Survival in scleroderma

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Scleroderma is one of the commoner connective tissue diseases, with a wide range of clinical expression and considerable variation in prognosis. As such its initial diagnosis comes within the ambit of many specialties: the dermatologist because of morphoea, sclerodactylly, or telangiectasia; the vascular surgeon because of Raynaud’s phenomenon; the rheumatologist because of a synovitis; the gastroenterologist because of dysphagia or malabsorption; and the cardiologist because of dyspnoea. This propensity for visceral involvement is now well recognized; since the original description by Ehrmann (1903) of oesophageal involvement, most of the major organs have been recorded as affected in varying degrees by a sclerosis of their supporting tissues.

This has led to the adoption of the more rational name of 'systemic sclerosis'. In a disease with such a wide variation in manifestations and involvement of viscera, it is not surprising that estimations of its prognosis have varied considerably and have often been hindered by the semantics of classification. Attempts have been made to differentiate between a form of the disease characterized by predominant sclerodactylly and Raynaud’s phenomenon (acrosclerosis) and a generalized form (O'Leary and Waisman, 1943; Truelove and Whyte, 1951), the former being said to have a good prognosis and the latter a poor prognosis. However, it has become apparent that many patients initially presenting with acrosclerosis already have systemic involvement and that most of those who do not will subsequently develop visceral changes. At the opposite extremes of the disease spectrum there is a general agreement about the outcome. There are those patients with localized patches of thickened indurated skin (morphoea) who have an excellent prognosis and those with the rare form, characterized by a rapidly progressing cutaneous sclerosis with multisystemic involvement, who have a uniformly poor prognosis (Tuffanelli and Winkelmann, 1961). However, the majority of patients seen in clinical practice fall into a large 'middle-group' where a universally acceptable classification is lacking and the natural course of the disease is varied and uncertain. The clinician, on diagnosing scleroderma, has little data on its course and the factors influencing it to which he can refer for guidance. The lack of such information is partly the result of the problems inherent in the follow up of any chronic disease. These can be largely overcome by analysing the data by 'Life Table' methods. Using this approach, we have attempted to provide an estimate of the prognosis in scleroderma and also to evaluate those factors influencing survival when the patients are first seen.

Material and methods

Between 1947 and 1970, 67 patients have been seen at Hammersmith Hospital with a diagnosis of systemic sclerosis. The criteria for inclusion in this survey has been either typical skin changes, or Raynaud’s phenomenon with a characteristic oesophageal abnormality, as seen radiologically in patients with a normal skin. Only two patients came into this latter category: one of these has now been followed up for 13 years and is just beginning to develop cutaneous sclerosis around the mouth; the other patient has been followed up for 18 months. Those with morphoea were specifically excluded.

Of the 67 patients in the survey, 26 are known to be dead, 31 have been followed up to the present time, and ten could not be traced (Fig. 1 overleaf).

The following data were extracted from their medical records: date of definitive diagnosis; date last observed; whether alive or dead; features at time of initial diagnosis (usually during the first hospital admission): blood urea, electrocardiogram, oesophageal involvement, radiological pulmonary involvement, calcinosis, telangiectasia, and erythrocyte sedimentation rate (Westergren); duration of Raynaud’s phenomenon before diagnosis; presence or absence of sclerodermatous trunk involvement (not including the neck).

The prognosis has been expressed in terms of the percentage survival from the time of initial diagnosis. These survivorship figures have been calculated by the method of Life Table analysis (Merrell and Shulman, 1955). The standard error of survivorship was calculated as described by Greenwood (1926). The features at the time of initial diagnosis which
might influence prognosis were studied by comparing their incidence in two groups: those dying in 6 years from diagnosis and those surviving more than 6 years.* The significance of the frequency distribution of these features was assessed by conventional statistical methods. Certain features, namely hypertension, uraemia, heart disease, and radiological lung disease, are usually considered to be associated with an increased morbidity irrespective of the primary disease. In these features the level of significance was expressed from a 'one-tailed' distribution. In all other cases the level of significance was based on a 'two-tailed' distribution.

Results

The mean age at diagnosis of our patients was 46.2 years (S.D. 15.6). There were 56 females and 11 males. Evidence of visceral involvement was found in 86 per cent. of patients at the time of initial diagnosis and its distribution by our criteria (which in some cases will tend to underestimate its incidence) is seen in Table I. Raynaud's phenomenon was a presenting symptom in 70 per cent. of patients; its

mean duration before a definitive diagnosis of scleroderma was made being 5.3 years (S.D. 7.5).

Prognosis

On the basis of the Life Table analysis, the overall prognosis (Fig. 2) in this series is a 73 per cent. 5-year survival (S.E. 7.5) and a 50 per cent. 10-year survival (S.E. 8.5). Beyond the 10-year point the conventional statistical limits of ±2 Standard Errors (S.E.) are seen to diverge markedly—a result of the diminishing numbers in our survey beyond this point.

When our patients are divided into two age groups (Fig. 3), those under 40 years at diagnosis and those 40 years and over, it is seen that there is a marked and significant difference in survival. Those over 40 years have a 50 per cent. 5-year survival (S.D. 10) and a 30 per cent. 10-year survival (S.E. 10), whilst

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* The explanation for a 6-year period is given under 'Results'.

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**Table I Organ involvement at diagnosis in 67 patients**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>35</td>
</tr>
<tr>
<td>Small bowel</td>
<td>10</td>
</tr>
<tr>
<td>Heart (abnormal ECG)</td>
<td>28</td>
</tr>
<tr>
<td>Kidney (abnormal blood urea)</td>
<td>9</td>
</tr>
<tr>
<td>Lung (abnormal chest x ray)</td>
<td>17</td>
</tr>
<tr>
<td>Subcutaneous calcinosis</td>
<td>11</td>
</tr>
<tr>
<td>Trunk involvement</td>
<td>22</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>26</td>
</tr>
</tbody>
</table>
those under 40 years have a 95 per cent. 5-year survival (S.E. 7) and a 70 per cent. 10-year survival (S.E. 16).

On examination of the survival curves in these two age groups, it is seen that they have a similar slope except for the initial 6 years, when in the over 40 age group there is a sharp fall in survival. Indeed, of all the recorded deaths, 73 per cent. died in the first 6-year period from diagnosis (Fig. 4). Thus it appears that there is a group of patients in the over 40 age group who rapidly succumb to the disease.

FACTORS AFFECTING SURVIVAL (Figs 6 and 7)

Those features at initial diagnosis which may contribute towards a group with a poor prognosis in the Pulmonary involvement $P < 0.05$

ESR $> 25 \text{mm./hr}$ $P > 0.2$

Oesophageal involvement $P > 0.7$

Telangiectasis $P > 0.2$

Raynaud’s < 1 yr $P > 0.2$

B.P. $> 150$ mm.Hg $P > 0.25$

Sex incidence in those dying within 6 yrs $P > 0.2$

FIG. 4 Distribution of deaths.

This finding is most easily explained by postulating that this group contained those patients in the more elderly range and they would thus have been expected to have a considerably reduced life expectancy. This, however, does not fully explain the age distribution in the two groups (Fig. 5): the mean age at diagnosis of those dying in 6 years from diagnosis being 55 years (S.D. 12.2) and of those surviving more than 6 years being 42 years (S.D. 14.7). This distribution suggests other features, in addition to the age related factor as contributing to a poorer prognosis in those aged 40 or over.

FIG. 6 Factors affecting prognosis.

FIG. 7 Factors not apparently affecting prognosis.
over 40 age group, have been evaluated by comparing their incidence in those patients dying in 6 years from diagnosis with those surviving more than 6 years (Figs 6 and 7). A 6-year point was found more suitable than a 5-year point in this particular study, as 73 per cent. of those dying did so in 6 years as against 50 per cent. in 5 years. It is seen that a blood urea over 40 mg./100 ml. and trunk involvement both have an adverse effect on survival ($P < 0.005$). An abnormal electrocardiogram is common in both groups but significantly so in those dying in 6 years ($P < 0.05$). Lung involvement is not so common but is seen to be of significance ($P < 0.05$). Factors not indicative of a poor prognosis are an erythrocyte sedimentation rate of over 25 mm./1st hr, oesophageal involvement, telangiectasia, Raynaud’s phenomenon of less than 1 year, blood pressure over 150/90 mm. Hg, and the patient’s sex. However, this is not to say that these factors will not play some part in influencing the survival after the initial

Table II Causes of death and post mortem findings

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cause of death</th>
<th>Heart</th>
<th>Lung</th>
<th>Gut</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>130128</td>
<td>Intestinal obstruction</td>
<td>LVH and RVH</td>
<td>Left bronchopneumonia</td>
<td>Faecal impaction and oesophageal involvement</td>
<td>Cancer stomach</td>
</tr>
<tr>
<td>121411</td>
<td>Myocardial infarction</td>
<td>Pericarditis</td>
<td></td>
<td></td>
<td>Generalized scleroderma</td>
</tr>
<tr>
<td>49716</td>
<td>Bilateral lobar pneumonia</td>
<td>Pericardial effusions</td>
<td>Basal lobar pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105166</td>
<td>Pulmonary oedema</td>
<td>Myocardial sclerosis</td>
<td>Bronchitis and pulmonary oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41289</td>
<td>Congestive cardiac failure. (No post mortem)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>339257</td>
<td>Cancer lung</td>
<td></td>
<td>Cancer lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>132643</td>
<td>Pulmonary oedema</td>
<td>Myocardial sclerosis</td>
<td>Pulmonary oedema</td>
<td>Oesophagus, stomach, small and large bowel</td>
<td>Small thyroid</td>
</tr>
<tr>
<td>142779</td>
<td>Congestive cardiac failure. (No post mortem)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>186134</td>
<td>Pulmonary oedema</td>
<td>Rheumatic heart disease—mitral and tricuspid valves</td>
<td>Pulmonary oedema</td>
<td>Benign gastric ulcer</td>
<td></td>
</tr>
<tr>
<td>182737</td>
<td>Peritonitis</td>
<td>Myocardial and endocardial fibrosis</td>
<td></td>
<td>Ulceration of caecum and duodenal dilatation</td>
<td></td>
</tr>
<tr>
<td>246648</td>
<td>Anaemia</td>
<td>Pericardial effusion and LVH</td>
<td>Oedema</td>
<td></td>
<td>Kidneys enlarged with superficial punctate haemorrhages</td>
</tr>
<tr>
<td>243958</td>
<td>Congestive cardiac failure. (No post mortem)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>291877</td>
<td>Aspiration pneumonia</td>
<td>Pericardial effusion</td>
<td>Fibrosis right lower lobe</td>
<td>Duodenal dilatation</td>
<td></td>
</tr>
<tr>
<td>161898</td>
<td>Peritonitis</td>
<td></td>
<td>Chronic bronchitis</td>
<td>Cancer stomach with perforations</td>
<td></td>
</tr>
</tbody>
</table>
6-year period from diagnosis. In fact, some of them may be of importance in determining the relatively similar slopes of the survival curves after the first 6 years.

CAUSES OF DEATH
The causes of death (Table II) are known in fourteen of the patients who died, and of these eleven had autopsies.* In seven patients the cause of death was directly attributable to cardiac causes and in nine of the eleven patients coming to autopsy the heart was abnormal. In four of these there was evidence of pericarditis, a feature seldom diagnosed during life in patients with scleroderma. Two patients had cancer of the stomach and one carcinoma of the bronchus. The high incidence of electrocardiogram abnormalities is analysed (Table III) and it is seen that the changes are mainly of a non-specific nature.

Table III  Electrocardiogram abnormalities

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>4</td>
</tr>
<tr>
<td>Flat T waves</td>
<td>12</td>
</tr>
<tr>
<td>ST depression</td>
<td>5</td>
</tr>
<tr>
<td>Low voltage</td>
<td>5</td>
</tr>
<tr>
<td>RBBB</td>
<td>3</td>
</tr>
<tr>
<td>LBBB</td>
<td>1</td>
</tr>
<tr>
<td>LVH</td>
<td>5</td>
</tr>
<tr>
<td>RVH</td>
<td>4</td>
</tr>
</tbody>
</table>

EFFECT OF TREATMENT
The only drugs used often and long enough to assess their effect on survival were the corticosteroids. During the course of the 23 years covered by this survey, eighteen patients were given corticosteroids for varying lengths of time; all took them for at least 1 year and our longest survivor for 23 years. They had no apparent effect on survival, either favourable or unfavourable. Other forms of clinically ineffective treatment used in a few patients included, epsilon-aminocaproic acid, relaxin, potassium para-aminobenzoate, penicillamine, and sympathectomy.

Discussion
Scleroderma is a chronic disease in which progression will be variable in different patients and also in the course of the individual patient. Thus the prognosis will be related to the hazards of ageing, the presence of other diseases, host resistance, environmental changes, and in some cases the efficacy and side-effects of treatment. With so many variables, any estimate of prognosis must be viewed critically, especially as regards selection of patients. Some patients will have had their disease for varying lengths of time before consulting a doctor, others may not have considered themselves ill enough to need medical help, and some will have died of other causes. However, similar selective processes operate in all hospital populations and although our estimates of prognosis will tend to err on the side of a reduced survival, they are of value in the context of patients in one's own clinic, in comparing results from different clinics, and as a possible guide for large-scale prospective studies.

The usually estimated 5-year survival rate, obtained by dividing the number of patients known to be alive at 5 years by the number originally diagnosed, inevitably tends to underestimate the survival as it does not take into account those patients lost to follow-up in the 5-year period, those who have died, and those still alive but not having completed a 5-year follow-up. The analysis of survival data by 'Life Table' methods makes appropriate adjustments for these possible sources of error.

Our survival figures for scleroderma are the first to be based on Life Table methods. The majority of studies point to a poor prognosis in most patients while conceding that some individuals can survive for many years (Farmer, Gifford, and Hines, 1960; Orabona and Alban, 1958; Masi and D'Angelo, 1967). However, our overall survival figures agree closely with those of Tuffanelli and Winkelmann (1961), but their paper did not analyse the marked effect of age on survival demonstrated by our findings.

The features found at initial diagnosis which suggest an adverse prognosis (Fig. 6) are those representing involvement of important viscera, with the exception of trunk involvement. This latter association with poor prognosis is probably due to an association with more extensive and rapid visceral involvement. Farmer and others (1961) found that cardiac involvement, renal involvement, oesophageal involvement, and an erythrocyte sedimentation rate over 50 mm./1st hr were associated with poorer prognosis, but that pulmonary involvement was of little prognostic significance. As in our study, they found that sex, the duration of Raynaud's phenomenon, calcinosis, and telangiectasia were of no prognostic import. However, they made no allowance for variations in the course of the disease in that they compared features in two groups: those living and those dead. This probably accounts for differences between our two studies.

The absence of any significant relationship between a raised blood pressure (> 150/90 mm. Hg) and a poor prognosis is rather surprising. Of the patients with a much higher BP at diagnosis, one (200/120 mm. Hg) died within one year but another (210/120 mm. Hg) died after 13 years and 3 more (175/105, 180/100, and 210/100 mm. Hg) are still living at 16, 2, and 4 years respectively after diagnosis.

* Several patients (all Caucasians) came from overseas and later died without an autopsy being performed.
Repeated minor episodes of inhalation pneumonia due to oesophageal involvement can lead to lung involvement. Thirteen of our seventeen patients with radiological lung involvement also had oesophageal changes, suggesting an association. But, on the other hand, of 35 patients with oesophageal involvement, only thirteen had radiological pulmonary involvement. Of the seventeen patients with an abnormal chest x-ray, eleven had defects in 'pulmonary diffusion' as measured by the single-breath carbon monoxide method. However, ten of these patients also had oesophageal involvement. As the transfer factor for carbon monoxide can also be low in ventilation/perfusion disturbances as well as in 'alveolar capillary block', these changes could be compatible with secondary lung involvement rather than a primary interstitial sclerosis. Further studies are indicated to elucidate this point. The remaining six patients did not have pulmonary function tests performed. But two patients with normal radiographs had abnormalities of carbon monoxide transfer, a finding consistent with early parenchymal lung involvement and indicative of a probable underestimation of total lung involvement if only patients with abnormal radiographs are included (Godfrey, Bluestone, and Higgs, 1968). Unlike Farmer and others (1961) we found that pulmonary involvement at initial diagnosis had some bearing on prognosis.

As one of the commonest causes of death in scleroderma is cardiac failure (Table II), it is not surprising that electrocardiogram abnormalities are associated with a poor prognosis. Our overall incidence of abnormal electrocardiograms at initial diagnosis is 51 per cent. On analysis (Table III) no characteristic changes particularly diagnostic of scleroderma have emerged. Most of the common findings (low voltage, 'T' wave flattening, and 'ST' segment changes) are fairly non-specific and probably represent sclerotic involvement of the myocardium or of the pericardium as seen in some of the post mortem material (Table II). More specifically, the occurrence of left and right ventricular hypertrophy was associated with hypertension and pulmonary involvement respectively. Some of the patients dying in cardiac failure had predominantly left ventricular disease caused by hypertension, possibly exacerbated by myocardial sclerosis. Similarly, pulmonary involvement is associated with an adverse prognosis, and it is logical to assume that its presence helps to tip the balance in some patients on the verge of right ventricular failure caused in some instances by myocardial sclerosis.

It is interesting to note that, although the presence of renal involvement was of high prognostic significance, none of our patients for whom the cause of death is known died of renal failure. It may be that renal involvement, like trunk involvement, is only present when there is already extensive visceral involvement elsewhere. It is well recognized that some patients die of a rapidly progressive malignant hypertension and that this is usually associated with renal involvement.

Of the ten patients known to have small bowel involvement radiologically (mainly duodenal dilatation), four died in 6 years. However, only a small proportion of those surveyed had specific reports on small bowel radiographs and thus this feature has not been included in our analysis of significant prognostic factors. Some patients rapidly become emaciated and do badly, partly through fear of eating too much, because of oesophageal involvement, and partly as a result of malabsorption due to small bowel involvement. However, Bluestone, MacMahon, and Dawson (1968) found that small bowel involvement was relatively common and not usually associated with malabsorption. Obviously a long-term prospective study is needed to clarify this point.

Some have considered that patients presenting with acrosclerosis have a good prognosis (O'Leary and Waisman, 1943). Thus it might be expected that the duration of Raynaud's phenomenon before obvious cutaneous sclerosis would affect survival. However, this is not so and it is now clear that acrosclerosis does not preclude progressive systemic involvement, rather it is a common mode of presentation and the course is similar to that of other varieties of the disease. Particularly interesting in our study was that the mean duration of Raynaud's phenomenon before a definite diagnosis of scleroderma could be made was 5·3 years (S.D. 7·5). Hence, if a patient presents with Raynaud's phenomenon, one will in some cases have to follow him up for 20 years before one can say with 95 per cent certainty that he will not develop scleroderma.

In the course of the 23 years covered by this survey, many different forms of treatment have been tried, including epsilon-aminocaproic acid, relaxin, potassium para-aminobenzoate, penicillamine, and sympathectomy. The only therapy used long enough to warrant consideration as being of possible value was corticosteroids. The patients who received steroids naturally comprised a highly selected group and thus it is not possible to evaluate the precise effect of steroids in every type of patient. However, in our particular group, steroids did not seem to affect survival. Indeed, when one is dealing with a disease with an overall 5-year survival of 73 per cent. and a 90 per cent. 5-year survival in the under 40 age group, any therapy will have to exhibit a dramatic effect before it can be regarded as fully successful.
Summary

We have attempted to evaluate, for the first time, using 'Life Table' methods, the survival and factors influencing prognosis in scleroderma. The prognosis is very good, with a 73 per cent. 5-year survival overall and a 90 per cent. 5-year survival in the under 40 age group. Of those patients dying, 73 per cent. do so in the first 6 years. The features found at initial diagnosis which predispose towards an early death are trunk involvement, blood urea over 40 mg./100 ml., electrocardiogram abnormalities, radiological pulmonary involvement, and age over 40 years.

We should like to thank Prof. C. V. Harrison's Department of Pathology for performing the autopsies, Dr D. K. Peters for the generous use of an electronic calculator, and the many people who, over the years, have helped to investigate, document, and manage these patients.

DISCUSSION

DR. E. N. GLICK (London) Have you any information on the influence of treatment, particularly steroids or ACTH, on survival?

DR. BENNETT We did look at the effect of treatment in our series. The only group of drugs used often and long enough to assess their effect on survival were corticosteroids. Eighteen patients took them for at least one year and our longest survivor for 23 years. They were found to have no apparent effect on survival, either favourable or unfavourable. Other forms of treatment used and found to be clinically ineffective were epsilon-aminocaproic acid, relaxin, potassium para-aminobenzoate, penicillamine, and sympathectomy. When one is dealing with a disease with a 5-year survival of 73 per cent. and a 90 per cent. 5-year survival under the age of 40, any therapy producing a further significant effect on survival will be difficult to confirm.

DR. M. WILKINSON (Perth) Where does morphea end and scleroderma begin? Is it the size, or the distribution of the lesion? How do you exclude morphea?

DR. BENNETT Morphea was taken as a sharply localized plaque or hard sclerotic skin which ended up as a depressed atrophic area. The important differentiating features was its obvious border and its nonprogressive nature.

DR. W. W. BUCHANAN (Glasgow) One of the fallacies in cohort prospective studies, described by Neyman (1955), is that, if one starts the study after the disease has been present for some time, one may miss patients who have already died. Thus, if the study is started 5 years after the onset of the disease and there is a high mortality in the first 5 years, this observation will be missed. Did you attempt to analyse your results in patients with disease of only 1 or 2 years duration?

DR. BENNETT I think this criticism is perfectly valid. It can, of course, be levelled at any retrospective study of hospital patients and we realize that our survival figures strictly apply only to our own selected group of patients. However, one hopes that these figures will be of use in comparing results from other centres and a guideline for any future long-term prospective study. As for the question whether the study is started from the time of diagnosis or a predated starting point; though the temptation is great to attempt the latter, this is of necessity dependent upon usually vague early subjective symptoms, which inevitably lead to a fictitious result.

DR. F. DUDLEY HART (London) Although this is called progressive systemic sclerosis, did any remit, and for how long?

DR. BENNETT The natural progression of the disease is, of course, one of intermittent relapses and remissions. Some of our patients had apparent remissions lasting several years, but none has shown a complete regression of the disease.

DR. J. T. SCOTT (London) In a previous study in the U.S.A. a low haemoglobin was found to be related to bad prognosis. What were your findings?

DR. BENNETT In a pilot study we looked at the initial haemoglobin readings and found them to have no significant effect on subsequent survival. I think the study you are quoting (Farmer, Gifford, and Hines, 1961) did not specifically look at this feature at the time of initial diagnosis and this probably accounts for the discrepancy.

DR. D. PITKEATHLY (Manchester Region) One important feature in the prognosis may be the acuteness of onset of the systemic sclerosis. One sees patients with very swollen hands, who later develop tight shiny skin and clawed fingers.

DR. BENNETT We did not specifically look at the acuteness from the point of view of the skin involvement. But we did look at the effect of a raised ESR, which Farmer and others (1961) found augured an adverse prognosis. However, we found that a high ESR at initial diagnosis did not predispose towards a poor prognosis.

References


ORABONA, M. L., AND ALBANO, O. (1958) Acta med. scand., Suppl. 333, p. 5. (Systemic progressive sclerosis (or visceral scleroderma)).


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