the age pattern shown in Table I; the increased heart weight in the patients with massive lesions is of interest, and will be discussed later in the paper.

TABLE IV

COMPARISON OF RANDOM SERIES AND PATIENTS WITH MASSIVE LESIONS. FIGURES REPRESENT MEAN VALUES AND THEIR STANDARD ERRORS

Selection group	Mean age (years)	Mean heart weight (g.)	Mean coronary ostial diameter (mm.)	
			Right	Left
Random sample men (n=75)	63.8 ±1.4	457 ±14	3.8 ±0.1	4.4 ±0.1
Men with massive lesions (n=57)	63.5 ±1.2	572 ±22	3.3 ±0.1	4.2 ±0.1
Random sample women (n=62)	66.1 ±1.4	393 ±16	3.3 ±0.1	4.4 ±0.1
Women with massive lesions (n=22) ..	71.9 ±1.7	476 ±23	2.8 ±0.1	3.9 ±0.1

The prevalence of diabetes mellitus in men and women in the selected and unselected groups showed a striking difference: of the random men 3 per cent had diabetes as compared with 2 per cent of the men with massive lesions; but in the random women the prevalence was 6 per cent, compared with 23 per cent of the women with massive lesions, who had diabetes mellitus.

B. The Large Lesions

Of the 79 patients, 46 had a single large lesion, 30 had two lesions, and 3 had three lesions. We found 54 lesions involving predominantly the anterior left ventricle, 52 involving predominantly the posterior left ventricle, 6 involving the septum only, and 3 the lateral left ventricle only. The shortest lesion occupied 9 of the 4-mm. heart slices (3.6 cm.); the smallest lesion, in terms of area, was 2 cm.² and the smallest volume was 7.2 cm.³

Histological Features of Lesions. The histological age of the lesions on the criteria suggested by Mallory *et al.* (1939), recorded on the preliminary "blind" examination of multiple sections from each lesion, was found to correlate closely with the clinical age of the lesion in those patients in whom a clear-cut episode had occurred. The first clearly-recognizable stage of large lesion development is

FIG. 1.—Heart muscle fibres from massive lesion, showing variable staining. (P.T.A.H.: $\times 265$.)

FIG. 2.—Polymorphonuclear leucocyte infiltration in massive lesion. (H. and E.: $\times 152$.)

FIG. 3.—Endocardial aspect of massive lesion, showing zone of surviving muscle fibres on surface and necrotic fibres surrounded by polymorphs below surface layer. (Trichrome: $\times 90$.)

FIG. 4.—Healing massive lesion showing lymphocytes, fibroblasts, and young collagen fibres. (H. and E.: $\times 350$.)

FIG. 5.—Endocardial aspect of healing massive lesion showing surviving muscle around small vessel and on endocardial surface of lesion (cf. Fig. 3). (Trichrome: $\times 68$.)

marked variability of muscle fibre staining. This may be the only detectable change in the first 24 hours, and can be readily seen on hæmatoxylin-eosin preparations, some fibres being intensely eosinophilic. With Mallory's phosphotungstic-acid-hæmatoxylin stain the fibres no longer stain uniformly, but show a granular appearance (Fig. 1). From the second to the sixth day infiltration with neutrophil polymorphonuclear leucocytes is the characteristic feature (Fig. 2), and during this phase the affected muscle fibres become necrotic, with the exception of a zone of spared muscle on the endocardial surface of the lesion (Fig. 3). It seems probable that these surviving fibres are being nourished by the blood in the ventricular cavity. At the end of the first week, the healing phase and the removal of necrotic fibres begins, the characteristic cellular pattern during this period being an infiltration with lymphocytes, some plasma cells, and a fibroblastic proliferation (Fig. 4). The removal of dead muscle fibres often produces a striking appearance in the endocardial aspect of the lesion, the surface zone and the perivascular zones being spared (Fig. 5). Like Mallory *et al.* (1939) we have found the presence of pigment-containing macrophages to be a useful criterion of the age of the lesion, appearing at the end of the first week, being most conspicuous in the second and third weeks, and then gradually disappearing. On the other hand, we consider that the eosinophil infiltration which they found from the seventh to the fourteenth days is an inconstant feature. When present, eosinophils are a useful guide to the age of the lesion, but their absence does not mean that the lesion is outside the one-to-two-week group. We have not attempted to carry

histological ageing beyond the fourth month of development of the lesion. At this stage the necrotic muscle has been removed, neutrophils have disappeared, and the lesion consists of dense collagen with a few lymphocytes, and new blood vessels. Lesions with these features have been grouped together as "over 4 months" of age.

C. Coronary Arteries in Patients with Large Lesions

Using the coronary stenosis score as an overall index of the number and degree of stenosing lesions, Fig. 6 compares male patients with large lesions with the male patients from the unselected necropsy series without large lesions: Fig. 7 compares female patients in the same way. Considered as a group, patients with large lesions have higher scores (and therefore more severe coronary narrowing) than unselected patients of comparable age without large lesions. It should be noted that there are some patients with large lesions whose coronary scores are conspicuously low, and indeed we found one woman with a large lesion whose coronary arteries showed no narrowing at any point.

FIG. 6.—Coronary scores of men with large lesions compared with men from the random necropsy sample without large lesions.

FIG. 7.—Coronary scores of women with large lesions compared with women from random necropsy sample without large lesions.

As the large lesion group consists of patients with different numbers of lesions and with lesions of different ages and sizes, we have analysed them further. Fig. 8 shows that men with multiple lesions have more severe coronary stenosis than men with one lesion. Fig. 10 compares the coronary scores of patients who died within two weeks of the development of their first large lesion, with the unselected sample, and shows that this group, especially the younger men, differs less from the random necropsy sample than does the large lesion group as a whole.

Another reason for lack of homogeneity in the whole group of patients with large lesions is the wide variation in lesion size. Fig. 9 shows that the length of the lesion is closely correlated with the degree of coronary stenosis. These three factors—number of lesions, age of lesions, and size of lesions, must be borne in mind when patients with large lesions are compared with other groups.

FIG. 8.—Coronary scores of men with a single large lesion compared with men with more than one large lesion.

FIG. 9.—Correlation between coronary score and length of large lesion as determined by the number of transverse heart sections on which the lesion was present. The horizontal lines indicate the mean coronary score of each group.

FIG. 10.—Coronary scores of men and women with a single large lesion of less than 2 weeks' histological age, compared with men and women from the random necropsy sample without large lesions.

Stenosis of Individual Arteries. So far we have considered the coronary arterial tree as a whole by using the coronary score as an overall index of severity. Fig. 11 and 12 show the percentage prevalence of the three grades of stenosis in the named arteries in men and women in the random necropsy sample and in men and women with large lesions. The patients with large lesions show a high prevalence of severe narrowing in every artery, and as in the random group, the left coronary branches are more severely narrowed than the branches of the right coronary artery. It will also be noted that the marked sex difference in the prevalence of severe stenosis seen in the random series is abolished in the patients with large lesions, the men and women having a similar prevalence of severe narrowing.

FIG. 11.—Comparison of degree of stenosis in individual named branches of the coronary arteries in men with massive lesions (M.L.) and men from the random necropsy sample (R.). The results are shown as the percentage of each group of patients with the specified grade of stenosis in each artery.

LCT=Left coronary trunk. LAD=Left anterior descending. LAD 1 and 2=2 main branches of LAD. L.circ=left circumflex. L.marg=left marginal. RCT=Right coronary trunk. R.circ=right circumflex. R.marg.=right marginal. RPD=right posterior descending.

FIG. 12.—Comparison of degree of stenosis in individual named branches of the coronary arteries in women with massive lesions (M.L.) and women from the random necropsy sample (R.). The results are shown as the percentage of each group of patients with the specified grade of stenosis in each artery. Key to arteries as in Fig. 11.

Coronary Occlusion. In our random survey we showed that in patients without large lesions, the prevalence of coronary occlusions was 4 per cent, whereas in the group of cases with large lesions it was 70 per cent. We have studied this aspect of coronary disease in more detail in the whole group of 79 patients with large lesions. As in the random survey, by "occlusion" we imply the total obliteration of the lumen, no injection mass being detectable in the artery when examined under the dissecting microscope. Where we have been in doubt as to whether there was a minute dye-filled channel, we have classified the lesion as "almost occluded." We have defined three types of occlusion or near-occlusion. (i) Thrombus (Fig. 13), a mass consisting of blood constituents, but distinguished from post-mortem blood-clot by having a non-homogeneous, often laminated structure, with a selective accumulation of platelets, white cells, and fibrin, and relatively few red cells (post-mortem clot being a homogeneous structure consisting of the blood constituents in their usual proportions enmeshed in fine fibrin filaments (Mitchell, 1961)). (ii) Recanalizing thrombus (Fig. 14), a mass showing multiple small channels. (iii) "Atheroma" (Fig. 15), a mass showing

none of the above characteristics of thrombus or recanalizing thrombus, and usually consisting of fibrous tissue, cellular aggregates, and lipid deposits. As emphasized by Duguid (1946) the distinction between these lesions and recanalizing thrombus is often an artificial one.

We found 103 completely occluded arterial segments in the 79 patients: no occlusion in 22 patients; 1 occlusion in 27 patients; 2 occlusions in 15 patients; and 3 or more occlusions in 15 patients. Bearing in mind, however, the heterogeneous character of the group of patients with large lesions, we have subdivided them into those with only one lesion and those with multiple lesions, further dividing them according to the histological age of the lesions (Tables V, VI, and VII). In the group of patients dying after their first large lesion (Table V) the occlusion frequency and type of occluding lesion is clearly related to the age of the lesion. Thus, of the 25 patients with single lesions under 4 months' histological age, 18 had complete occlusions (72%), 6 were almost occluded (24%), and only 1 (4%) had simple narrowing. Of the 41 occluding and near-occluding masses 31 (76%) were thrombus, 5 (12%) were recanalizing thrombus, and 5 (12%) were "atheroma." This group contrasts sharply with the 21 patients with large lesions of more than 4 months' histological age, of whom only 10 (48%) had occlusions, 4 (19%) were almost occluded, and 7 (33%) showed narrowing only. Of the 30 occluding or near-occluding masses, none was composed of thrombus, 24 (80%) were recanalizing thrombus, and 6 (20%) were "atheroma." It is clear that any study of occlusion frequency and nature must take into account the age of the cardiac lesion.

Table VI shows the corresponding figures for patients with more than one lesion. These patients will clearly have some residual arterial lesions from their previous episode, the frequency and

TABLE V

OCCLUSION STATUS AND NATURE OF OCCLUSION IN MEN AND WOMEN WITH SINGLE MASSIVE LESIONS OF VARIOUS HISTOLOGICAL AGES

Histological age of lesion	Number of patients				Nature of occlusion or near occlusion— as number of arteries		
	Total	With occlusions	Almost occluded	Neither	Thrombus	Recanalizing thrombus	Atheroma
Less than 2 days ..	10	7	3	0	15	0	1
2-13 days	11	7	3	1	15	1	1
2-4 weeks	2	2	0	0	1	3	0
1-4 months	2	2	0	0	0	1	3
Over 4 months ..	21	10	4	7	0	24	6
All ages	46	28	10	8	31	29	11

TABLE VI

OCCLUSION STATUS AND NATURE OF OCCLUSION IN MEN AND WOMEN WITH MORE THAN ONE MASSIVE LESION, ACCORDING TO HISTOLOGICAL AGE OF YOUNGEST MASSIVE LESION

Histological age of youngest lesion	Number of patients				Nature of occlusion or near occlusion— as number of arteries		
	Total	With occlusions	Almost occluded	Neither	Thrombus	Recanalizing thrombus	Atheroma
Less than 48 hours	6	5	1	0	9	5	5
2-13 days	13	13	0	0	21	8	6
2-4 weeks	5	4	1	0	3	6	3
1-4 months	9	7	2	0	1	15	5
More than 4 months	0	0	0	0	0	0	0
All ages	33	29	4	0	34	34	19

FIG. 13.—Coronary artery occluded by laminated thrombus. (P.T.A.H.: $\times 10$.)

FIG. 14.—Recanalizing coronary thrombus. (Trichrome: $\times 100$.)

nature of these occlusions depending on the time-lapse since the first lesion. To this will be added whatever arterial lesions are related to their second episode. This is reflected in the nature of the occlusions or near-occlusions which show a much higher prevalence of recanalizing thrombus and "atheroma" within four months of the second lesion than was found in patients with one lesion only. Table VII summarizes the findings in the whole group of 79 patients: 26 had experienced retrosternal chest pain lasting for more than an hour, associated with the development of pathological Q waves in the electrocardiogram, within four weeks of their death. As the findings in such patients are of considerable potential importance in their management we set out their occlusion status in Table VIII.

The anatomical distribution of the complete occlusions is shown in Table IX: 69 per cent of all occlusions occurred in branches of the left coronary artery, and the majority of these were in the anterior descending artery and its branches.

FIG. 15.—Coronary artery occluded by "atheroma." (Trichrome: $\times 15$.)

TABLE VII

OCCLUSION STATUS AND NATURE OF OCCLUSION IN WHOLE GROUP OF PATIENTS, ACCORDING TO AGE OF MASSIVE LESION, OR AGE OF YOUNGEST LESION WHEN MORE THAN ONE LESION PRESENT

Histological age of youngest lesion	Number of patients				Nature of occlusion or near occlusion— as number of arteries		
	Total	With occlusions	Almost occluded	Neither	Thrombus	Recanalizing thrombus	Atheroma
Less than 2 days ..	16	12	4	0	24	5	6
2-13 days	24	20	3	1	36	9	7
2-4 weeks	7	6	1	0	4	9	3
1-4 months	11	9	2	0	1	16	8
Over 4 months ..	21	10	4	7	0	24	6
All ages	79	57	14	8	65	63	30

TABLE VIII

OCCLUSION STATUS OF 26 PATIENTS WHO HAD AN EPISODE OF RETROSTERNAL PAIN LASTING MORE THAN AN HOUR ASSOCIATED WITH DEVELOPMENT OF PATHOLOGICAL Q WAVES, WITHIN FOUR WEEKS OF DEATH

Histological age of youngest lesion	Number of patients				Nature of occlusion or near-occlusion— as number of arteries		
	Total	With occlusions	Almost occluded	Neither	Thrombus	Recanalizing thrombus	Atheroma
Less than 2 days	5	4	1	0	6	4	2
2-13 days ..	16	13	2	1	25	4	6
2-4 weeks ..	5	4	1	0	3	7	3

TABLE IX

SITE OF OCCLUSIONS: NUMBER OF OCCLUSIONS FOUND IN EACH NAMED ARTERY EXPRESSED AS PERCENTAGE OF TOTAL NUMBER OF OCCLUSIONS

Occlusion frequency—as percentage of all occlusions			
Artery	%	Artery	%
Left coronary trunk	0	Right coronary trunk	11
Left anterior descending	23	Right circumflex	14
Left anterior descending 1st branch	17	Right marginal	3
Left anterior descending 2nd branch	11	Right posterior descending	3
Left circumflex	12		
Left marginal	4		
Left posterior descending	2		
All branches of left coronary artery	69	All branches of right coronary artery	31

TABLE X

PERCENTAGE PREVALENCE OF OTHER CARDIAC LESIONS IN MEN AND WOMEN WITH MASSIVE LESIONS, COMPARED WITH PREVALENCE IN UNSELECTED SERIES

Selection group	Percentage mean prevalence				
	Small lesions	Fibrosis			
		Interstitial	Perivascular	Endocardial	Papillary
Random sample men (n=75)	31	20	79	45	63
Men with massive lesions (n=57)	28	26	81	81	90
Random sample women (n=62)	21	21	69	47	60
Women with massive lesions (n=22)	18	14	55	73	73

D. Other Cardiac Lesions in Patients with Large Lesions

The mean percentage prevalence of the other types of lesion defined in the random necropsy survey is shown in Table X.

FIG. 16.—Length of all the replacement lesions found in the unselected and the selected necropsy sample.

(1) *Small Replacement Lesions.* Our survey of the unselected sample suggested that areas of muscle necrosis or replacement did not show a continuous size gradation, but segregated into two types of lesion, large and small. This view is strongly supported by the additional evidence available from the selected group of patients with large lesions; Fig. 16 shows the lesion length of all the replacement lesions found in the two groups and confirms that the size distribution is discontinuous. The random survey suggested that the small lesions did not relate to coronary stenosis or occlusions, and that there was no justification for regarding them as ischaemic in origin. If they were ischaemic, one would expect them to occur more often in patients with severe coronary disease or occlusion, and they should therefore be more common in the patients with large lesions than in the random sample. This is not the case (Table X).

(2) *Interstitial and Perivascular Fibrosis.* This appeared to bear little relation to coronary stenosis in the random population, and this view is reinforced by our failure to find an increased prevalence of fibrosis in the selected patients with large lesions (Table X).

(3) *Endocardial Fibrosis.* In our random survey a thick endocardial rind was found to occur in association with large lesions and this is confirmed by the increased prevalence of endocardial fibrosis in patients with large lesions (Table X) in whom it is almost twice as common as in the unselected sample. We consider that the fibrous rind may be the end result of organized mural thrombus. Fig. 17 shows a layer of recent thrombus over a large lesion. (The endocardial zone of relatively normal muscle is often absent or ill defined where a massive thrombus has formed.) Fig. 18 shows a cleft between papillary muscles in a large lesion in the healing phase: a zone of spared muscle is present and on the endocardial aspect of it is a layer of organizing thrombus. At a later stage, the mass becomes less cellular, but still contains areas of fibrin (Fig. 19). The final stage is shown in Fig. 13 of the random survey report, and this thick rind shows a marked elastosis, the inner layers forming a thick, undulating "internal elastic lamina" (Fig. 20).

(4) *Papillary Fibrosis.* Two types of papillary fibrosis occurred in the random sample; the first

FIG. 17.—Endocardial aspect of massive lesion showing ill-defined zone of surviving muscle overlaid with recent thrombus. (Trichrome: $\times 90$.)

showed endocardial and perivascular sparing and normal vessels (Fig. 5), whereas the second type surrounded small vessels (which were often abnormal) and spread to the endocardial surface. In the patients with large lesions we find an increased prevalence of papillary fibrosis, but the difference is less marked than for endocardial fibrosis, as one would expect if only one type of papillary fibrosis was related to the presence of large lesions. This is confirmed in Table XI which shows that although the marked grade of papillary fibrosis is more than twice as common in the large lesion group as in the unselected group, the prevalence of small vessel disease is virtually unchanged. We consider therefore that there are two mechanisms by which papillary fibrosis can arise, one being an extension of a large lesion, and the other being of unknown origin but showing a strong association with small vessel thickening.

(5) *The Subendocardial Plexus.* The stereo-radiographs of 6 patients in the random series (4%) showed a localized increase in vascularity in the ventricular wall, and all these patients had large lesions. Of the selected group of 79 patients with large lesions, 27 (34%) showed this phenomenon. On the micro-radiographs of the transverse slices the increased vascularity is seen to be due to a parallel mesh of vessels running in a circular fashion around the ventricular wall (Fig. 21) and contrasting sharply with the radially disposed branching system in the normal heart (Fig. 22). Histological examination of these areas showed that the vessels had a very thin wall, consisting only of a single layer of flattened cells, and there was no evidence of elastic or muscular tissue on conventional staining and microscopy (Fig. 23). The vessels looked like “giant capillaries” and were only seen

in healing large lesions. In the early healing phase, the channels were either empty or contained red cells only, and the injection mass did not penetrate to them. At a later stage, they filled with the injection mass, and therefore communicated with the coronary arteries by channels of more than 40μ diameter. The youngest lesion in which injected channels were seen was of 4 weeks' histological age. It is our impression that these channels are less prominent in large lesions with a clinical age

FIG. 18.—Endocardial aspect of healing massive lesion showing zone of surviving muscle separating organizing thrombus from healing lesion. (Trichrome: $\times 90$.)

TABLE XI

PERCENTAGE PREVALENCE OF PAPILLARY FIBROSIS AND SMALL VESSEL DISEASE IN MEN AND WOMEN WITH MASSIVE LESIONS, COMPARED WITH PREVALENCE IN UNSELECTED SERIES OF MEN AND WOMEN

Selection group	Percentage prevalence					
	Papillary fibrosis			Small vessel disease		
	Absent	Present	Marked	Absent	Present	Marked
Random sample men and women (n=137)	38	55	7	50	38	12
Men and women with massive lesions (n=79)	15	66	19	57	34	9

FIG. 19.—Endocardial aspect of massive lesion showing fibrin in organizing mural thrombus. (P.T.A.H.: $\times 20$.)

FIG. 20.—Endocardial aspect of massive lesion showing elastosis in endocardial fibrous rind, separated from surviving muscle by dense layer of elastic tissue forming an "internal elastic lamina." (Orcein-elastic: $\times 45$.)

FIG. 21.—Micro-radiograph of transverse section of injected heart. Histological examination showed a recent antero-lateral large lesion, and a healed postero-septal lesion. In this old lesion a mesh of circumferential vessels can be seen forming the so-called “subendocardial plexus.”

TABLE XII

PERCENTAGE PREVALENCE OF RADIOLOGICAL CORONARY CALCIFICATION, AND MEAN NUMBER OF CALCIFIED ARTERIES PER PATIENT WITH CALCIFICATION IN MEN AND WOMEN WITH MASSIVE LESIONS. FIGURES IN BRACKETS GIVE VALUES FOUND IN UNSELECTED SERIES OF MEN AND WOMEN

Age (years)	Percentage prevalence		Mean number of calcified arteries per patient affected	
	Men with massive lesions	Women with massive lesions	Men with massive lesions	Women with massive lesions
35–54	67 [20]	— [9]	1·4 [1]	— [1]
55–64	65 [58]	50 [21]	2·6 [2·1]	2·0 [2·3]
65–74	90 [90]	63 [16]	3·6 [2·5]	3·2 [2·5]
75 and over ..	94 [94]	70 [84]	4·2 [2·6]	3·0 [2·2]

FIG. 22.—Micro-radiograph of transverse section of injected normal heart.

of a year or more, but as histological ageing beyond 4 months is unsatisfactory, we have no clear evidence of this. We consider that the channels constituting the subendocardial plexus are possibly akin to the new vessels that occur in granulation tissue in healing lesions elsewhere in the body.

E. Other Results

Coronary Calcification. The prevalence of radiological calcification is shown in Table XII and is compared with that in the random sample. The men with large lesions show a much higher prevalence of calcification in the youngest age-group, but thereafter the difference narrows: the women with large lesions differ less from their male counterparts, age for age, than the men and women in the random sample. The mean number of calcified arteries in those patients who showed calcification is higher throughout the large lesion series than in the random sample, and there is only a slight difference between the sexes.

Dye Mixing. As in the random series we have recorded the frequency with which injection mass from one coronary artery was detected in branches of the other artery (Table XIII), and it is clear that cross-filling is more common, and more striking, in patients with large lesions. The increased prevalence of dye mixing is particularly marked in terms of left-to-right flow: in the random group we postulated that the smaller capacity of the normal right system allowed it to fill first and spill over into the as yet unfilled branches of the left. In the large lesion group, the higher incidence of severe disease in the branches of the left coronary artery may have so reduced its capacity as to allow left-to-right flow to occur.

Heart Weight. The mean heart weight of patients with large lesions is higher than that of unselected patients (Table IV). In Fig. 24 we have plotted heart weight against diastolic blood pressure for those patients in the random series who did not have large lesions, and for those patients with

FIG. 23.—“Subendocardial plexus” showing thin-walled vessels in a healing large lesion, containing injection mass from both coronary arteries. The upper vessels have filled with blue mass from the right coronary and the lower vessels with white mass from the left coronary. (Trichrome: $\times 90$.)

TABLE XIII
PERCENTAGE PREVALENCE OF DYE-MIXING IN MEN AND WOMEN WITH MASSIVE LESIONS COMPARED WITH PREVALENCE IN UNSELECTED SERIES OF MEN AND WOMEN

Selection group	Percentage prevalence						
	Absent	Right to left		Left to right		Both ways	
		Slight	Marked	Slight	Marked		
Random sample men	18	31	32	5	5	9	
Men with massive lesions	7	7	51	2	21	12	
Random sample women	24	31	37	4	4	0	
Women with massive lesions	14	14	44	0	19	9	

large lesions in whom valid readings were available. The readings accepted for patients with large lesions were (i) those recorded in the 12 months preceding the development of the large lesion, either by the patient's general practitioner or during a hospital visit or at life insurance examination; and (ii) those recorded 6 months or more after the development of the large lesion, when the patient was ambulant: other readings were not used. At each level of pressure, the heart weights are higher in patients with large lesions than in those without. We divided the patients with large lesions into those with clinical evidence of cardiac failure and those without, and found that this did not account

FIG. 24.—Relation between diastolic blood pressure level (mm. Hg) and heart weight in the random necropsy sample and in the selected sample with massive lesions, the latter being subdivided on the basis of the number and the age of the lesions.

FIG. 25.—Heart weights of patients (men and women) with single massive lesions of less than 4 months and those of over 4 months histological age, and with more than one massive lesion. The figures above each group show the mean heart weight in grams.

for the discrepancy. It is known that even after recovery from a large lesion the diastolic blood pressure may remain at a lower level than was found before the lesion, so it is possible that the second category of acceptable pressure readings gives falsely low values and that had we known pre-lesion pressures in all cases, the difference between the patients with and without lesions would have disappeared. We are reluctant to accept this explanation of the findings because of the remarkable gradation of heart weight seen in the patients with large lesions, when the number and age of lesions is considered (Fig. 25). Patients dying within four months of their first large lesion have a mean heart weight of 459 g., patients dying more than four months after the development of a single lesion having a mean weight of 534 g., and patients dying at any time with more than one lesion having a

mean weight of 590 g. As our study is of patients who did not survive, the apparent increase in heart weight may reflect an unfavourable prognosis in patients who have large hearts, or it may be that heart weight does increase after a large lesion has been sustained.

DISCUSSION

The group of patients reported in this paper is a selected one, in that in our attempt to study every patient with a large lesion on whom a necropsy was performed during the period concerned, we collected material from all patients who might conceivably have had such a lesion, processed them in a standardized way, and then extracted those who showed large areas of necrosis or scarring. One must remember that all these patients died of, or with, large lesions, that they had already been highly selected by virtue of their admission to hospital, and that some patients coming to necropsy with large lesions may not have been included because they failed to show any of the selection criteria laid down. Nevertheless, we consider that the group can yield useful information, especially in comparison with the random group, which was equally affected by the factors of hospital admission and death.

From the random survey we concluded that large lesions were commoner in men than women, that they occurred at an older age in the women, and that they were associated with severe coronary narrowing and coronary occlusions. This selected group confirms these findings, and in particular emphasizes the strong correlation with coronary occlusion. This is most clearly seen in the group of patients with a single lesion, which shows that recent large lesions are related to coronary thrombosis, and can therefore be accurately described as myocardial infarcts. As the lesion ages, the frequency of occlusion falls and thrombus is replaced by recanalizing thrombus or "atheroma" as the main type of occluding mass. This is of considerable importance when one realizes that nearly half our total group of patients with large lesions showed more than one lesion, and that their arteries would carry a legacy of their previous episode. One cannot assess then, from the whole group, what the state of the coronary arteries was before each patient's first lesion. The patients who provide most information on this important point are those with single recent lesions (Fig. 9), and it is significant that their coronary scores differ less from the random population than do those of the whole large lesion group. The factor that marks out these patients, therefore, is not the severity of coronary stenosis alone but the presence of coronary thrombosis. It is often suggested that wall disease must be present for a thrombus to form, but the main evidence for this concept is the rarity with which thrombosis occurs in a normal vessel. However, if one postulates that stenosis and thrombosis are not related, but are both age-dependent phenomena, thrombosis would thus be rare in normal arteries, for patients at risk from thrombosis would be unlikely to have normal arteries. There is considerable evidence however that thrombus and atheroma are not unrelated, but that organizing and recanalizing thrombus can produce arterial plaques (Duguid, 1946). We consider that our findings in lesions of different ages strongly support Duguid's view: the severe degree of stenosis seen in our complete group may in part relate to the presence in the group of patients with several lesions and with old lesions, whose arteries carry the residue of old occlusions.

We have found that the factor that marks out patients with recent large lesions from those without such lesions is the presence of occlusion. Previous studies have, however, given conflicting results on the frequency of occlusion (Davenport, 1928; Barnes and Ball, 1932; Gross and Sternberg, 1939; Blumgart, Schlesinger, and Davis, 1940; Master *et al.*, 1941; Master *et al.*, 1944; Yater *et al.*, 1948; Harrison and Wood, 1949; Snow, Morgan Jones, and Daber, 1955, 1956). Branwood and Montgomery (1956) reviewed some of these reports and described their own series of 101 cases, of which 61 had "recent myocardial infarction." Of this latter group, only 21 per cent had occluding thrombi, 38 per cent had recent non-occluding thrombus, and 18 per cent showed atheromatous occlusion. These authors commented that, "the incidence of coronary thrombotic occlusion is a direct function of the care and technique employed in the examination." We fully support this view, and consider that differences in technique may account for the discrepancy between our findings and

theirs. First, they used 2 mm. thick serial sections of frozen hearts, cut on the bacon slicer to assess coronary narrowing and occlusion. They comment that by this technique not all the coronary branches are seen in transverse section. In our experience, this applies to the whole length of the right coronary trunk, and both circumflex arteries, and we have tried to overcome this by using injection and radiography to supplement serial sectioning, by clearing the heart slices for examination under the dissecting microscope, and by cutting any obliquely-lying artery at right angles to its axis with a sharp blade before assessing its grade. Second, they do not define the age of their "recent infarcts," and as we have shown that the frequency of occlusion is strongly related to the histological age of the large lesions, different workers' results cannot be compared unless the age range of the lesions studied is known.

There were in our series 8 patients out of 79 whom we did not assign to the occlusion or near-occlusion groups. Of these, 4 had completely healed posterior lesions and in every case there was a localized area of very severe narrowing in the subtending circumflex artery. Although there was only a single channel, it is possible that these plaques represented the end result of a localized thrombus. Two patients had, in addition to their large lesions, mitral stenosis and sub-acute bacterial endocarditis and may have had coronary emboli. Of the remaining 2 patients who both had healed large lesions, one had completely normal coronary arteries, and the other had two tiny plaques that produced barely perceptible narrowing. Neither patient had any source of emboli or history of a period of low blood pressure or arrhythmia which could have affected coronary flow. Thus 2 patients of the 79 (3%) had large lesions for which our examination offers no explanation.

From the results of the random survey we concluded that small replacement lesions were not related to coronary stenosis or occlusion, and the present study confirms this view, in that the prevalence of lesions is no higher in the selected group, whereas severe stenosis and occlusion are more common, than in the random group. This is also true of perivascular and interstitial fibrosis and of the type of papillary fibrosis associated with small vessel thickening. On the other hand, papillary fibrosis with perivascular and endocardial sparing, and marked endocardial fibrosis are commoner in patients with large lesions, and we consider that the latter lesion may represent the end stage of mural thrombosis.

The local increase in radiological small vessel density that was noted by Fulton (1956) and called the "subendocardial plexus" was thought to be a compensatory phenomenon which might prevent further regional infarction. In our view, the vessels forming the plexus are a consequence of the healing process of a large lesion and are akin to vessels in granulation tissue elsewhere. Their functional significance is unknown, and we have no explanation for their circumferential orientation.

We have found that patients with large lesions have bigger hearts in proportion to their blood pressure levels than patients without large lesions, thus confirming the findings of Davis and Blumgart (1937) and Morgan (1956). We accept that one possible explanation of this discrepancy could be that some of the blood pressure readings in the large lesion groups are invalid, but the relation within the large lesion group between number and age of lesions and heart weight suggests that other factors are also of importance. Moreover, Barrett (1960) showed that arterial wall thickness, systemic blood pressure levels, and heart weight were clearly related in a control group of patients. Using arterial wall thickness as an index of blood pressure level, he found that patients with cardiac infarction had disproportionately large hearts. In the absence of congenital cardiac disease, and valvular disease, cardiac enlargement is often accepted as an index of high blood pressure (Dickinson and Thomson, 1960). We consider that until the relation between large lesions and heart weight is clarified, hearts with these lesions, like hearts with congenital and valvular disease, should be excluded from any study that uses heart weight as an index of blood pressure in life.

SUMMARY

Seventy-nine patients (57 men and 22 women) with large cardiac lesions consisting of necrosis or scarring were studied and compared with an unselected necropsy sample examined in the same way.

Large lesions showed a strong association with coronary occlusion and can be accurately described as myocardial infarcts. The age and number of the large lesions is related to the occlusion frequency and the type of occluding mass. The significance of this is discussed, with particular reference to the severe coronary narrowing associated with large lesions. Of the other cardiac lesions defined in the random survey, two types showed a strong association with large lesions—massive endocardial fibrosis and one type of papillary fibrosis. Small replacement lesions, perivascular and interstitial fibrosis, and the papillary fibrosis associated with small vessel thickening were no more common in patients with large lesions than in the random sample.

The histological appearance of the so-called "subendocardial plexus" is described, and the relation of this mesh of vessels to healing large lesions is emphasized.

The prevalence of coronary calcification and intercoronary anastomoses is compared with the random sample, and an association between increased heart weight and the age and number of large lesions is described.

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