THE LUNG IN PROGRESSIVE SYSTEMIC SCLEROSIS (SCLERODERMA)*

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Progressive systemic sclerosis (scleroderma) is a chronic disease of unknown aetiology. It affects women more frequently than men, and is classified with the collagen disorders. The aetiology is obscure, but recent evidence tends to suggest that auto-immune mechanisms are involved.[1]

The most striking manifestations are cutaneous, but other organs may be involved, notably the heart, lungs, gastro-intestinal tract and the kidneys. The skin of the hands shows the most characteristic changes and becomes smooth, waxy, leathery and tight, so that it cannot be lifted from the deeper structures (sclerodactyly). Painful, indolent ulcers develop over the ends of the fingers. Raynaud's phenomenon is common. Calcium is frequently deposited in affected areas. Hyperpigmentation, and occasionally depigmentation, of affected areas occurs.

Atrophy of the tissues of the face gives it a 'pinched' appearance. The myocardium may be primarily involved by fibrosis, or secondarily to systemic or pulmonary hypertension.[2]

Lung involvement was first described in 1891 by Finlay.[3] Pathological changes were described by Matsui in 1924.[4] The lungs may show diffuse fibrosis involving the alveolar walls with obliteration of capillaries and alveolar spaces. The fibrosis may involve the bronchial walls and peribronchial tissues, leading to the formation of bronchiectasis. There may be evidence of recurrent pulmonary infections.

Involvement of the gastro-intestinal tract may lead to dysphagia and malabsorption. Death from renal failure or malignant hypertension is not infrequent. Muscle changes similar to those seen in dermatomyositis and polymyositis have been described.

Studies of the deranged lung function in cases of scleroderma were first reported in 1949,[5] and others have been published more recently.[6-9] This paper reports studies of pulmonary function in 11 patients with scleroderma, and correlates these findings with clinical, radiological, electrocardiographic and pathological findings.

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MATERIAL AND METHODS

Eleven White patients were studied, 7 females (aged 19 - 68 years; mean 44·2 years) and 4 males (aged 33 to 63 years; mean 48 years). Of the 4 males, 2 were gold-miners.[10]

A full history and examination, radiography of the chest and electrocardiography were carried out in every case. The extent of systemic involvement was assessed clinically and by radiographic examination of the gastro-intestinal and urinary tracts. Renal function was further assessed biochemically. Biopsy of the skin was carried out in 9 of the 11 patients. Pulmonary function studies were carried out on every patient and included the following:

(*a*) Lung volumes and distribution of ventilation (Table I).
(*b*) Mechanics of breathing (Table II).
(*c*) Ventilation and oximetric studies during rest and exercise (Table III).

Techniques and predicted values used have been described in previous publications from this laboratory.[11-13]

In case 4 a thermocouple was introduced *per rectum* and the patient performed a 5-minute exercise-load (200 kg.-m./min.). Temperature readings were taken every 30 seconds during and for 5 minutes after the exercise.

RESULTS

Clinical Assessment

Table IV shows the symptoms and signs of the 11 patients.

The duration of symptoms varied between 1 and 26 years. Five of the patients were smokers. Cough was present in 6 patients, of whom 5 produced sputum, but only 2 smokers gave a history of cough. Dyspnoea was present

TABLE I. SUBDIVISIONS OF LUNG VOLUME AND LUNG CLEARANCE INDEX

	VC		*FRC*		*RV*		*TLC*				
Case No.	*Meas. litres*	*% pred.*	*Meas. litres*	*% pred.*	*Meas. litres*	*% pred.*	*Meas. litres*	*% pred.*	*FRC/TLC × 100*	*RV/TLC × 100*	*LCI litre/litre FRC*
Males											
1	4·66	84	5·36	124	2·95	131	7·65	101	79	38	2·02
2	3·67	81	3·35	105	1·80	105	5·48	87	61	32	1·70
3	3·34	80	1·91	58	1·01	46	4·35	67	44	23	3·94
4	3·65	91	5·14	142	3·46	157	7·11	115	72	49	1·85
Females											
5	2·84	86	1·76	69	1·14	64	3·98	80	49	34	3·47
6	3·32	92	2·92	98	0·92	56	4·24	81	69	22	3·15
7	1·95	60	3·38	101	1·89	86	3·84	73	88	47	2·71
8	2·55	84	2·93	97	1·79	107	4·39	95	65	35	2·36
9	1·78	47	3·08	95	1·46	101	3·24	64	94	45	2·53
10	2·71	89	3·55	146	2·39	176	5·09	116	70	47	5·57
11	2·38	91	2·53	96	1·49	97	3·93	96	64	38	4·06

VC = vital capacity; FRC = functional residual capacity; LCI = lung clearance index; RV = residual volume; TLC = total lung capacity; % pred. = percentage of predicted value; Meas. = measured.

TABLE II. VENTILATORY CAPACITY AND MECHANICS OF BREATHING

Case No.	MVV_F (litre/min.)		MMF (litre/sec.)	FEV_1 (litre/sec.)	FEV_1: FVC	Compliance (litre/cm. H_2O)		Non-elastic resistance (cm. H_2O/litre/sec.)			
								Inspiration		Expiration	
	Meas.	% pred.	meas.	meas.	%	Rest	Ex.	Rest	Ex.	Rest	Ex.
Males											
1	139	97	2·47	2·40	62	0·214	0·157	1·38	1·36	1·72	1·74
2	148	97	2·15	2·10	63	0·235	0·343	1·55	2·54	2·54	7·31
3	129	103	2·18	2·29	71	0·178	0·131	2·70	1·71	2·60	3·17
4	88	101	0·92	1·88	57	—	—	—	—	—	—
Females											
5	65	62	1·42	1·88	71	0·115	0·120	3·45	4·13	5·65	5·06
6	98	91	1·65	2·06	67	0·118	0·101	4·18	2·40	6·12	3·60
7	80	69	0·42	0·54	50	0·097	0·093	2·02	1·94	3·32	4·07
8	107	121	4·40	1·70	93	0·103	0·099	1·98	2·69	3·72	3·63
9	89	88	2·96	1·53	95	0·363	0·149	2·08	1·29	3·73	4·74
10	109	109	2·68	2·11	88	—	—	—	—	—	—
11	72	112	1·71	1·61	79	0·114	0·120	2·06	1·69	5·33	6·26

MVV_F = maximal voluntary ventilation (free); MMF = maximal mid-expiratory flow; Ex. = exercise; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

TABLE III. VENTILATION, OXIMETRY, HEART AND RESPIRATORY RATES DURING REST AND EXERCISE

Case No.	Load kg.-m./min.	Duration (min.)	Rest vent. (litre/min.)		Ex. vent. (litre/min.)		Heart rate per min.		Resp. rate per min.		Art. O_2 sat. %	
			Meas.	Pred.	Meas.	Pred.*	Rest	Ex.	Rest	Ex.	Rest	Ex.
Males												
1	200	5	17·4	10·4	53·1	31·2	92	132	28	48	94	92
2	300	5	7·7	10·2	22·5	30·5	72	120	12	16	93	90
3	150	5	14·5	10·9	37·0	32·7	84	112	36	46	—	—
4	200	5	13·3	11·0	32·7	33·0	52	100	24	36	93	89
Females												
5	200	5	13·0	10·1	38·2	37·6	80	164	28	38	93	86
6	300	5	12·5	8·6	38·8	31·6	96	164	24	30	91	85
7	200	5	11·2	8·3	25·9	30·4	78	134	20	28	89	84
8	100	5	14·2	7·2	24·9	26·2	96	122	28	30	94	98
9	100	5	14·2	6·9	24·7	25·3	114	158	30	28	88	89
10	250	5	15·6	8·6	26·8	31·9	84	148	36	32	88	81
11	100	1	21·8	7·4	34·0	27·1	84	88	40	40	89	85

Vent. = ventilation; Ex. = exercise; Resp. = respiratory; Art. O_2 sat. % = percentage arterial oxygen saturation; *Predicted value for 300 kg.-m./min.

in 7 cases, and Raynaud's phenomenon in 8 cases. All the patients except case 7 had sclerodactyly, but she had involvement of the trunk and face. Dysphagia was present in 4 patients, but only 2 had an abnormal barium swallow.

Six patients gave a history of previous pulmonary infection. Persistent crepitations were present in 4 patients. Four patients had been in congestive cardiac failure. Of these 4, 2 had clinical pulmonary hypertension (cases 8 and 9) and 3 left ventricular enlargement (cases 5, 7 and 9). Case 1 had pulmonary hypertension without failure. Two of the 3 patients with left ventricular enlargement (cases 5 and 9) had systemic hypertension and both had renal involvement. The third patient with left ventricular enlargement (case 7) had had a previous myocardial infarction. Case 5 had evidence clinically of both disseminated lupus erythematosis and dermatomyositis: LE cells were present on 1 occasion and the skin and muscle biopsy showed the presence of both dermatomyositis and scleroderma. Six of the patients had calcinosis, for which they had received steroids and ethylene-diamine-tetra-acetic acid without significant improvement. Ten of the 11 patients had received steroids.[14] Three patients were, or had been, attending a peripheral vascular clinic for severe intermittent claudication.

Radiology

Radiological assessment revealed 5 patients with normal appearances of the lung parenchyma. In the group without parenchymal abnormalities 4 patients had prominence of the pulmonary artery segment and 3 of these had supportive clinical or electrocardiographic evidence of pulmonary hypertension. Six patients showed lung abnormalities, including classical sclerocystic honeycomb patterns, nodular changes, and broad-band basal infiltrations as well as mixed lesions.

The bases tended to show the most marked changes, as noted by other workers.[15] In case 3, a miner, radiographs were available from 1956, 1957, 1958 and 1964. There were no changes in 1956 but by April 1957 basal nodular opacities were apparent (Fig. 1). In 1958 the changes were well established and by 1964 there was granular honeycombing and the nodular changes were much more emphatic (Fig. 2).

Rib erosions[16] were not detected in any of the radiographs.

Pulmonary Function Studies

Details of the individual cases may be seen in Tables I - III. All 11 patients had some disturbance of lung function. The pattern of disturbance in the majority of cases was of combined restriction and obstruction, and no single case exhibited features of pure restriction, obstruction or ventilatory or diffusion defects.

TABLE IV. SYMPTOMS AND SIGNS IN PATIENTS WITH SCLERODERMA

			Symptoms						*Signs*									
Patient	*Duration of symptoms (yrs)*	*Cigarettes per day*	*Dyspnoea*	*Raynaud's phenomenon*	*Cough*	*Sputum*	*Previous pulmonary involvement*	*Dysphagia*	*Hands*	*Trunk*	*Face*	*Calcinosis*	*Crepitations*	*Blood pressure*	*Heart*	*Congestive cardiac failure*	*Renal involvement*	*Peripheral vascular disease*
1	7	15	+	+	+	−	Pneumoconiosis	−	+	+	+	+	−	130/80	Pulmonary hypertension	−	−	−
2	15	−	−	+	−	−	—	−	+	+	+	+	−	140/90	—	−	−	+
3	?	20	+	?	+	+	Pleural effusion	+	+	?	?	?	+	140/90	?	−	?	+
4	2½	35	−	+	−	−	Pleurisy	−	+	−	+	−	−	140/90	—	−	−	+
5	6	−	+	−	+	+	Bronchitis, pneumonia	+	+	+	+	+	+	180/105	Left ventricular hypertrophy	+	+	−
6	13	−	−	+	+	+	—	−	+	+	+	+	−	120/70	—	−	−	−
7	5	−	+	+	+	+	—	+	−	+	+	+	+	180/80	Left ventricular hypertrophy, mitral incompetence	+	−	+
8	5	10	+	+	−	−	Pneumonia	−	+	+	+	+	+	110/80	Pulmonary hypertension	+	−	−
9	1	−	+	+	−	−	—	+	+	+	+	+	−	186/124	Left ventricular hypertrophy, pulmonary hypertension, gallop rhythm	+	+	−
10	2	−	−	+	−	−	—	−	+	−	+	−	−	110/70	—	−	−	−
11	26	20	+	−	+	+	Pneumonia on 3 occasions	−	+	+	+	−	+	104/60	—	−	−	−

+ = presence — = absence ? = information not available

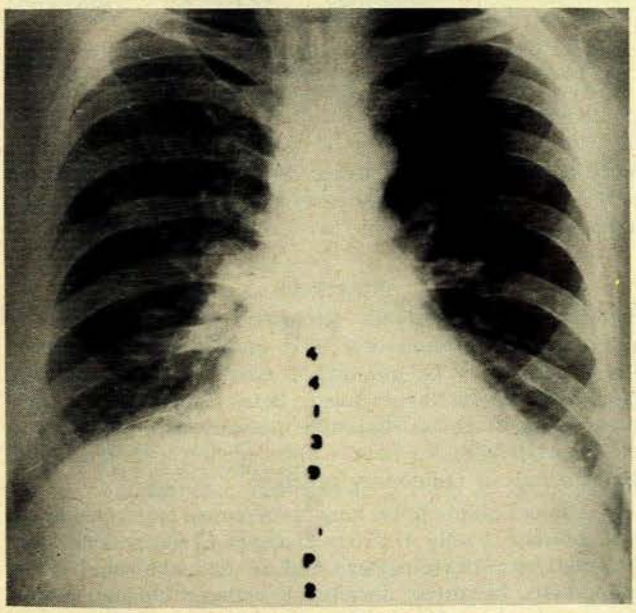

Fig. 1. Chest radiograph of case 3, a gold-miner, taken in 1957. Nodular opacities are present in the bases.

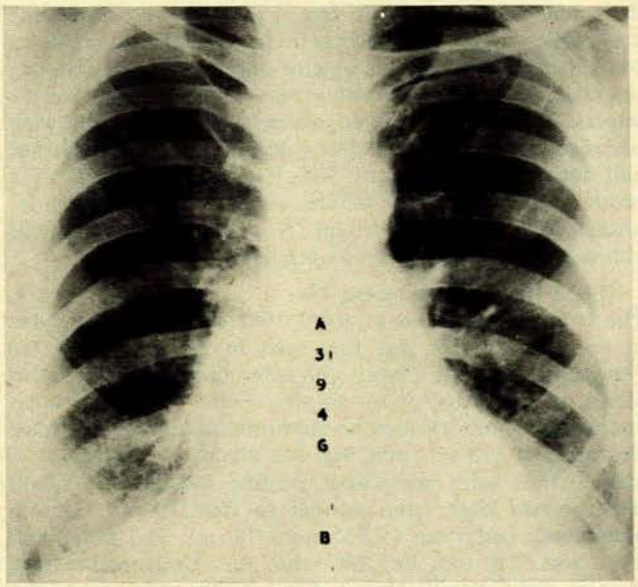

Fig. 2. Chest radiograph of case 3 taken in 1964. Nodular opacities in the bases are more extensive and are accompanied by granular honeycombing.

All patients had vital capacities below the predicted value. Total lung capacity was reduced in 5 patients, indicating the presence of restrictive lung disease. These same 5 cases had a raised lung clearance index, indicating uneven intrapulmonary distribution of the inspired gas.

The tests of ventilatory capacity, such as the maximum voluntary ventilation, maximal mid-expiratory flow-rate, and the forced expiratory volume in 1 second, were not very often or consistently disturbed. Only case 5 had evidence of airway obstruction in all the tests. Compliance was reduced in nearly all cases and the non-elastic resistance increased in approximately half the patients, so that the work of breathing was increased in most patients.

All except 1 patient had an increased minute volume at rest and during standardized exercise. Nine patients had a fall in arterial oxygen saturation during exercise. These features are consistent with the alveolar-capillary block syndrome, and suggest that diffusion defects contribute to the hypoxaemia. Uneven distribution of ventilation also would contribute to the hypoxaemia.

Case 2 hypoventilated at rest and during exercise, yet his arterial oxygen saturation was not significantly reduced. His oxygen consumption was 149 ml./min. (STPD). It seems possible, therefore, that this patient had hypothyroidism, but unfortunately no tests were done to confirm this.

Case 4 repeated the exercise test with measurements of rectal temperature. Ventilation at rest was 11·9 litre/min. and during a 200 kg.-m./min. exercise load, ventilation rose to 34·9 litre/min. The temperature at rest was 37·3°C and during the exercise it fell slightly to 36·9°. In the post-exercise period it varied between 36·8° and 37°C, but at no time did the temperature exceed the resting level.

Course

There were 6 deaths in the series, 4 females and 2 males. Three of the 4 female deaths were directly attributable to their scleroderma. Patient No. 7 died on the operating table following a local anaesthetic for a cervical sympathectomy, her condition at the time of operation being extremely grave. Operative intervention was due to gangrene of the fingers. Patient No. 8 died severely cachectic, following malabsorption, diarrhoea and vomiting, as well as cardiac and renal failure. Patient No. 9 died in uraemia as a result of chronic renal failure associated with gastro-intestinal haemorrhage. Patient No. 5 committed suicide although at the time she was relatively well.

The 2 male deaths were No. 3, a miner, and No. 4. The latter patient died in April 1967 of renal failure due to scleroderma. He was first seen in April 1966 at the Peripheral Vascular Clinic, with sclerodactyly and indolent ulcers on the pulps of his fingers. Renal function studies done at that time revealed no abnormalities and a creatinine clearance of 118 ml./min. He was admitted to hospital in March 1967 with congestive cardiac failure. His blood pressure had risen from normal to 160/110 mm.Hg and blood urea had risen to 535 mg./100 ml. The potassium level was 7·5 mg./100 ml. and the electrocardiogram showed right bundle-branch block with marked peaked symmetrical T waves indicative of hyperpotassaemia. In spite of peritoneal dialysis the patient died in renal failure. A needle biopsy of his kidney showed the typical onion-skin appearance of the arteries in scleroderma.

The postmortem examination of the lung revealed fibrous pleural adhesions and marked centrilobular emphysema without macroscopic evidence of interstitial fibrosis. There was evidence of acute bronchopneumonia in both upper and lower lobes (Fig. 3). Microscopically moderate interstitial fibrosis was detected. Postmortem examinations were performed on 3 other cases and revealed similar pulmonary pathology.

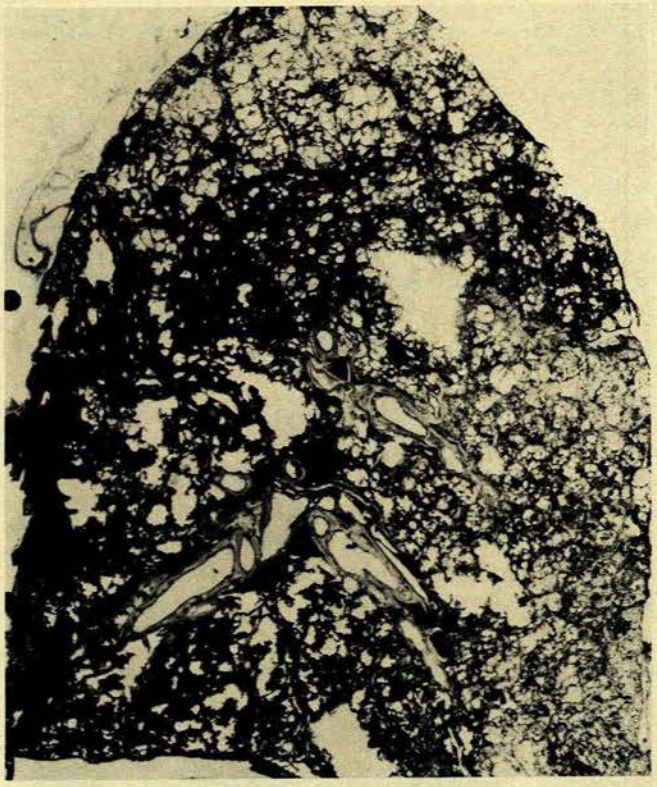

Fig. 3. Whole-lung section of case 4. Note centrilobular emphysema and foci of consolidation in posterior region of lower lobe and upper lobe. The pale triangular area in the upper lobe is an artefact.

DISCUSSION

The diagnosis of systemic sclerosis is not usually made unless there is unequivocal skin involvement. However, skin changes may be minimal in cases in which there is significant visceral involvement. Bates and Christie[17] suggest that the diagnosis should be considered in any patient who presents with Raynaud's phenomenon and detectable abnormalities of pulmonary function.

On clinical examination lung involvement was considered to be present in only 4 of our 11 cases. Seven patients had abnormal electrocardiograms and 10 had abnormal chest radiographs. No direct correlation between clinical, radiological, electrocardiographic and pulmonary functional assessments was detected. Only 4 electrocardiograms

showed probable evidence of right ventricular strain. Although 2 of our cases had complete right bundle-branch block, Escudero and McDevitt[18] did not find this among 60 cases of scleroderma.

Pulmonary function tests detected abnormalities in all 11 patients. There is no uniform pattern, probably because of the progressive nature of the disease and the fact that cases were studied in different stages of involvement with varying location and extent of the disease process.[19] A restrictive pattern dominates the functional disturbance and where obstruction is present its degree is usually much less marked than in cases of airway obstruction from other causes.[20] The alveolar capillary block syndrome, for which evidence was present in a number of our cases (although we did not make direct measurements of diffusing capacity), has also been well described.[21] The 1 patient who had hypoventilation may have had systemic involvement of the thyroid gland causing hypothyroidism, but unfortunately no definitive tests for this were carried out.

The presence of chronic cough and sputum in non-smokers suggests that these symptoms may well be due to bronchial involvement. The latter can also result in hyper-inflation distal to areas of peribronchial fibrosis. Three of our patients (cases 1, 4 and 10) were hyperinflated but none of them had significant airway obstruction. This may be explained by the possibility that the inflated areas were very peripheral in the lung, beyond peribronchiolar fibrosis. Peripheral bronchiolar narrowing would contribute little to an increased airway resistance.[22] Our series contained 3 non-smokers with chronic cough and pulmonary function tests indicating raised non-elastic resistance and uneven distribution of inspired air.

In case 4 an attempt was made to determine whether the hyperventilation was due to an inability of the body surface to lose heat because of the scleroderma. Rectal temperatures were measured at rest, during exercise and during recovery, but at no time did the rectal temperatures rise above the resting level. Unfortunately the experiment is not conclusive as it is possible that heat loss and temperature control were maintained by hyperventilation even if heat loss through the skin had been less than normal.

None of our cases had significant involvement of the skin of the thorax and we presume that lung function tests were not significantly altered by this factor.[23] Subclinical hypertensive left ventricular failure in cases 5 and 9 may have influenced the pulmonary function tests. The systemic hypertension present in these 2 patients may have been related to scleroderma lesions in the kidney confirmed at postmortem examination in case 9. Case 4 developed both systemic hypertension and scleroderma of the kidney a year after his initial tests. Cases 1 and 3 were gold-miners and both had been exposed to a dusty atmosphere for over 20 years and were cigarette-smokers. The lung function tests revealed a combined pattern of restriction and obstruction. Erasmus found a higher incidence of scleroderma among Witwatersrand gold-miners than in the general population.[10] An increased incidence of this disease in miners has been confirmed.[24]

A recent review of 98 unselected patients with scleroderma revealed that pulmonary disease tended to be associated with skin involvement of the head and neck, with oesophageal abnormality and with Raynaud's phenomenon, but not with the duration of the disease.[25]

SUMMARY

Pulmonary function in 7 females and 4 males with scleroderma is reported and correlated with clinical, radiological, electrocardiographic and pathological findings.

Duration of symptoms, the commonest being dyspnoea and Raynaud's phenomenon, varied from 1 to 26 years. The electrocardiogram and chest radiograph were abnormal in most cases. Some disturbance of pulmonary function was detected in every case, a pattern of combined restriction and obstruction being common. Hyperventilation at rest and during standardized exercise accompanied by a fall in arterial oxygen saturation (the alveolar-capillary block syndrome) was very frequent. There was no uniform pattern, probably because the disease is progressive and cases were studied in different stages of involvement.

Six patients died during the period of observation and the modes of death are described.

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