SPECIAL ARTICLE

THE NATURAL HISTORY OF PROGRESSIVE SYSTEMIC SCLEROSIS (DIFFUSE SCLERODERMA)*

Progressive systemic sclerosis (diffuse scleroderma) is now recognized to be a widespread disturbance of connective tissue, which in addition to characteristic involement of the skin (scleroderma), is marked by changes in the synovium and a number of internal organs, particularly the heart, lung, gastrointestinal tract, and kidney (1-11). The present report is devoted to a description of the clinical course of this disease and is based on a study of 100 patients who have been observed by the author over the past 9 years. This group includes all patients with progressive systemic sclerosis who have been referred to the University of Pittsburgh Medical Center since 1955 and a small number first seen at the National Institute of Arthritis and Metabolic Diseases in 1953-55.

COMPOSITION OF SERIES

The numbar of women (62) was greater than that of the men (38), as in the general experience; 87 of the patients were white and 13 Negro. In a majority of cases the initial symptoms appeared between the ages of 30-50 years. There were 11 patients who were well until after age 60, howevr, and 6 whose illness began before the age of 20.

OCCUPATIONAL HISTORY

The principal occupations of the 37 adult men in this series are indicated in table 1. Of interest is the observation that 17 patients had worked as coalminers or in other jobs marked by heavy exposure to coal and/or silica dust. Although It is difficult to be certain of the significance of this observation because of the character of the industrial activity in the area from which these patients are drawn, it may be noted that Erasmus has described the occurrence of a peculiarly fulminant type of diffuse scleroderma amongst gold-miners in South Africa (12). This observation is thus deemed worthy of further study.

INITIAL SYMPTOMS

The presenting symptoms of 95 patients are indicated in table 2. Sixty-one were first troubled by either digital Raynaud's phenomenon or painless swelling or thickening of the skin of the hands and fingers. While it is not unusual to find Raynaud's phenomenon reported as preceding the development of cutaneous changes by periods of as long as several years, it is often difficult to be certain of this temporal relationship because of the subtlety of the early skin changes and the remarkable inability (or reluctance) of patients to recognize the existence of even

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marked scleroderma. In 29 cases the initial symptoms consisted of articular complaints, which were often migratory in nature. A number of patients described the occurrence of swelling, redness and warmth of joints, usually the fingers and knees, and, as might be expected, were considered at first to have rheumatoid arthritis and received a variety of medications for this condition.

TABLE 1.

Occupational activities of 37 men with progressive systemic sclerosis.

*Coal miner	10
Machinist	4
Steel worker	3
*Foundry worker	2
*Enamel worker	1
*Sand blaster	1
*Potter	1
*Brick yard worker	1
*Glass worker	1
Miscellaneous	13

*Exposure to coal and/or silica dust.

There were 5 patients whose initial symptoms implicated neither the skin nor the joints. Two of these were first troubled by exertional dyspnea, two by dysphagia, and one by vomiting, abdominal pain, and diarrhea resulting from severe intestinal involvement.

SYSTEMIC INVOLVEMENT

Symptoms may long remain confined to abnormalities in the skin and joint and there are often changes in these complaints and in the physical findings (see below) sufficiently marked to be considered indicative of periods of spontaneous remission and exacerbation. In most cases, however, there is a gradual worsening in the disease of the skin and steadily progressive involvement of the gastrointestinal tract, lung, and heart (table 2). There are only 9 patients who have not shown some evidence of visceral dysfunction; 3 of these are children and only one of the group has had definite scleroderma for more than 3 years.

a. *Skin*: 95 of the patients developed diffuse scleroderma, affecting first (in all but one instance) the skin of the fingers and distal portions of the upper extremities, and spreading in most and in varying degree to the forearms, arms, face, neck, upper anterior chest, abdomen and back. In the early stages of the disease

TABLE 2.

Clinical findings in 100 patients with progressive systemic sclerosis.

Initial Complaints

a. Raynaud's phenomenon	35
b. Skin	26
c. Joints	29
d. Other	5

Systemic Involvement	
a. Skin (scleroderma)	95
Raynaud's phenomenon	83
b. Joints	61
Leathery crepitus,, ...	9
c. Heart	22
Abnormal EKG	48/73
d. Lungs	29
Abnormal chest x-ray	32
e. Esophagus	54
Apnormal esophagram	51/70
f. Intestine	10
Abnormal x-ray study	8
g. Kidney	21

the fingers tend to be tightly swollen, and have been aptly compared to sausages in their appearance. The sparing of the lower extremities in many patients with severe involvement of the arms is notable Many patients develop flexion contractures of the fingers and are troubled by recurrent ulcerations and infections of the fingertips which prove extremely refractory to treatment. As a result of such recurrent infections, and on occasion in the absence of any such complication, there tends to be a progressive loss in the soft tissue and bony substance of the fingertips which may result in eventual dissolution of one or more terminal phalanges. Roentgenograms of the hands have frequently disclosed subcutaneous calcinosis and several patients have noted the drainage of calcific matter from the finger-tips and from areas of intra-cutaneous nodulation on the elbows and knees. Thickening of the skin of the face leads to difficulty with ingestion and with dental work. We have seen a number of women who have had this latter problem for years before the recognition of changes in the skin of their fingeas.

Of special interest are the 4 patients in this series who failed to show any sign of scleroderma despite the development of severe, indeed fatal visceral sclerosis, and a fifth who had only two small patches of morphea (13).

b. *Joints:* 61 of the patients developed evidence of joint disease, marked most frequently by polyarthralgia, swelling, and stiffness of the fingers, wrists, and knees, as well as other peripheral joints, and less commonly by signs of frank arthritis, including swelling, redness, warmth, and synovial effusion. There were 2 patients who described noises coming from their knees and a total of 9 who were found to have a peculiar leathery type of crepitus on passive flexion of their knees or wrists. Roentgenographic changes in the larger joints were limited for the most part to narrowing of the cartilage space and juxta-articular osteoporosis.

TABLE 3.

Serum protein concentrations of 63 patients with progressive systemic sclerosis (PSS).

	Total protein	*Albumin*	*Globulin*			
			alpha-1	*alpha-2*	*beta*	*gamma*
PSS (63)	7.23*	3.9	0.29	0.66	0.82	1.54
Normal adults (50)	7.13	4.7	0.27	0.52	0.66	0.96

* Average values in gram %.

c. *Heart:* There were 22 patients who developed evidence of heart disease, manifested by cardiomegaly, various arrhythmias, and symptoms of myocardial insufficiency. Thirty-four of the 62 adults in whom the intensity of the heart sounds was carefully assessed were noted to have accentuation of the pulmonic second sound, and in a few cases cardiac catheterization of such patients, none of whom were in failure, revealed the existence of pulmonary hypertension. Abnormalities were present in the electrocardiograms of 48 out of 73 cases. These consisted, most commonly, of such findings as low voltage, incomplete or complete bundle branch block, numerous premature ventricular contractions, atrial fibrilla tion, and ST-T wave changes. Those patients who developed cardiac failure responded poorly to digitalis, tending to become intoxicated with its continued administration. Several died after a protracted period of circulatory shock while others expired rather suddenly, presumably as a result of cardiac arrhythmia.

d. *Lung:* There are 29 patients who (have) had exertional dyspnea and/or a chronic non-productive cough (and rarely pleurisy), which are believed to be the result of pulmonary involvement. Physical examination has occasionally revealed tachypnea and basilar rales but more often has proven unremarkable. In most, but not all of these patients, roentgenographic examination of the chest has revealed a pattern of interlacing linear densities which are most pronounced in the lower two-thirds of the lung fields, and which in some cases has assumed the appearance of diffuse mottling or honeycombing, indicative of cystic lesions. Measurements of pulmonary function have been made on 20 patients, only 4 of whom had exertional dyspnea and 8 of whom had chest films which were considered compatible with pulmonary fibrosis (14). These, and the recent studies of others have revealed that the earliest and dominant disturbance lies in gas exchange, i.e. diffusion. Low diffusing capacities have been noted in the absence of any significant alteration in ventilation and in the absence of any roentgenographic evidence of fibrosis. The electron microscopic examination of lung of a single patient with such a disturbance in pulmonary gas exchange has disclosed marked widening of the basement membranes both of alveoli and smaller blood vessels. In addition to the disturbance in diffusion there has been evidence in some cases of restrictive ventilatory disease marked by reduction in vital capacity and total lung capacity (which may be ascribed,

to impairment of chest motion and diffuse peribronchial fibrosis) and of obstructive disease, manifested by a reduction in maximum breathing capacity and increased residual volume. Despite these disturbances, however impairment in pulmonary function is rarealy sufficiently severe to dominate tne clinical picture, except in the case of complicating infection, which unfortunately is not uncommon.

e. *Esophaqus:* Dysphagia has proven to be the most frequent manifestation of visceral involvement in this group (54 patients). There are a unmber of cases in which a disturbance in swallowing has been the dominant feature in the patient's illness, and at least 3 instances in which this symptom has occurred in the absence of any cutaneous disease (13). Early in the course of this complaint the patient may note only unusual fullness in the lower chest upon completion of a meal. Later there is difficulty in the passage of solids such as bread or meat, pieces of which may become impacted in the esophagus and require instrumental removal.

Roentgenologic examination of the upper gastrointestinal tract has revealed abnormalities in 51 of 70 patients. consisting chiefiy of a diminution to total lack of peristaitic activity of the esophagus and dilatation (less commonly narrowing) of the lower one-third or two-thirds of the organ. A number of patients have been found to have hiatal hernias as well. It is important to note that a disturbance in motility may long precede any change in the size or contour of the esophagus and that *Fluoroscopic* study is of particular value in its detection.

f. *Intestine:* 10 patients have been troubled by serious intestinal disease, marked by symptoms such as abdominal bloating, vomiting, and chronic con-

TABLE 4.

Duration of illness and cause of death in 42 patients with progressive systemic sclerosis.

Duration of Illness	
Less than 1 year	4
1-3 years	19
3-10 years	13
More than 10 years	6
Cause of Death	
Renal involvement	21 (14)
Cardiac failure	9 (7)
Intestjnal disease	2 (2)
Other	5 (4)
(esophageal perforation and mediastinitis, aspiration pneumonia, myocardial infarction, miliary tuberculosis, pulmonary infarction).	
Unknown (patients died out of hospital) ...	5
Total	42 (27)

( ) Number of cases having postmortem examination.

stipation interrupted by episodic diarrhea. Half of these cases have become marked by malnourished as a result of a disturbance in intestinal absorption; it may be of some significance that in all these latter patients. cutaneous involvement has been either nondiscernible or when present has been minimal in degree–a discrepancy recorded in a number of other reports (13). Roentgenologic study, abnormal in 8 of the 10 patients with abdominal symptoms, has shown marked delay in transit of the barium meal and irregular dilatation and hypersegmentation of loops of small (and large) intestine.

Single patients each have developed symptoms limited to the large intestine (increasing constipation), the rectum (prolapse), and the anus (incontinence).

g. *Kidney:* 21 patients in this series have developed a form of malignant cardio–vascular renal disease indicated by the sudden occurrence of severe hypertension with grade 3–4 retinopathy, cardiac failure, convulsions, and rapidly progressive renal insufficiency (7). All have died within a period of several days to weeks, despite the use of adrenocortical steroids and a variety of anti-hypertensive medicines, and have been found to have characteristic changes in the kidneys (see below). While it is not clear whether the administration of ACTH and/or adrenocortical steroids in some cases may have been associated with the induction (or aggravation) of these renal lesions, there were several instances in which this dread disturbance occurred in petients who had received n one of these medications.

h. *Miscellaneous:* There were 2 patients with Sjögren's syndrome, one of whom also had Hashimoto's thyroiditis. Another patient was found to have a neuropathy involving a radial and anterior tibial nerve, of a type believed to represent a specific feature of progressive systemic sclerosis (15). Another patient had an explained hemolytic anemia of severe degree.

SERUM PROTEINS AND SEROLOGICAL REACTIONS

Fully half of the patients tested were found to have hypergammaglobulinemia (table 3). In most cases the increase was only moderate in degree (1.4–2.0 gram %); values greater than 3.0 gram % were noted in 4 patients (2 white, 2 Negro). There have been no instances of hypogammaglobulinemia in this group. Immunoelectrophoresis of the sera of 15 patients disclosed a variety of abnormalities including increases in alpha-1 globulin and alpha-2 macroglobulin and in approximately half the cases increases in beta-2 macroglobulin and a peculiar increase and splitting in the gamma globulin arc (16).

Positive latex agglutination reacitions have been found in 15 of 68 patients (22%). In 10 cases the titer was 1:160 or less. Two patients (one with Sjögren's syndrome) had titers of 1:2560. Three out of 59 patients whose sera were checked for the L.E. cell reaction were found to be positive; none of these individuals has presented any clinical findings particularly indicative of lupus erythematosus, however. Nineteen of 27 sera examined by an immunofluorescent technique revealed patchy staining of nuclear membrane and chromatin, unlike that seen in

systemic lupus erythematosus, and 3 contained factor (s) with a specific affinity for nucleoli; 5 sera were negative for either reaction (17).

Creatine excretion: Urinary creatine was measured in 24 patients on an unrestricted diet. Of this number, only 6 (one a child) excreted more than 100 mgm/24 hours, the highest value being 270 mgm/24 hours.

COURSE OF DISEASE

As of Decemer 1962, 57 of the patients in this series were alive (average duration of illness = 8.5 years) and 42 had died. The duration of illness and the cause of death in these patients is indicated in table 4. It will be noted that half died of malignant hypertension and renal insufficiency (3 after an illness of less than a year)*, and about a fourth of cardiac disease. Two men succumbed because of severe malnutrition resulting from intestinal disease. A woman who died as a result of mediastinitis following perforation of the esophagus and another who died of unsuspected miliary tuberculosis had been receiving massive amounts of adrenocortical steroids. None of the patients examined *post mortem* were found to have alveolar cell carcinoma or any other type of malignant neoplasm.

When the fate of two races represented in this series is compared, it appears that the prognosis is poorer for the Negro patient than for the white. Nine of the 13 Negroes have died (usually after 3 years or less of illness), 3 are living and 1 is missing from follow-up.

PATHOLOGICAL FINDINGS

Postmortem examinations were done in 27 cases. The frequency of involvement of various organs is shown in table 5. As might be expected, in many cases visceral changes were encountered which had produced no symptoms. There were 4 cases wherein extensive visceral sclerosis was present with minimal or no cutaneous changes (13).

a. *Skin:* Examination of biopsies obtained from areas of skin with more advanced clinical changes disclosed such classical histopathologic findings as atrophy of rete pegs of the epidermis, homogenization of dermal collagen exhibiting a parallel arrangement to the epidermis, atrophy of dermal appendages, and hyalinization of arterioles (18). In the cases considered clinically to have "early" scleroderma, however, the only distinctive feature has been the minimal homogenization of collagen. Since identification of this alteration rests upon subjective interpretation of a degree of change from the normal, and may be observed in other disorders, positive diagnosis of scleroderma at this stage by means of skin biopsy has proven to be difficult and unreliable.

b. *Joints:* Samples of synovium were obtained by biopsy and/or at postmortem examination from 29 patients. The specimens taken from patients with

* It should be noted that 6 of these patients were seen in consultation at other hospitals because of a special interest in this problem (7). Hence the frequency of renal involvement is somewhat higher than that which would occur in a completely unselected series of (hospital) patients.

clinical evidence of acute joint inflammation generally revealed a synovitis marked by the infiltration of lymphocytes and plasma cells, present as focal aggregates or scattered diffusely throughout the tissue. Later in the course of the disease, sections showed intense fibrosis of the synovium, atrophy of lining cells, and sclerosis of blood vessels, the appearance of the synovium resembling that of scleroderma-tous skin.

c. *Heart:* Small irregular patches of interstitial myocardial fibrosis, prominent in, but not limited to, peri-vascular areas were found in a majority of cases. In those patients with more serious heart disease, there was extensive replacement of myocardial fibers. Infiltrations of inflammatory cells and thickening of smaller coronary vessels were commonly present.

d. *Lung:* The principal lesion in most cases was thickening of alveolar septa and mural and perivascular fibrosis of arterioles and smaller arteries. In some instances there was coalescence and cystic dilation of alveolar spaces. Also noted were pleural and interstitial fibrosis.

e. *Gastrointestinal tract:* The mucosa of the esophagus was thinned and often found to be ulcerated in the lower portion of the organ. The lamina propria and submucosa tended to be thickened by dense collagen throughout all portions of the gastrointestinal tract and there were many cases in which the inner and outer layers of the muscularis were almost totally replaced by scar tissue. Small arteries and arterioles were frequently surrounded by periadventitial deposits of collagen. Cellular infiltrates were present in the submucosa, often surrounding blood vessels.

TABLE 5.

Pathologic findings in autopsies of 27 patients with progressive systemic sclerosis.

Organ Involvement	
Skin	23
Heart	21
Lung	20
Esophagus	20
Kidney	19
Small intestine	11
Large intestine	11
Synovium	10
Urinary bladder	4

f. *Kidney:* The organs of patients dying of renal insufficiency generally were larger than normal and usually contained a number of small infarcts. The lesions found on microscopic examination in these cases were predominantly focal in distribution, and included such changes as localized or diffuse thickening of glomerular basement membranes (with occasional instances of wire-loop changes indistinguishable from those seen in lupus erythematosus), fibrinoid necrosis of the walls of afferent arterioles and glomerular tufts, and hyperplasia of interlobular arteries, the intimas of which contained large deposits of acellular material rich in acid

mucopolysaccharides (19). The appearance of the kidney in these cases is indistinguishable from that encountered in "ordinary" malignant nephrosclerosis, and it is of interest that in both conditions immunohistochemical analysis of fibrinoid vascular lesions has shown a preferential concentration of fibrinogen and not of gamma globulin (20).

CONCLUSION

In seems clear that nearly all patients with scleroderma, if followed for a long enough period of time, will develop evidence of visceral sclerosis. The determination of prognosis with respect both to disability and death has proven to be most difficult. In general, the outlook is poor in those cases marked by rapid progression of dermal disease, severe malabsorption, or cardiac failure, and is seemingly uniformly fatal, at this time, in those patients who devlop renal involvement. In many cases, however, disability incident to systemic involvement may be only moderate in degree and not necessarily threatening to long life.—Gerald P. Rodnan, M. D. Pittsburgh, Pa.

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