THE HEART IN SCLERODERMA

BY

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Scleroderma is one of the collagen diseases, namely one that attacks primarily the mesenchymal collagen fibres of connective tissue. Those collagen fibres already present usually become thickened, but also new ones are formed. The effects of the disease are therefore not confined to the skin, as was thought originally, but are widespread throughout the body, and the term scleroderma is thus a misnomer. In addition to the skin, the main structures to be affected clinically are skeletal muscle, the alimentary system, especially the œsophagus, the lungs, kidneys, endocrine glands, bones, and joints, and the heart. The disease is prone to remission and relapse, but ultimately proves fatal whether it pursues a fulminating course of a few months or even weeks (MacCallum, 1926) or the more usual chronic course over several years.

Lewin and Heller, who as early as 1895 produced a monograph on the subject and reviewed the 451 cases that had been recorded before that date, credit Lusitanus (1634) with the first description of the disease and believe that Gintrac (1847) introduced the term scleroderma.

Systemic scleroderma has been described in an infant (Langmead, 1911) where it was noticed shortly after birth, but it is commonest in the fourth and fifth decades, the average age in our series being 54·5 years. The sex ratio is one male to three female patients. The generalized disease is probably twice as common in women, but in the present series with cardiac involvement the proportion was two men to three women.

When a fatality occurs in the first few years, it is due either to renal or cardiac failure; later malnutrition and pulmonary complications are important contributory causes of death.

Involvement of the Heart

We are concerned with the disease only as it affects the heart, and it is necessary to point out that, compared with other viscera such as the œsophagus or lungs, the heart is only rarely directly affected by the sclerodermatous process. It is difficult to assess the frequency with which the heart is affected in generalized scleroderma. Of 19 patients seen personally by one of us (S.O.), 11 had evidence of cardiac involvement. On the other hand, in a series reported by O'Leary and Nomland (1930), none of 48 generalized examples showed cardiac symptoms or signs. Of 26 patients with generalized scleroderma described by Rossier and Hegglin-Volkmann (1954) 7 showed clinical evidence of cardiac involvement, and of 63 showing only acrosclerosis 5 had abnormal electrocardiograms (Windesheim and Parkin, 1958). There is no doubt that many examples of very extensive sclerodermatous involvement occur; yet the heart escapes, not only clinically but histologically.

It was Matsui (1924) who first pointed out that the heart could be specifically and directly involved in scleroderma, and in 1934 Brock reported a generalized case in which the cause of death was

congestive heart failure due to myocardial fibrosis. This was followed in 1943 by the classical paper of Weiss *et al.* who, as a result of study of 9 patients with two autopsies, concluded that scleroderma heart disease was a pathological and clinical entity. The lesion affects the lungs more commonly than the heart, and often both organs are involved. The resultant fibrotic changes in the lungs help to produce pulmonary heart disease, and this plays a considerable part in the causation of right ventricular failure in many patients in whom both organs are affected. At times chronic cor pulmonale is the only type of failure present in those patients whose myocardium is itself unaffected by the disease (Bauer, 1955): similarly, left ventricular failure may rarely result from hypertension, secondary to renal scleroderma or steroid treatment.

Direct cardiac involvement by scleroderma most commonly affects the myocardium predominantly, and is often confined to it. Less commonly the pericardium is the sole site, with or without the production of a pericardial effusion. At times both the pericardium and myocardium are affected. If the endocardium or valves are affected, this is almost always in association with severe myocardial damage from the disease, but rarely they may be the sole site of the lesion and give rise to a condition similar to the non-bacterial verrucous endocarditis described by Libman and Sacks (1924) in cases of systemic lupus erythematosus.

Chronic cor pulmonale usually results from the disease affecting the lung tissue and bronchi, but aggravating factors are the restriction of chest expansion that results from involvement of the skin and muscles of the chest wall, and the tethering of the lung through involvement of the pleura and diaphragm in the disease process. In Matsui's early account (1924) of six patients, all women, with cardiovascular involvement, he noted mainly right-sided cardiac hypertrophy as a result of what he termed chronic productive interstitial pneumonia.

Patients Studied. Study of the papers about scleroderma, particularly the earlier ones, has convinced us that there is often considerable doubt concerning the accuracy of the diagnosis of scleroderma. There is even more doubt as to whether the heart condition that accompanies the suspected scleroderma is, in fact, the result of that disease. In many patients it could have been coincidental.

It needs to be emphasized that the mere presence of a cardiac or vascular lesion in a patient with scleroderma does not of necessity establish its sclerodermatous nature. The number of cases where both a good history of symptoms and detailed clinical examination have been correlated with autopsy findings is not great, and for that reason we have recorded only those reported examples where both clinical and autopsy findings have been adequate. We were able to find 28 such patients (Table I).

In addition, we have added 21 of our own with generalized scleroderma where we have felt confident that the cardiac symptoms and signs were the direct result of involvement of the heart by the sclerodermatous process (S.O., Cases 1, 2, and 4–12; W.S., Cases 3 and 13–21). The total

TABLE I

CARDIAC AND PULMONARY NECROPSY FINDINGS IN 28 REPORTED CASES

Heart	Weight in grams,	300 or less	9
		300–400	5
		400–500	7
		500 and more	4
		Not stated	3
	Myocardium		25
	Pericardium		20
	(Effusion more than 100 ml., 7)		
	Endocardium		9
	Mitral and tricuspid valves		2
	Mitral valve		2
	Chordæ		1
	Epicardium		6
	Calcification		1
Lungs	Fibrosis only		15
	Fibrosis and cystic change		4

from which the clinical analysis has been made is thus 49, on 32 of which autopsies were performed. The cardiac and pulmonary findings at autopsy in our four patients (Cases 1, 2, 3, and 15) follow, three at once and Case 15 as an addendum.

Necropsy Findings

Case 1. Man, aged 56. *Cardiovascular System.* Heart weight 360 g. Pericardium normal, no effusion. Right ventricle distinctly hypertrophied (wall 6–8 mm.). Myocardium normal to naked eye with no evidence of infarction or fibrosis. Valves macroscopically normal. A few white patches of endocardial fibrosis in the right ventricle. Considerable atheroma of the main pulmonary artery and smaller branches, with adherent mural thrombus, probably three or four weeks old, in the right pulmonary artery near the origin of the branch to the right lower lobe. Microscopically, replacement of parenchyma by collagen was present particularly in the muscle of the left ventricle.

Respiratory System. Bronchiectatic lower lobes, particularly on right side. Elsewhere individual peripheral bronchi had become dilated, usually in relation to cystic parenchymal lesions. Small serous effusion (300–400 ml.), slightly blood-stained, in each pleural cavity. No adhesions. Visceral pleura generally thin and finely wrinkled by subpleural cysts and fibrosis. Both lungs pale, finely wrinkled, and a little smaller than normal, reduction in size being greatest in lower lobes. On section large areas of parenchyma seen to be cystic. The cysts were thin-walled, smooth and glistening, most of them ranging in size from 5 mm. downwards, merging imperceptibly with what appeared to be normal parenchyma. The more severely affected areas contained cysts up to 1 cm. and in one part of the left lower lobe several cysts of this size had become confluent forming a bulla. The right lower lobe was the most uniformly cystic and at first sight its thin-walled, dilated bronchi were not easily distinguished from the cysts which surround them. The middle lobe contained a firm, raised, subpleural infarct.

Death was from pulmonary embolism.

Case 2. Woman, aged 62. *Cardiovascular System.* Heart weight 845 g. Myocardium mottled but of normal consistency; no obvious fibrosis on the cut surface. Valves normal. Moderate atheroma of coronary arteries and abdominal aorta. Microscopically, patches of sclerodermatous change scattered throughout areas of normal heart muscle. Arterioles numerous and unaffected.

Respiratory System. Twenty oz. (600 ml.) of clear yellow fluid in the left pleural cavity, 32 oz. (960 ml.) in right. Saccular bronchiectasis in moderately contracted right lower lobe but no obvious fibrosis on cut surface. Oedema and nodules of pinkish-grey pneumonic consolidation in all other lobes. Lung weight: right, 695 g.; left, 718 g. Some digital involvement, but her other systems, including the œsophagus, normal.

Case 3. Woman, aged 64. *Cardiovascular System.* Heart weight 567 g. Moderate enlargement due to hypertrophy of both ventricles. Both layers of pericardium a little thickened and densely adherent over the whole surface. No pericardial effusion. Valves and coronary arteries normal. Myocardium generally soft and pale.

No evidence of old or recent infarction.

On microscopy, diffuse fibrosis showed and in some areas this seemed to be replacing muscle fibres, many of which were small and atrophic. Fibrous pericarditis was present.

Respiratory System. Both surfaces of pleura considerably thickened and adherent over most of the opposing surfaces, except where bilateral loculated effusions of about 600 ml. had compressed the lung. Much passive collapse of both lower lobes. On cut section, no evidence of an inflammatory lesion but parenchyma intensely œdematous and firm.

Microscopically, patchy fibrosis, in places very marked in the interalveolar connective tissue, some alveoli being almost non-existent. In some areas of the lung, however, no increased fibrosis.

Kidneys. Both of normal size and capsules stripped easily. On section, surfaces paler than normal and complete loss of cortico-medullary differentiation. Many linear fibrotic areas and plaques throughout.

A few completely fibrosed glomeruli and a little patchy hyaline change in some of the other glomeruli, besides a generalized increase in interstitial fibrosis. In some arterioles adjacent to glomerular tufts, much hyaline thickening of the wall with narrowing of the lumen.

Clinical Findings in Scleroderma Heart Disease

As the heart in scleroderma is the primary interest in this communication, presentation of other aspects of the clinical picture is not given in full to save space: instead we have tabulated the salient clinical features in Table II. The evidence of cardiac involvement by scleroderma in our twenty-one cases is given in Table III.

The Heart. As a rule, cardiac symptoms do not appear until late in the disease. For example, in the case of Goetz (1945) there was an interval of 14 years before cardiac involvement became obvious, although the interval is usually less than this. Once cardiac symptoms appear, the duration of life is usually a matter of a few years, and rarely it can be measured only in days. The average

TABLE II

SALIENT CLINICAL FEATURES OF OUR 21 CASES

Case No., Age, and Sex	Raynaud's phenomenon (Acrosclerosis)	Skin and Muscle	Joints	Dysphagia / Ba Swallow — Œsophagus	Clinical / X-ray — Lungs	Comment
1. M. 56	+	+			++	Lungs more extensively involved than heart. Death from pulmonary embolism (Fig. 1 and 5).
2. F. 62	+	+			++	Less than 6 months from onset of acrosclerosis to death from left ventricular failure (Fig. 7).
3. F. 64	+	+	+		++	Ventricular muscle extensively involved. Severe cardiac pain in absence of coronary artery disease histologically.
4. F. 37*	+		+	++	+	Widespread calcification in neck, left shoulder, hands, nose, ears, and lungs. EC. showed pathological changes over left ventricle. B.P. normal. (Fig. 4a and 6).
5. F. 55		+	+	+	++	Cardiac size increased *pari passu* with worsening of scleroderma in skin but improvement in lungs. LBBB and cardiac pain (Fig. 2).
6. M. 52	+	+				EC. appearance that of postero-apical infarct but no cardiac pain.
7. F. 76	+	+	+		++	Amputation of left hand because of gross Raynaud's disease.
8. F. 49	+				++	Cirrhosis of liver also present.
9. F. 46*	+	+		++	+	Severe skin and œsophageal lesions with progressive heart failure over 3 years.
10. F. 57*			+		++	EC. appearance that of coronary insufficiency yet no cardiac pain. Extensive pulmonary involvement but no cor pulmonale. Thibierge-Weissenbach syndrome (Fig. 3).
11. M. 35		+				Considerable dyspnœa due to involvement of chest wall, not lungs. EC. that of postero-apical infarction, but no cardiac pain.
12. F. 56	+	+			++	Congestive heart failure 12 years after the onset of scleroderma: fatal within less than a year.
13. M. 42†	+	+	+			Raynaud's syndrome since childhood. Pericarditis at 42 with subsequent increase in heart size, partial heart block, and notched P waves.
14. F. 47		+	+	+	++	Pulmonary changes originally thought to be sarcoid but later typical scleroderma of chest wall.
15. F. 74*	+	+	+		++	Antero-septal infarction appearance without coronary pain. Multiple calcium deposits in right shoulder region (Fig. 4b).
16. F. 41†	+	+	+	++		Partial RBBB preceded Raynaud's syndrome, dysphagia, and scleroderma of skin.
17. F. 67	+	+	+	+		Raynaud's phenomenon, telangiectases of face and dilated atonic œsophagus. Short P–R interval associated with RBBB.
18. F. 44	+	+		+		Severe Raynaud's syndrome, angina, and paroxysms of atrial tachycardia: followed 4 years later by skin changes of scleroderma.
19. M. 52†		+				Unexplained pericarditis preceded progressive skin scleroderma by a little over one year.
20. M. 58*	+	+	+		+	Raynaud's syndrome, followed 8 years later by skin changes of scleroderma, RBBB, and two linear patches calcification right lung.
21. F. 77*†	+	+	+	++	+	Thibierge-Weissenbach syndrome, œsophageal obstruction, mitral regurgitation, and short P–R interval.

* These six patients had calcinosis (Thiberge-Weissenbach syndrome).
† These four patients showed other intestinal involvement.

duration of life after the onset of cardiac symptoms is 30 months in our series, the range being from nine days to eleven years. Progressive myocardial symptoms do not necessarily follow episodes of pericardial involvement, as recorded in two of our male patients (Cases 13 and 19). The former, grossly restricted in activities by parietal and intestinal disabilities, complained of no symptoms directly related to his heart in spite of partial heart block and steadily increasing heart size in the following seven years. The latter (Case 19) had no further cardiac symptoms in the subsequent six years; nor was there obvious myocardial deterioration on objective evidence.

It is exceptional for cardiac symptoms to precede the more obvious skin lesions, and when they do, the cause for them is hardly ever diagnosed at the time. Five patients in our series presented in this manner (Table IV). Other reported examples are those of Goldman *et al.* (1954) who recorded an example in a man aged 50, where cardiac symptoms were present for about 30 months, and only during the last 6 months of life did the diagnosis of scleroderma become obvious. Similarly, in three of the nine cases described by Weiss *et al.* (1943) cardiac symptoms preceded changes in the skin, as they did also in the case of Spain and Thomas (1950) and that of Bauer (1955). In general, both the progress of the cutaneous disease and its relation to cardiac symptoms are extremely variable.

The commonest cardiac symptom is dyspnœa, but its significance in scleroderma is difficult to assess because of the frequent association of pulmonary and constrictive parietal lesions. All

TABLE III

EVIDENCE OF CARDIAC INVOLVEMENT BY SCLERODERMA (21 CASES—ALL HAD ALSO SCLERODERMA ELSEWHERE)

Case No.	Age and Sex	Clinical	B.P.	Radiological		Electrocardiogram	Cardiac Involvement†
				Heart	Lungs		
*1	M. 56	3rd H.S.; P2+; H.F.	160/100	Enlarged	Coarse basal reticulation	Right ventricular preponderance	E
*2	F. 62	Mitral s.m.; acute L.V.F.	140/95	Enlarged	Basal bronchopneumonia	Supravent. ExS. T inverted V1–4	
*3	F. 64	Left parasternal murmur; P2+; angina; C.H.F.	140/75	Large, triangular	Basal fibrosis and congestion	Low voltage. T inverted II, III, VF. Later frequent supraventricular. ExS.	P
4	F. 37	H.S. normal; extrasystoles	120/80	Normal	Infiltration diffuse	L.V. hypertrophy—ischæmia. Atrial and ventricular ExS.	
5	F. 55	Angina	124/82	Enlarged	Opacity upper lobes	LBBB	
6	M. 52	Extrasystoles	128/80	Normal	Emphysema	Ventricular ExS. Postero-apical infarct.	
7	F. 76	A.F.; C.H.F.	135/80	Greatly enlarged	Collapse right base	Atrial fibrillation. All T waves flat	
8	F. 49	S.m. internal to M.A.; 3rd H.S.; H.F.	140/95	Normal	Opacity right base	Low voltage. Low T I, II, III, V5–6	E
9	F. 46	Mitral s.m.; P2+; H.F.	116/65	Normal	Fibrosis right base	Ventricular ExS. S–T slightly depressed in L.V. leads	E
10	F. 57	C.H.F.; no cardiac pain	110/70	Moderately enlarged	Infiltration diffuse	Ventricular ExS. Coronary insufficiency changes	
11	M. 35	H.S. normal; pulmonary dyspnœa; no pain	140/90	Normal	Normal	T inverted in VF, V5 and 6→normal→post. apical infarct	
12	F. 56	C.H.F.	120/80	Moderately enlarged	Infiltration diffuse	P–R 0·22. Low or inverted T waves	
13	M. 42	Pericardial rub	110/55	Slow enlargement	Emphysema	Temporary pericarditis changes. P notched II, III, VF. P–R→2·4 sec. Low voltage	P
14	F. 47	3rd H.S.; P2+; C.H.F.	110/70	Normal	Reticular opacity mottling	P–R 0·24 sec. P pulmonale. T1 flat T inverted II, III, V1–7	
*15	F. 74	Aortic outflow murmur only; C.H.F.	160/110	Triangular enlargement. Mainly L.V.	Basal opacity	P–R 0·25 sec. Resembled antero-septal infarct. Ventricular ExS.	PE
16	F. 41	Normal	140/90	Slightly large	Basal shadows increased	Partial RBBB. Ventricular ExS. P increased and bifid	
17	F. 67	Split H.S.; RBBB	220/120	Normal	Normal	RBBB. L.V. stress. P–R 0·12 sec.	
18	F. 44	Angina of effort; H.S. normal; atrial tachycardia	120/80	Normal	Normal	P–R 0·24 sec. P rounded and prominent low voltage. Paroxysms of atrial tachycardia	
19	M. 52	Pericardial friction; H.S. normal	125/80	Slow enlargement	Normal	Pericardial changes temporary. Slurred R in V3. Atrial and ventricular ExS.	P
20	M. 58	RBBB only	130/90	Normal	Linear calcification	RBBB	
21	F. 77	Mitral s.m.; L.V. heave; C.H.F.	150/90	Enlarged mainly L.V.	Patchy mottling right base	P–R 0·14 sec. Peaky T wave in V3	E

* With necropsy.

† The myocardium was involved in all cases: P and E indicate involvement of pericardium and endocardium.

nine of the series of Weiss *et al.* (1943) had dyspnœa, five had orthopnœa, and two paroxysmal nocturnal dyspnœa. Leinwand *et al.* (1954) are of the opinion that dyspnœa is more frequently symptomatic of cardiac than of pulmonary involvement and that its onset is of grave prognostic importance. It was mentioned in 40 of these 49 cases. Right-sided heart failure with œdema of the ankles is very common and occurred in about one half, and at times there may be gross anasarca. As a rule, cyanosis is absent or only moderate, but one of Goetz's (1945) patients presented a picture of a "black cardiac."

TABLE IV

RECOGNITION OF CARDIAC INVOLVEMENT RELATED TO APPEARANCE OF SCLERODERMA ELSEWHERE

No. of Cases	Scleroderma diagnosed before cardiopathy	Cardiopathy preceded recognition of scleroderma	Concurrent recognition
Previously recorded (28)	19	6	3
Personal series (21)	8	5	8
Total (49)	27	11	11
Approximate percentage of total series	55	22·5	22·5

Clinical detection of cardiac enlargement may be difficult if the chest wall is infiltrated. The heart sounds are usually of normal or less than normal intensity, and gallop rhythm is common, and when described fully is more usually protodiastolic than presystolic. It presumably results either from a sound due to rapid ventricular filling, or later, when failure sets in, from atrial gallop. With progress of the disease the pulmonary second sound is apt to increase in intensity, presumably as a result of progressive rise in pressure of the pulmonary artery following lung changes, and at times it may become widely split (Bauer, 1955) owing to delayed closure of the pulmonary valve.

A systolic murmur of variable intensity is commonly heard at or near the apex but is rarely very loud. We have been unable to find an example where a diastolic murmur has been present, although the rare case with mitral valve nodules may be mistaken for rheumatic heart disease. Rather surprisingly, when one considers the frequency with which pericarditis is found at autopsy (Table I), a pericardial friction rub is an uncommon finding and was mentioned only rarely in the reported cases and heard only in two of our present series.

In scleroderma heart disease the heart usually fails in normal rhythm, although extrasystoles, both supraventricular and ventricular, especially the latter, are common. Atrial fibrillation occurred in two of our patients and atrial flutter in one. Conduction defects are common, too; partial heart block led to complete heart block in one patient (East and Oram, 1947), three other new patients had a P–R interval of 0·24 sec. or over, and three had right bundle-branch block. On the other hand, the P–R interval was only 0·12 sec. in one and 0·14 sec. in another.

Pain in the chest is surprisingly common, occurring in 12 of these 49 patients. Its description is sometimes not unlike that resulting from coronary disease, although even the finer branches of the coronary vessels are rarely affected microscopically. No convincing explanation has been given for its origin, but it is likely that some examples are due to pericardial or pleural involvement, and others to involvement of the lower œsophagus. The direct relation to exertion of the anginal pain in some patients, whose coronary arteries are found to be patent and not ischæmic at autopsy, might be explained by a nutritional change, associated with the fibrosis, actually in the heart muscle.

The Lungs. Pulmonary symptoms are commoner than usually thought, and may be present long before any abnormal physical signs can be elicited clinically or any radiological change seen. At autopsy extensive pulmonary fibrosis may be found, in spite of a persistently normal X-ray

picture. One such case, which necessitated tracheotomy twice, has been described by Talbot and Ferrandis (1956). Cough is frequent and commonly non-productive.

Spain and Thomas (1950) have divided the effect on pulmonary function into two types, the ventilatory and respiratory. Ventilation is impaired because involvement of the skin and muscles of the thoracic cage restricts normal chest expansion, and fibrosis of the diaphragm and pleura impedes the lung movement: in addition there may be diffuse peribronchial fibrosis with obstructive emphysema (Murphy *et al.*, 1941). Respiratory gaseous interchange in the alveoli is impaired by thickening of the alveolar walls, and by changes in the blood vessel walls leading to narrowing and obliteration, as previously described. This may be demonstrated by a decreased oxygen content of the arterial blood following exercise (Fox, 1947). Pulmonary râles, usually basal, are the commonest finding, and signs of bronchiectasis may be present. Recurrent attacks of pneumonitis and pleurisy are not uncommon, often associated with spillover as a result of an œsophageal lesion. At times pulmonary œdema may result from uræmia.

The Kidneys. From microscopical studies it appears to be the exception for hypertension to result from renal involvement (Moore and Sheehan, 1952); in fact, several authors, among them Gil (1951) and Goetz (1951), have emphasized the tendency of the blood pressure to drop as the disease progresses. Even so, when hypertension is severe, retinal exudates and hæmorrhages may accompany it, and it may constitute the cause of death (Ellman, 1938). In a series of 38 patients with renal involvement studied by Evans *et al.* (1953), only two had hypertension. When the kidneys are extensively involved, death is usually from renal failure, but there is no doubt that occasionally the disease, by involving the kidney, can lead to hypertension pre-terminally, as in two patients described by Pollack (1940), or can result in sudden hypertensive heart failure with pulmonary œdema (Barnes Hospital Report, 1953). Moore and Sheehan (1952) collected eleven reported instances of major renal impairment, and although all showed a raised blood urea there was no example of malignant hypertension among them. On the very rare occasion that malignant hypertension is found, together with sclerodermatous renal changes, histological studies of the kidney may fail to reveal which disease came first, as the microscopic appearances may be identical (Kincaid-Smith *et al.*, 1958). When hypertension arises as a result of sclerodermatous renal involvement, it is usually pre-terminal and sometimes appears to be precipitated by cortisone therapy (Sharnoff *et al.*, 1951).

Investigations

Cardiac Radiological Findings. The cardiac silhouette may be enlarged, and Weiss *et al.* (1943) found that all six of their patients with radiographs showed a strikingly similar appearance, with moderate to considerable cardiac enlargement giving a triangular outline to the heart. Cardiac pulsation was apt to be of poor amplitude. The appearance did not suggest hypertensive or valvular disease, but suggested rather myxœdema or a pericardial effusion. The latter, of course, is not infrequently found at autopsy.

Sometimes the appearance is typical of left ventricular enlargement (East and Oram, 1947). Although at times enlargement may develop during the course of the disease, as in some of our patients, there would appear to be no specific or even suggestive shape to the heart radiologically (see Fig. 1 and 2). It is not uncommon for the heart silhouette to be normal, notwithstanding electrocardiographic evidence of myocardial involvement. Most of Goetz's (1951) patients had a normal cardiac silhouette, although the kymogram showed blunting of the cardiac excursions in four of them, and in three that came to autopsy the lesion was confirmed histologically.

Lung Radiological Findings. There is no doubt from autopsy studies that the radiograph may give little or no hint of surprisingly extensive microscopic changes in the lungs. The first case that we can find in which changes in the lungs due to scleroderma were diagnosed radiologically is that of Murphy *et al.* (1941). In the present series of previously reported cases pulmonary fibrosis, with or without cystic change, was diagnosed radiologically in nine, but at autopsy the changes were present in seventeen. When present, radiological change often begins in the central portion of the

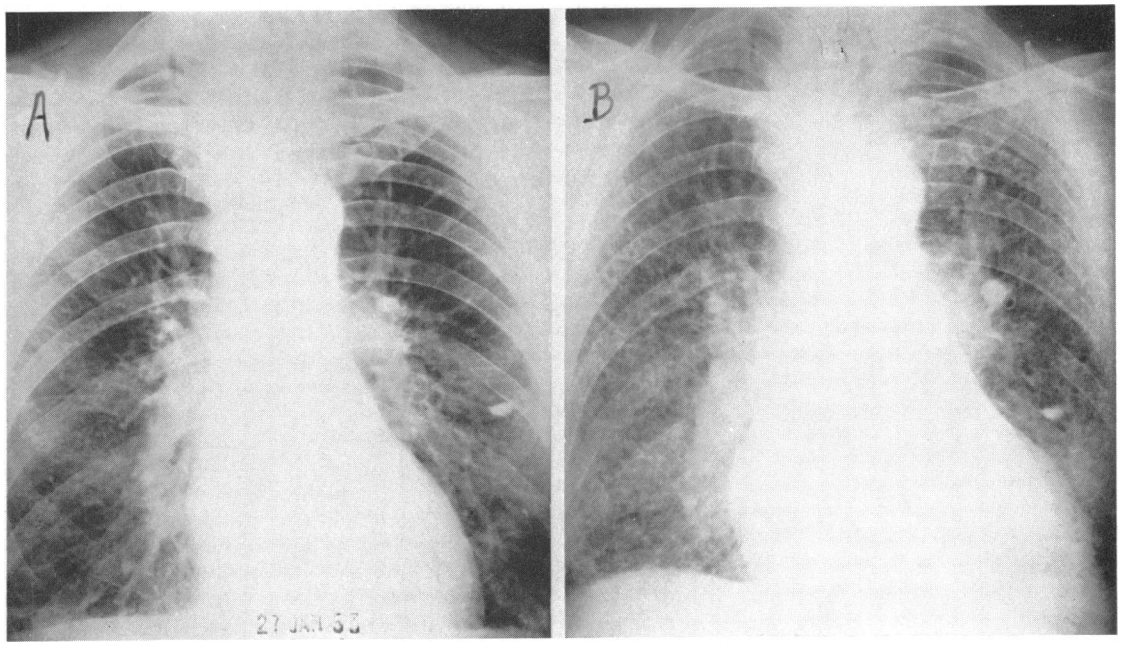

FIG. 1.—Gradual increase in size of the heart and in the degree of reticulation of lungs over a period of three years. (A) 27/1/53. (B) 15/12/55. Case 1.

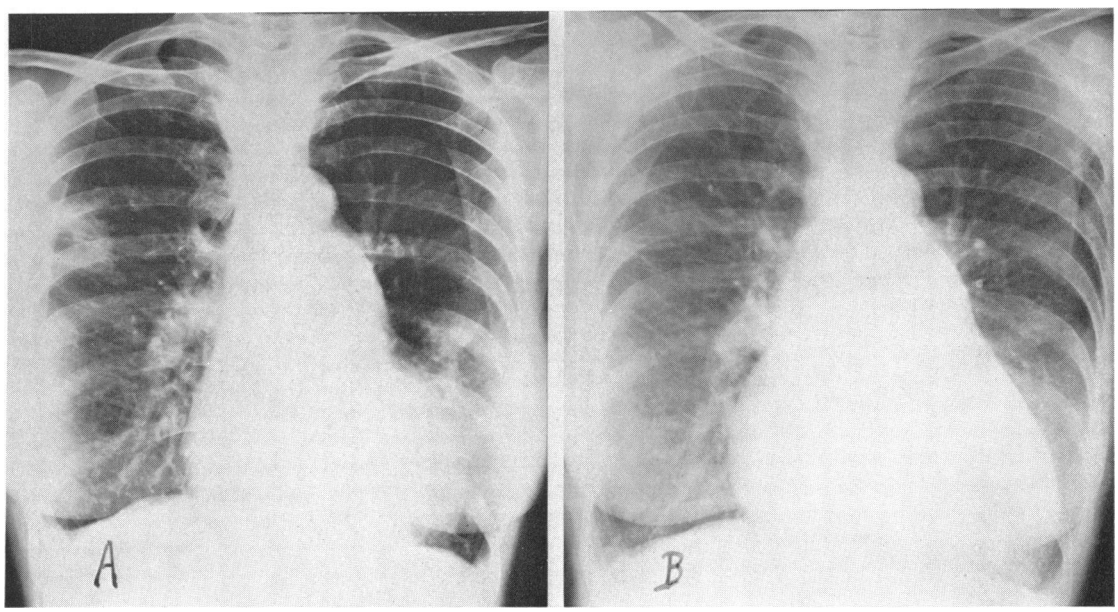

FIG. 2.—Increase in heart size, also over three years. The cardiac silhouette is, however, of different shape compared with Fig. 1, the pulmonary artery shadow being prominent. The lung fields have become clearer. There was no evidence of cor pulmonale. (A) 6/5/55. (B) 20/6/58. Case 5.

lower zone, either interstitial fibrosis or cyst formation. Cystic change is often present at autopsy but unsuspected during life; and it is sometimes more readily demonstrated in an over-exposed film (Aronsen and Wallerstein, 1950). It may result in spontaneous pneumothorax. Sometimes unilateral or bilateral pleural effusions are present. The progressive fibrosis of the lungs is related to the generalized sclerodermatous process (Lloyd and Tonkin, 1948), but undoubtedly some of the recurring episodes of localized pneumonitis and pleurisy are the result of "spillover" from the disease leading to œsophageal atony or obstruction, and it is interesting that some of the cases reported by Weiss *et al.* (1943) were thought to show an appearance suggestive of bronchiectasis or lipoid pneumonia. Nevertheless, Lloyd and Tonkin (1948) have published illustrations of four patients showing a remarkable similarity in their chest radiographs: the appearances were those of a diffuse fibrosis, which was obviously generalized and yet at the same time predominantly basal in distribution. This appearance can exist in the absence of detectable dermatological changes. At times pulmonary calcification is seen (Leinwand *et al.*, 1954), as in our Case 20. An X-ray of the chest in all cases with the Raynaud phenomenon might well reveal further cases of systemic scleroderma. Apparently the appearance has not been recorded in association with dermatomyositis.

X-ray of Soft Tissues. In systemic scleroderma, deposits of calcium may be found scattered throughout the body, at times unaccompanied by other evidence of the disease. Their detection in any cardiopathy of obscure nature is of obvious importance. The commonest site is the fingers especially near the tips, and such patients invariably have severe and obvious sclerodactyly—the so-called Thibierge-Weissenbach syndrome (1910) (Fig. 3). However, at times the calcinosis does

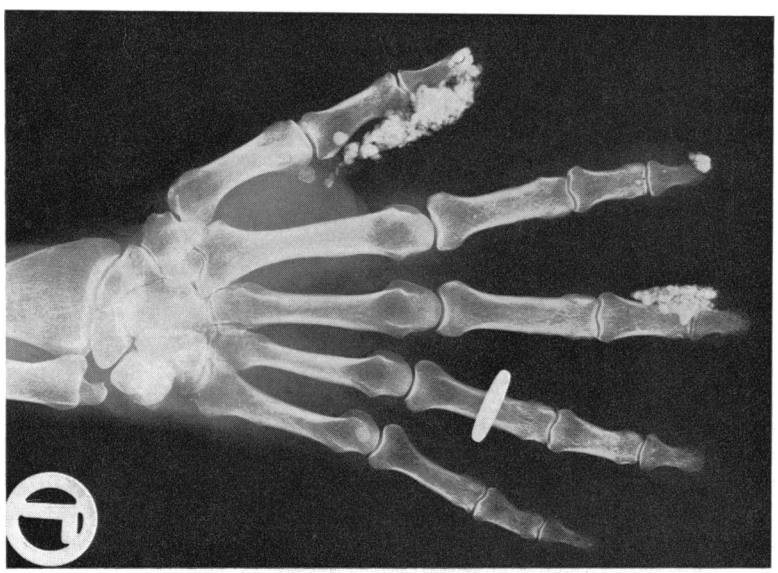

FIG. 3.—Circumscribed calcium deposits in the fingers (Thibierge-Weissenbach syndrome). Case 10.

not reveal itself clinically and may be discovered unexpectedly by the radiologist. Common sites for such deposits are the region of the shoulder joints and in the neck (Fig. 4).

Electrocardiogram. Although it is certain that the electrocardiogram may at times be normal when the heart is involved in the sclerodermatous process, and indeed Leinwand *et al.* (1954) quote such a case with extensive myocardial changes, the electrocardiogram was, in fact, abnormal in 48 of the present 49 cases (Table V). However, the changes are non-specific and at times may be due to the resultant chronic cor pulmonale or to digitalis. Nevertheless, the importance of the

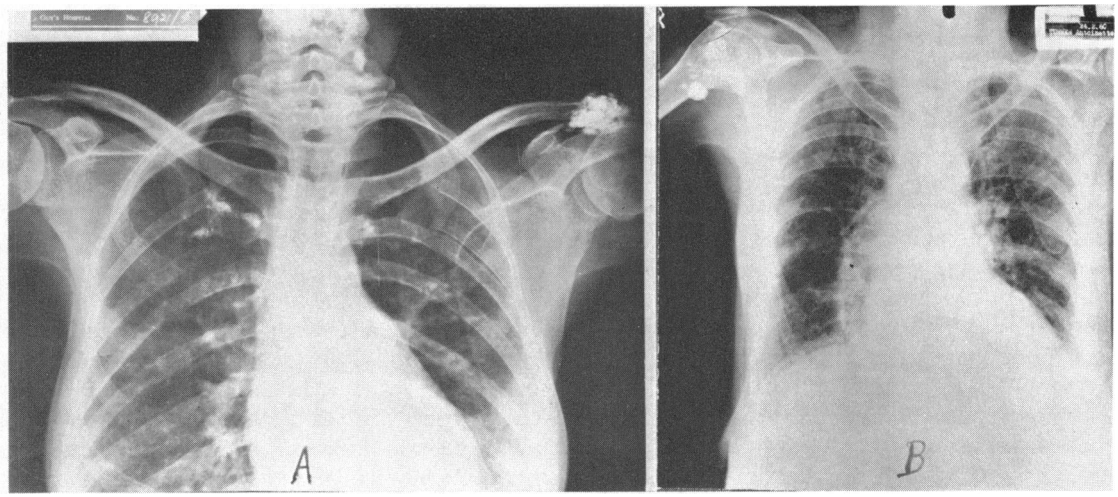

FIG. 4.—Showing calcinosis in soft tissues other than the heart. (A) Calcium deposits in region of left shoulder and larynx and in both lungs. Moderate cardiac enlargement and some sclerodermatous infiltration at both lung bases. Case 4. (B) Calcinosis in region of right shoulder. Moderate cardiac enlargement. Case 15.

TABLE V

ELECTROCARDIOGRAPHIC FINDINGS IN 49 CASES* OF SCLERODERMA HEART DISEASE

Altered Rhythm		Conduction Defect		Ischæmic Change		Unclassified	
Extrasystoles:		Prolonged P–R interval	10	T wave inversion	5	R.A.D. & R.V.P.	4
ventricular	11	Short P–R interval	2	Resembling infarct	3	L.V.P.	5
atrial	6	R.B.B.B.	8	T waves flat or low	5	Notched P waves	2
multifocal	3	L.B.B.B.	3	S–T depression	4	Prominent P waves	3
Atrial fibrillation	2	Complete heart block	2				
Atrial flutter	1						
Ventricular fibrillation	1						

* 48 patients had one or more electrocardiographic abnormality.

electrocardiogram cannot be over-emphasized, because, although the changes are in no way specific and are commonly slight, they may represent the first and indeed the only clinical evidence of cardiac involvement. Of 31 patients with typical scleroderma of the skin but without clinical or radiological evidence of visceral involvement, Escudero and McDevitt (1958) found that 8 had abnormal electrocardiograms which could not be explained otherwise.

The commonest finding due to myocardial involvement is an abnormally low voltage. Sinus rhythm is the rule, but extrasystoles, usually ventricular and sometimes multifocal, are very frequent. Partial heart block (Weiss *et al.*, 1943), which at times may proceed to become complete (East and Oram, 1947), has been noted, and both right bundle-branch block (Goldman *et al.*, 1954) and left (Weiss *et al.*, 1943) have appeared. Right bundle-branch block may at times be transient as in one of our patients, or at other times it appears gradually over a period of months or years (Fig. 5). In one of Goetz's (1945) cases all the heart beats were extrasystoles, which originated from eight different foci. We have records from one patient that suggested considerable hypertrophy of the left ventricle, yet there was only moderate enlargement radiologically and the blood pressure was normal (Fig. 6). Ischæmic T-wave changes occurred in five patients, and at times the cardiographic appearance may be apparently diagnostic of cardiac infarction, as in three of our patients. We

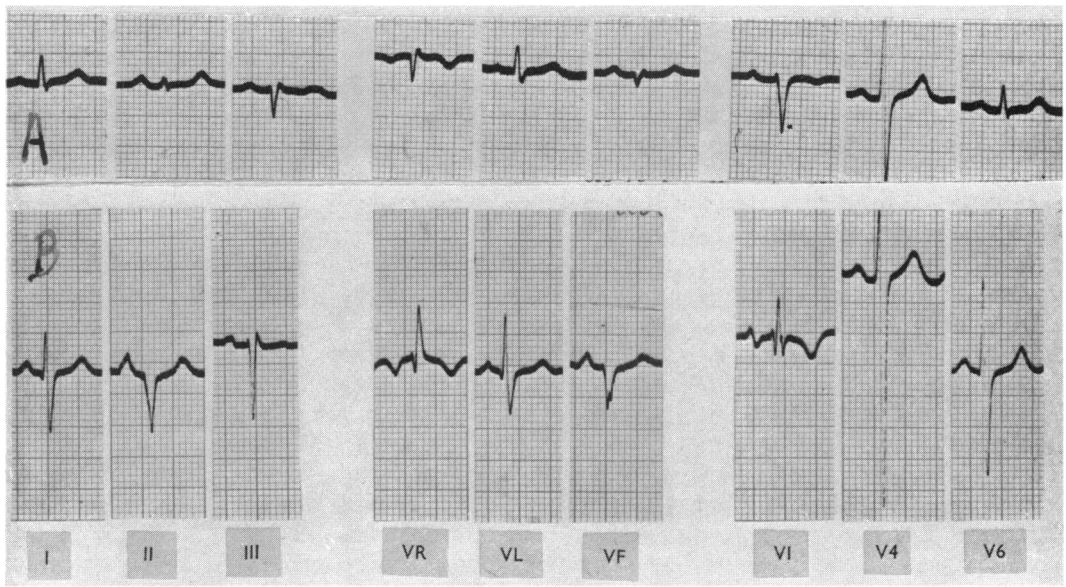

FIG. 5.—Electrocardiograms showing increasing right axis deviation and the development of incomplete right bundle-branch block. (A) 19/2/54. R in V4 was 20 mm. (B) 2/1/56. Case 1.

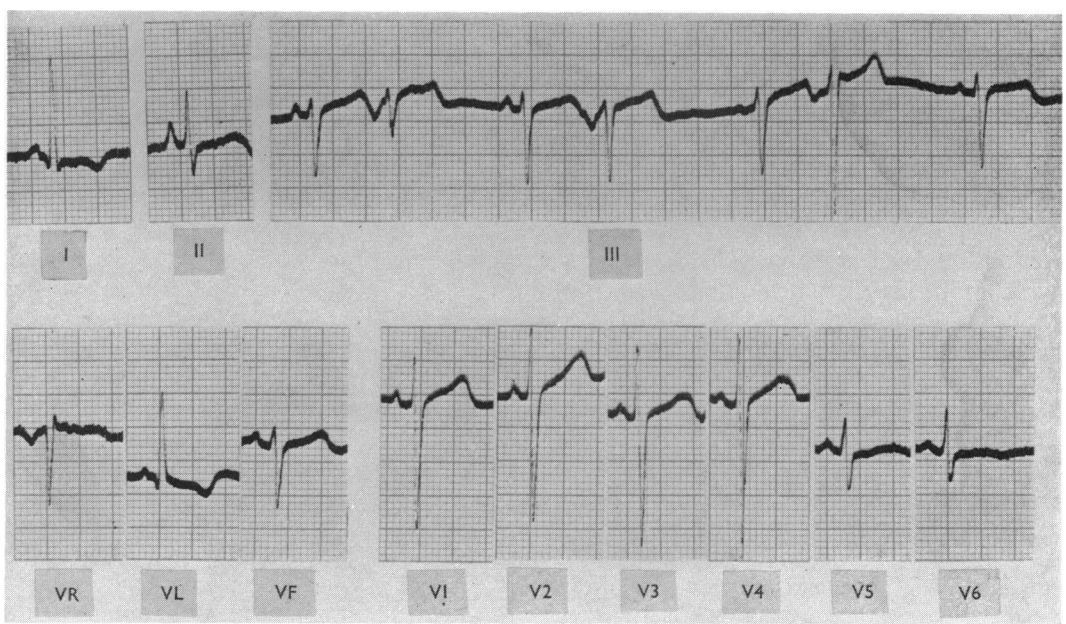

FIG. 6.—The electrocardiogram suggests hypertrophy of the left ventricle in spite of only moderate enlargement radiologically. Supra-ventricular and ventricular extrasystoles are present. Case 4.

were struck by the complete absence of cardiac pain in three of these (Cases 6, 11, and 15) although in two of the three, the electrocardiogram showed the appearance of postero-apical infarction, and in the third of antero-septal infarction. We suggest, therefore, that the association of an electrocardiogram apparently pathognomonic of cardiac infarction and of the absence of cardiac pain may have some diagnostic value. If hypertension comes on rapidly the appearance of left ventricular strain may be found on the electrocardiogram (Barnes Hospital Report, 1953).

Notching of P waves in standard leads was reported by Escudero and McDevitt (1958) in 45 per cent of a group of 31 patients with scleroderma but without evidence of visceral involvement, and in 60 per cent of a second group of scleroderma with clinical or radiographic evidence of visceral lesions. We have found this in an occasional electrocardiogram but do not regard notching of the P waves as a common characteristic of scleroderma hearts. Slurring of the R or S waves was similarly met, but this feature was not outstanding among the wide variations of abnormalities noted. Mustakallio and Sarajas (1954), examining cardiograms from seven sclerodermatous patients with no clinical evidence of cardiac involvement, found that minor abnormalities, including a full-length P–R interval and slightly prolonged QRS, were common and the Q–T interval was prolonged in all.

Cardiac Catheterization. We have been unable to find a published report of catheter study in scleroderma heart disease. From consideration of the extensive myocardial involvement and the presumed interference with contraction and relaxation, findings not unlike those of any other cardiopathy, such as amyloidosis or isolated myocarditis, might be expected, namely a right ventricular tracing showing a sharp dip in early diastole, followed by a flat diastolic plateau. Possibly, too, the atrial tracing would show a steep *y* descent and trough.

Pathology

The Heart. The essential lesion, as pointed out by Weiss *et al.* (1943), is found in the myocardium itself, and consists of scars of unusual type. Of 28 cases previously recorded with autopsy reports, the myocardium was involved in 25 (Table I). As a rule, the weight of the heart is not grossly increased, being 500 g. or more in only four, and in more than half it weighed less than 400 g. The lesion involves predominantly the myocardium and extends to the epicardium and endocardium only secondarily and to a slight degree. The scarring may form white or yellowish streaks or grey translucent speckling throughout the whole thickness of the myocardium, or may merely cause some naked eye pallor of the muscle. The lesions are not in any particular relationship to arteries, and even the finer branches of the arterioles usually remain unaffected. In contrast to the scarring of vascular lesions, hæmosiderin deposits are entirely absent. The change in the myocardium is usually patchy, normal areas of muscle fibres being interspersed with areas where a rather unusual type of connective tissue is increased (Fig. 7A). In the early stages connective tissue contains numerous fibroblasts and the collagen fibres are not coarse with an increased calibre, as are those found when the skin is involved (Fig. 7B). Sometimes there are so many capillaries present that the histological appearance resembles that of young granulation tissue as in the patient described by Hurley *et al.* (1951), but later extensive hyaline scarring appears.

Some workers are of the opinion that the muscle fibres atrophy as a result of pressure from the sclerodermatous tissue, but East and Oram (1947) thought from the microscopic appearance of the lesions that probably, for some unknown reason, patches of muscle fibres died and were then replaced by the sclerodermatous process, and likened the pathological event to Strauss's tone poem *Death and Transfiguration.* Whatever the cause of the atrophy of the cardiac muscle fibres may be, it is certainly not the result of any interference with the blood supply to the myocardium.

In the cases examined at autopsy, pericarditis is common, with or without effusion, and occurred in two-thirds of our collected series (22 of 31 cases). Lewin and Heller (1895) found that pericarditis was present in 8 of 29 cases that came to post-mortem examination, but it is possible that some of these were due to other causes such as tuberculosis and rheumatism. Two of the six cases

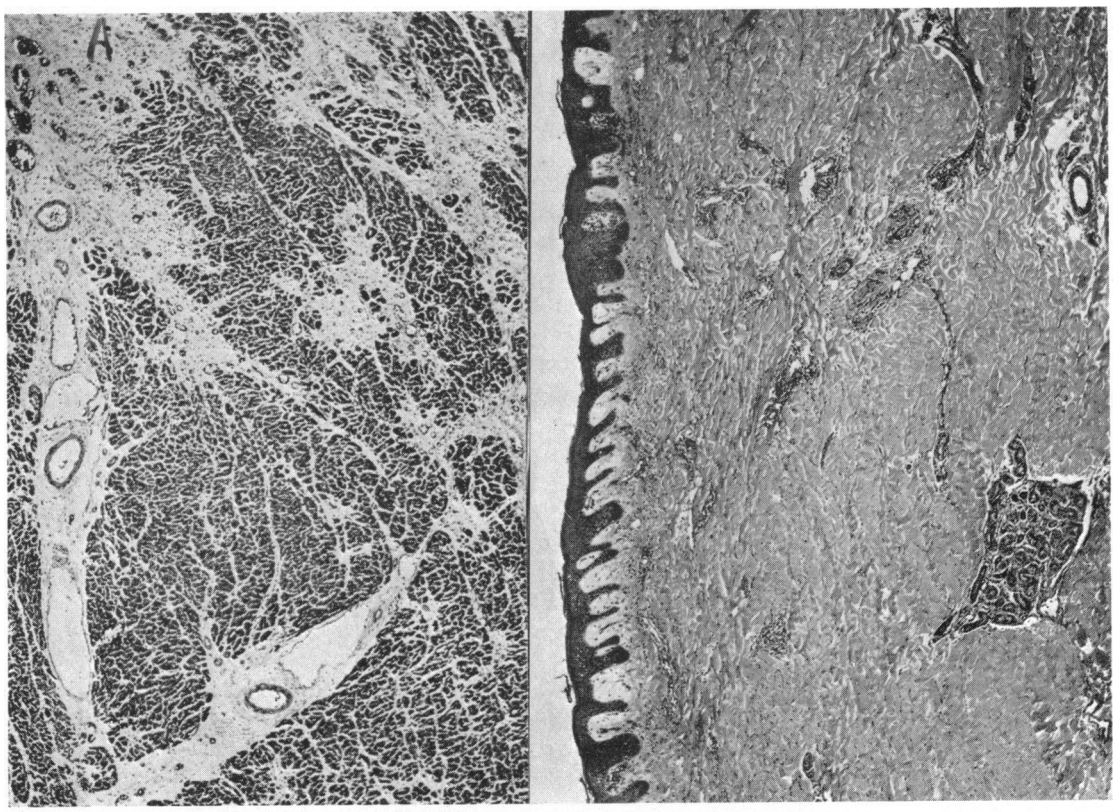

FIG. 7.—(A) Heart muscle. (B) Skin. The heart shows patchy microscopic changes with normal areas of muscle fibres interspersed with areas of increased connective tissue. The collagen fibres are not coarse or dense, unlike those in the skin. In the heart the arterioles are plentiful in the collagenous tissue and remain unaffected by it, but in the skin they tend to be obliterated. Both sections stained with hæmatoxylin and eosin. Magnification, ×36. Case 2.

reported by Matsui (1924) had a pericardial effusion, and Bevans (1945) states that pericarditis is not uncommon and is not necessarily due to uræmia, which may terminate the disease.

The epicardium may be œdematous or fibrotic, and microscopically flecks of calcium are sometimes detectable (Durham, 1928). At least one, and possibly two, examples of atypical non-bacterial verrucous endocarditis occurring in generalized scleroderma have been reported by Spühler and Morandi (1949). At autopsy, in addition to diffuse scleroderma with chronic interstitial pneumonia and fibrinous pericarditis with effusion, there were, on the atrial surface of the anterior mitral cusp, several pea-sized craggy vegetations resembling the non-bacterial verrucous endocarditis of Libman and Sacks (1924; their Case 1). Two of our collected series of previously reported autopsies had involvement of both the mitral and tricuspid valve, two had the mitral valve affected only, and in one the chordæ tendineæ were involved.

The Lungs. The first description of pulmonary lesions in scleroderma has been credited to Finlay (1889). Thickening of the alveolar septa due to infiltration with mononuclear cells, plasma cells, and polymorphonuclear leucocytes may occur, and lead to diffuse fibrosis of the alveolar wall and obliteration of the capillaries. This fibrotic change may become hyaline, and Getzowa (1945) has described a cystic type of sclerosis in the interstitial tissue of the lung parenchyma caused by hyaline fibrotic change. Church and Ellis (1950) think that obstruction and associated infection lead to emphysematous bulla formation and that this is responsible for some of the cystic change.

The muscle coat of many of the smaller bronchi may be replaced by fibrous tissue, and the arteries and arterioles may show thick walls with sclerosis (Aronsen and Wallerstein, 1950). There is no doubt, too, that infarction of the lung from spillover due to oseophageal involvement by the disease is responsible for some of the pulmonary findings, and bronchopneumonia is one mode of death.

The pleura may be thickened, and unilateral or bilateral effusion is not uncommon, but its appearance is often late in the disease and then sometimes results from cardiac failure.

The Kidneys. As in the myocardium, the pathological change may be patchy and normal areas may appear in juxtaposition with severe involvement or with minimal change. The surface of the kidney may be uneven and show pinpoint hæmorrhages (Germuth and Alexander, 1953), or closely resemble a shrunken arteriosclerotic kidney if the vascular changes are widespread (Matsui, 1924). Kincaid-Smith *et al.* (1958) record details of a woman aged 38, who died as the result of fulminating malignant hypertension and scleroderma, which led to rapidly progressive renal failure and oliguria: these workers are of the opinion that where the renal vessels are involved in scleroderma, the lesions may be virtually identical with those found in malignant hypertension. A severe degree of narrowing of the interlobular arteries due to cellular intimal hyperplasia results, and fibrinoid necrosis in the afferent arterioles and glomeruli occurs in cases of scleroderma, both in those with raised and those with normal blood pressure (Moore and Sheehan, 1952). Kincaid-Smith *et al.* (1958) were unable to confirm the claim of these authors that the renal changes histologically are specific and that this condition can usually be differentiated histologically from malignant hypertension. Sometimes the vessels are occluded by organizing thrombi, and the glomeruli may show hyalinization with thickening of Bowman's capsule and the so-called wire-loop appearance, originally thought to be typical of systemic lupus erythematosus. Rarely, calcium deposits are present in the kidneys (Kusunoki, 1939; Horn, 1941).

Until the final phases there may be little indication that the kidneys are affected, the blood pressure rising with the onset of azotæmia (Leinwand *et al.*, 1954; and Moore and Sheehan, 1952). Hungarian observers have recently suggested that normal results to common tests of glomerular function until the terminal stages might be explained by a spasm of the efferent vessels that compensates for the reduced flow in the preglomerular arteries. According to these authors (Urai *et al.*, 1958) the characteristic pattern of "true scleroderma kidney," instead of developing at a terminal stage, might be of earlier origin: clinical manifestations would rapidly occur when the compensatory mechanism fails.

Modes of Clinical Presentation

Systemic scleroderma may present to the cardiologist either as a cardiac abnormality or as a result of a false symptom or sign incorrectly assumed to be of cardiac origin, in one or more of the following ways.

(*A*) *Cardiac Abnormalities*

1. *Heart Failure*
   (*a*) Primary myocardial involvement, with either a normal, or an abnormal rhythm.
   (*b*) Secondary to (i) chronic cor pulmonale, (ii) valvular incompetence, mitral most commonly, or (iii) hypertensive renal scleroderma or steroid therapy.
2. *Pericarditis.* May be mistaken for infective origin or for cardiac infarct when pericarditis precedes other evidence of scleroderma.
3. *Cardiac Pain.* Resembling angina of coronary ischæmia or infarct.
4. *Arrhythmia.* Extrasystoles; atrial fibrillation, flutter, or tachycardia; or rarely ventricular tachycardia.
5. *Syncope.* Stokes-Adams attacks and conduction defects.
6. *Incidental Findings on Routine Examination without Symptoms.*
   (*a*) Cardiomegaly.
   (*b*) Heart block—any degree.

(*c*) Electrocardiograms of unexplained low voltage or mimicking ischæmia or infarct, etc.
(*d*) Murmurs, most commonly mitral regurgitation.

(*B*) *False Symptoms and Signs arising Outside the Cardiovascular System*

1. Pain in chest and upper abdomen.
   (*a*) Œsophageal.
   (*b*) Parietal.
   (*c*) Pleural.
   (*d*) Peritoneal.
   (*e*) Pulmonary infarct.
2. Dyspnœa.
   (*a*) Pulmonary scleroderma, accentuated by infective or obscured by congestive elements, and by pleural effusions.
   (*b*) Parietal scleroderma—constriction of thoracic integument with weakness and fibrosis of respiratory muscles.
   (*c*) Uræmia.
   (*d*) Anæmia—nutritional.
3. Œdema.
   (*a*) Local, in early phases of advancing scleroderma of periphery.
   (*b*) Dependent from anæmia, poverty of movement, or low serum proteins.

Treatment

Treatment is unsatisfactory as the cause of the disease is still unknown, but there is no doubt that some patients can be improved and life prolonged by the use of adrenal glucocorticoids and corticotrophin provided a high dose is used. As a rule the underlying scleroderma is not greatly benefited, and skin biopsy shows little or no alteration; but we have seen four patients where movement of the shoulder girdle and the degree of chest expansion were improved remarkably after other therapy had failed to benefit. Unfortunately, when therapy is stopped, the patient's condition usually regresses rapidly to its former state (Kierland *et al.*, 1952). A word of warning is necessary regarding both corticosteroid and corticotrophin therapy, namely that great caution is necessary if these hormones are used in the presence of renal involvement. Sharnoff *et al.* (1951) give details of a patient where cortisone and corticotrophin appeared to cause severe and fatal malignant hypertension within ten weeks. On the other hand, Leinwand *et al.* (1954) mentioned two patients with hypertension whom they treated with cortisone, and in one the blood pressure fell satisfactorily though the other was unaffected.

Summary

Involvement of the heart by scleroderma is comparatively rare. Only twenty-eight reported patients have been found in whom adequate clinical description has been coupled with autopsy confirmation. In our own series of twenty-one cases, evidence that the heart was affected by scleroderma was beyond doubt and confirmed by autopsy in four.

Heart failure in systemic scleroderma is more commonly due to chronic cor pulmonale than to direct cardiac involvement. Clinical evidence of cardiac involvement usually arises late in the disease, but may precede the recognition of scleroderma elsewhere in the body. The myocardium is most commonly affected, the pericardium next, and the valves and endocardium least frequently. The pericardial lesion is usually clinically silent.

The earliest evidence of scleroderma heart is found in the electrocardiogram, which should not be omitted from the investigation of any case of systemic scleroderma. The cardiographic changes are numerous and not specific, but the diagnosis is suggested if the appearance resembles that of cardiac infarction in the absence of any history of cardiac pain.

In any obscure cardiopathy evidence of calcinosis should be sought, not only in the heart, lungs, and pleura, but elsewhere in the body in apparently unaffected soft tissues.

Addendum: Necropsy of Case 15

Case 15. Woman, aged 77. *Cardiovascular System.* Heart weight 595 g. Slight excess of pericardial fluid. Much left ventricular hypertrophy with some thickening of right ventricular muscle and dilatation of left atrium. Tricuspid valve little stenosed; mitral valve increased fibrosis of cusp margins. Pulmonary valve normal. Aortic valve gross thickening and calcification of all cusps. Myocardium extremely firm on slicing but no macroscopic evidence of fibrosis.

Microscopically, diffusely arranged, newly-formed fibrous tissue splitting up muscle fibres and in places leading to their degeneration. Much lymphocytic infiltration and some collections of histiocytes. Beneath the pericardium and under the endocardium, lymphocytic infiltration and some increase in fibrosis. No evidence of cardiac infarction.

Respiratory System. Large bilateral serous pleural effusions. Lungs greatly reduced in size, left more than right, due to fibrosis of lower lobes, especially at the periphery.

Microscopically, considerable fibrosis of interstitial tissue with a number of spaces lined by darkly staining cuboidal epithelium.

Kidneys. Little reduced in size. Capsules stripped with difficulty, leaving coarsely granular surface. On section, blurring of cortico-medullary margins. Microscopy showed chronic pyelonephritis.

We wish to record our grateful thanks to the following for permission to use the records of their patients: Dr. Howard Nicholson (Case 1), Dr. Michael Good (Case 3), Dr. Peter Bishop (Case 4), Dr. Gwyn Evans (Case 5), Dr. Bevan Jones (Case 6), Dr. J. L. Livingstone (Case 8), Dr. D. I. Williams (Case 10) and Dr. Sydney Thomson (Case 11); also to Dr. D. S. Wilkinson for dermatological opinion and to Dr. H. J. Harris for pathological reports (Case 3).

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