Systemic Sclerosis

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Sydney Watson Smith, who died in 1950, was Honorary Consulting Physician and Dermatologist to the Royal Victoria and West Hampshire Hospital, Bournemouth, and in 1934 was President of the British Medical Association. His bequest to the College, in memory of his wife and himself, stipulated that an annual lecture be given on any subject in medicine, including dermatology. It seemed appropriate to choose a subject which demonstrates that dermatology is probably one of the few specialties embracing all aspects of clinical and investigative medicine from childhood to old age.

My interest in systemic sclerosis started over 25 years ago. Research has been carried out on many features of this disease but I want to concentrate on three aspects: first, clinical subsets of the disease; second, immunological abnormalities; third, genetic aspects and possible initiating and precipitating factors. My experience is based on the study of 131 patients at Leeds since 1958.

Although systemic sclerosis has been described under various names since the early 19th century[1], it was Goetz in 1945 who named the condition progressive systemic sclerosis[2]. As many patients live for years, I feel that the term progressive is unnecessarily daunting for patients, and prefer the shorter title systemic sclerosis. Scleroderma means sclerosis of the skin, which can occur in various conditions, and to avoid confusion this term should not be used for the disorder.

Systemic sclerosis is a multi-system disease and starts with Raynaud's phenomenon in over 90 per cent of patients. After an interval, which is longer for females than for males, changes occur in the skin. The skin of the face becomes shiny, the nose is beaked, there are radial furrows around the mouth and mat-like telangiectases on the cheeks. Mouth opening is restricted. In the early stages the hands may be swollen but later the skin of the hands becomes tight and shiny with absorption of the terminal phalanges and small ischaemic scars on the tips of the fingers. Calcinosis develops in the soft tissues of the hands and elsewhere. It occurs predominantly in females. The skin of the arms and frequently of the neck below the clavicle becomes tight and shiny. Pigmentation occurs in one-third of cases and may resemble Addison's disease. Changes occur in the feet, with loss of toes due to ischaemia. Ischaemic leg ulcers occur in 30 per cent of patients. The oesophagus is dilated, air-containing and lacking in peristalsis. The results of radiology in 50

Table 1. Radiological observations of the oesphagus in 50 patients with systemic sclerosis.

	No.	%
Radiological involvement demonstrated	38	76
Dilatation	30	60
Absent or diminished peristalsis	32	64
Gastro-oesophageal reflux	20	64
Hiatus hernia	13	26
Stricture	6	12

patients are shown in Table 1. Oesophageal reflux is more common than dysphagia. Stricture occurs in 12 per cent. Oesophageal manometry shows abnormalities more frequently than does radiology but it is not required as a routine investigation. The third part of the duodenum may be dilated and aperistaltic segments and strictures occur in the ileum. We evaluated small intestinal involvement in 20 patients by jejunal biopsy, small bowel radiology and tests for bacterial overgrowth and malabsorption, and in 55 per cent found abnormalities which were unrelated to disease in other organs[3]. Malabsorption is not due to poor intestinal permeability. In 17 patients permeability was normal[4]. Malabsorption is mainly due to bacterial overgrowth which is found in one-third of patients[5]. Barium enema shows characteristic wide-mouthed diverticulae of the colon. The extent of the involvement of the gastrointestinal tract is shown in Table 2. The oesophagus, duodenum and colon are most frequently involved. Basal fibrosis of the lungs can be shown radiologically in nearly half the patients, but abnormalities of pulmonary function occur before radiological changes. Impaired gas transfer is, in our experience, the

Table 2. Radiological involvement of the gastrointestinal tract.

	%
Oesophagus	76
Stomach	6
Duodenum	34
Jejunum	11
Ileum	17
Colon	43

most delicate test and is abnormal in 75 per cent[6]. The heart can be involved, electrocardiographic abnormalities being the most frequent findings. Even the teeth show changes. Widening of the periodontal membrane occurs in 30 per cent and is not related to the degree of involvement elsewhere[7].

In my series 73 per cent of patients had radiological oesophageal involvement, 49 per cent had an abnormal ECG, 46 per cent had radiological signs of fibrosis of the lungs and 41 per cent had impaired renal function.

The overall five-year survival rates reported are between 34 per cent[8] and 73 per cent[9], the differences between series depending upon different clinical criteria and the proportion of males and females. The prognosis of systemic sclerosis is worse in males than in females[10, 11]. The disease also advances more rapidly in men than in women. The shorter mean interval between the onset of Raynaud's phenomenon and the onset of cutaneous changes, when they can be dated, in my series is shown in Table 3. All the men had developed cutaneous changes

Table 3. Mean interval between onset of Raynaud's phenomenon and onset of cutaneous changes of systemic sclerosis when this could be dated.

Males	0.25 ± 0.8 years
Females	5.10 ± 7.0 years
	$P < 0.005$

within two years, in contrast to females in whom the interval was as long as 28 years.

The criteria for diagnosing systemic sclerosis have recently been considered by a sub-committee of the American Rheumatism Association[12] and are shown in Table 4. These preliminary criteria gave a 97 per cent

Table 4. Preliminary criteria for systemic sclerosis 1980[12].

Sole major criterion *or*	Proximal scleroderma
Two or more minor criteria	Sclerodactyly
	Digital pitted scars of fingertips or loss of substance of distal finger pad
	Bilateral basilar pulmonary fibrosis

sensitivity and 98 per cent specificity for definite systemic sclerosis in 797 patients seen in 29 American medical centres between 1973 and 1977. Patients with advanced disease are not difficult to diagnose but these criteria do help to provide standards for identifying mild cases and allow comparison between series.

Subsets of Systemic Sclerosis

Undoubtedly there are subsets of systemic sclerosis and their recognition will become increasingly important in relation to immunological and other factors, to prognosis and to treatment. In 1962 Tuffanelli and Winkelmann studied 727 cases from the Mayo Clinic[13]. They considered that systemic sclerosis should be divided into diffuse and acrosclerotic forms. The diffuse form was rare, involving approximately 5 per cent of patients. The sex distribution was equal, as compared with four females to one male in acrosclerosis. In the diffuse group Raynaud's phenomenon was absent or infrequent, sclerosis was generalised and the course was more rapid and likely to be fatal within a few years. It is difficult to be certain whether diffuse systemic scleroderma is an entity or not. Undoubtedly the sex distribution differs and the condition has a poor prognosis but some patients with acrosclerosis also have a short course; one of my patients died within two years of onset of the disease.

Since 1964 considerable interest has been shown in the so-called CRST syndrome of calcinosis, Raynaud's phenomenon, sclerodactyly and telangiectasia[14]. With the addition of oesophageal involvement this later became the CREST syndrome, the E representing the American spelling of oesophagus. Is this an entity? In an analysis some years ago[11], 12 of 84 (14 per cent) of my patients with systemic sclerosis showed features of CRST. All had involvement of the internal organs characteristic of systemic sclerosis, and two died from malignant hypertension, so all cases do not have a good prognosis, as has been claimed. The male to female sex ratio of patients with CRST syndrome did not differ from that of the whole series and the mean interval between the onset of Raynaud's phenomenon and the onset of cutaneous changes, if these could be dated, did not differ between patients with CRST syndrome and patients without these features. From the clinical point of view I would regard the CRST or CREST syndrome as only mild systemic sclerosis, but I will deal later with some immunological evidence to suggest that it might be a definite subset.

In 1972 Sharp[15] described 25 patients with features of systemic lupus erythematosus, systemic sclerosis and polymyositis, using the term mixed connective tissue disease. A haemagglutinating antibody to saline extractable antinuclear antigen (ENA) could be demonstrated in all. This was RNA-ase sensitive. All had speckled antinuclear factor (ANF), none had Sm antibody, and anti-DNA antibody, if present, was in low titre. Clinically, renal disease was infrequent, the prognosis was good and patients responded to oral corticosteroids. Further observations showed that 80 per cent were women and one-third present like rheumatoid arthritis, one-third like systemic sclerosis and a few like systemic lupus erythematosus. Probably the most characteristic clinical feature is the swelling of the back of the hands with sausage-shaped swelling of the fingers. The face may also be swollen and shiny. The skin manifestations fall into three main groups: those of systemic sclerosis with erosions of the finger tips and disorders of pigmentation; those of lupus erythematosus, either scarring discoid or non-scarring subacute cutaneous lupus erythematosus, and those of dermatomyositis with violaceous appearance of the eyelids, plaques on the chest and periungual telangiectasia. Raynaud's phenomenon occurs in 90 per cent and vascu-

lar changes may be very severe, resulting in gangrene which may involve the whole hand. Arthritis is the most common feature and may resemble rheumatoid arthritis. There may be features of muscle involvement, as in polymyositis, and changes in the gastrointestinal tract and other organs identical to those of systemic sclerosis. The immunological abnormalities included speckled ANF and antibody to ribonucleoprotein (RNP), immune complexes in 90 per cent and decreased T cells. Patients with overlap of polymyositis and systemic sclerosis may also have precipitating antibodies recently designated PM-Scl[16] and Ku[17]. In some cases direct immuno-fluorescence of normal exposed skin shows particulate staining of epidermal cells[18] and occasionally nucleolar staining[19]. Immunoglobin at the dermo-epidermal junction occurs in one-third. The inflammatory aspects rapidly respond to prednisone but over the course of time about half the patients are left with the features of chronic systemic sclerosis[20].

Is mixed connective tissue disease a subset of lupus erythematosus or of systemic sclerosis? Many patients fulfil the American criteria for systemic lupus erythematosus, despite having the digital erosions, oesophageal changes and colonic diverticulae of systemic sclerosis. Anti-RNP antibodies have been demonstrated in one-third of my patients with systemic sclerosis, although only 10 per cent have had other evidence of mixed connective tissue disease. Antibody to RNP is found in 25 per cent of patients with systemic lupus erythematosus and occasionally in other patients[21]. Do these patients then have latent mixed connective tissue disease? Examination of nail-fold capillaries suggests a link with systemic sclerosis. Of the patients with mixed connective tissue disease 54 per cent have the capillary changes of systemic sclerosis[22]. Do these abnormal capillaries indicate the patients that go on to systemic sclerosis? Or is mixed connective tissue disease an entity in its own right? Two aspects suggest that it may be. Abnormalities of immuno-regulating T-cell circuits in mixed connective tissue disease are different from those found in systemic lupus erythematosus, systemic sclerosis and rheumatoid arthritis[23]. Second, although one cannot define this disorder only by antibody to RNP, there is some evidence that patients with RNP antibodies may be genetically different from patients with uncomplicated systemic lupus erythematosus, systemic sclerosis or polymyositis[24, 25].

About 10 per cent of patients with systemic sclerosis have ragged cuticles and nail-fold capillaries visible to the naked eye. Capillary microscopy shows a characteristic pattern of capillary abnormalities in over 90 per cent of patients with systemic sclerosis. Normal nail-fold capillaries occur as regular loops evenly spaced, whereas in systemic sclerosis the nail-fold capillaries are enlarged and distorted and there is loss of capillaries and disruption of the normal capillary bed. Haemorrhage is frequent. There does not appear to be any correlation with the extent of cutaneous disease[26], but Maricq, who has done the most work on this subject, suggests that there may be correlation with the extent of visceral involvement[27]. Loss of capillary loops characterises the changes in systemic sclerosis and it may be that this

vascular ischaemia is the factor related to disease duration and systemic involvement[28]. The systemic sclerotic type of pattern of skin capillaries is also seen in dermatomyositis and mixed connective tissue disease and it has been suggested that the nail-fold capillary changes may indicate some common pathogenic factor. Abnormal nail-fold capillary changes occur in some patients with Raynaud's phenomenon[29], and future long-term prospective studies may show that nail-fold microscopy is a useful tool in predicting those patients with Raynaud's phenomenon who will develop systemic sclerosis. It is difficult to estimate the proportion of patients with Raynaud's phenomenon who will eventually develop systemic sclerosis. From the evidence available, I suggest it may be about 1 per cent of females and 6 per cent of males.

Patients with systemic sclerosis do not usually notice any precipitating factor, so what about so-called occupational scleroderma? About 6 per cent of polyvinyl chloride workers develop a syndrome resembling systemic sclerosis[30]. The skin of the face is shiny and tight, the hands are ischaemic with shortened bulbous finger tips. Patients have various immunological abnormalities and immuno-histology of the skin shows an immune complex vasculitis[31]. A genetic susceptibility is indicated by the increased incidence of DR5 in patients compared with controls and of B8 and DR3 in those severely affected[32]. Similar syndromes have occurred after exposure to organic solvents, pesticides and the vapour of epoxy resins, but these are very rare[33]. There is also an association between a systemic sclerosis-like illness and silicosis. Because of the occupational risk—to miners, sandblasters and quarrymen—the condition occurs almost exclusively in men. In East Germany[34] it has been estimated that males exposed to silica dust are 25 times more likely to develop a systemic sclerosis-like illness than are males not exposed to silica. Although visceral symptoms resembling those of systemic sclerosis occur in about half the cases and ANF can be demonstrated in one-third, I am not yet convinced that they suffer from true systemic sclerosis. The incidence is much higher than the suspected gene frequency of classical systemic sclerosis, and the situation is rather similar to the relationship of the systemic lupus erythematosus syndrome due to drugs like hydralazine and procainamide and true systemic lupus erythematosus. We do not know how silica acts but it may be by stimulating the production of collagen directly or indirectly by macrophages. Alternatively, occupational substances may inhibit a defence mechanism to which I will refer later. These syndromes should alert us, however, to possible unsuspected environmental triggers. Sclerodermatous skin changes are a late feature of the Spanish toxic oil syndrome[35], the nature of which is also unknown, but there is some evidence that there are genetic differences between affected and unaffected individuals.

Immunological Aspects

A variety of humoral and cellular immunological abnormalities can be demonstrated in the disease. Over 20 years ago, Beck et al., using rat liver as substrate, found

ANF in 78 per cent of patients at Leeds and Glasgow with systemic sclerosis[36]. Homogeneous factor was most frequently demonstrated, but nucleolar factor occurred more frequently in systemic sclerosis than in other connective tissue diseases. Recent experience at Leeds using rat liver has given an almost identical figure of 77 per cent but speckled ANF is now more frequent than homogeneous. In the last few years tissue culture cells have been used as the substrate as an alternative to rat or mouse liver, and antinuclear antibody has been detected in almost all cases of systemic sclerosis. Tan and his colleagues[37], using Hep 2 cells—a human laryngeal carcinoma cell line—showed that 96 per cent of sera were positive for ANF which is similar to our figure of 94 per cent. Various staining patterns have been described[38]. Centromere staining results from the presence of an antibody which reacts with the centromere region of metaphase chromosomes. This is shown as large, bright, round or ovoid granules occurring through the interphase nucleus and on the chromosomes of dividing cells. Other staining patterns using Hep 2 cells include homogeneous, peripheral (specific to systemic lupus erythematosus), fine and gross speckling and a diffuse 'frosted glass' pattern which is seen only in sera containing an antibody to Scl 70 antigen. Scl 70 antibody is usually demonstrated by a precipitin reaction to a soluble nuclear antigen Scl 70 which occurs in about 20 per cent of patients with systemic sclerosis. In addition, three distinct nucleolar patterns have been described—homogeneous, speckled and clumpy.

Ninety per cent of patients with anticentromere antibody have CREST syndrome[38] and 50–70 per cent of patients with CREST syndrome have anticentromere antibody. Anticentromere antibody is associated with long duration of disease, a low incidence of pulmonary involvement and rarity of renal involvement[39]. There is no consistent change in titre with time[40]. Anticentromere antibody, however, is not always present in patients with the CREST syndrome. It may be present in patients with Raynaud's phenomenon before the clinical features of the CREST syndrome occur[41], and be useful, like nail-fold capillary changes, as a marker to distinguish patients with Raynaud's phenomenon who are likely to develop systemic sclerosis. Anticentromere antibodies occur in about 2 per cent of patients with Raynaud's phenomenon, 6 per cent of patients with systemic lupus erythematosus and 6 per cent of patients with mixed connective tissue disease. Anticentromere antibody has been found in about 9 per cent of patients with primary biliary cirrhosis and these patients had the CREST type of systemic sclerosis[42]. Of patients with primary biliary cirrhosis 17 per cent have systemic sclerosis[43].

Anti-Scl 70 antibody occurs in about 20 per cent of patients with systemic sclerosis and appears to be particularly associated with a high frequency of lung involvement[44]. It may be a marker for systemic sclerosis, as it has not been found in other diseases such as systemic lupus erythematosus or rheumatoid arthritis[37].

Tuffanelli and his colleagues[45], using cells from a rat kangaroo epithelial cell line as substrate, reported four patients with an antibody to centriole, which is a reproducing cellular organelle that organises the mitotic apparatus during cell division. One patient had Raynaud's phenomenon with telangiectasia, another had CREST syndrome and the other two definite systemic sclerosis.

The relevance of these and other humoral antibodies to pathogenesis is not known. They may, however, define immunological subsets.

Various aspects of cell mediated immune mechanisms have been studied at Leeds and Sheffield in co-operation with Dr Hughes and his colleagues. Delayed skin reactions are depressed. Leucocyte migration inhibition occurs with a wide variety of autologous and homologous antigens—autologous lymphocytes, liver microsomes and mitochondria, and human myelin basic protein, but not to porcine thyroglobulin[46]. In our experience lymphocyte transformation to phytohaemagglutinin (PHA) is also depressed and the degree of depression is related to the severity of the disease, elevation of the ESR and the incidence of circulating antibodies[47]. There is a strong correlation between decreased lymphocyte transformation to PHA and deficiency of circulating T cells. Both total and T lymphocytes are reduced in systemic sclerosis as compared with controls. In our research work we have found it useful to have a grading system to define mild and severe systemic sclerosis (Table 5). Addition of points

Table 5. Criteria of systemic involvement in patients with systemic sclerosis.

System involved	Criteria	Disease score (points allotted for involvement)
Skin	Sclerosis—face	1
	hands	1
	trunk	1
GI tract	Radiological changes	3
Lungs	Radiological changes and/or abnormal CO_2 transfer factor	3
Heart	ECG changes	3
Kidneys	Creatinine clearance <60 ml/min and/or proteinuria	3
Other	Sjögren's syndrome, myositis, etc.	3

allocated to the features shown gives a disease score. Using this grading there is a positive correlation between the deficiency of T lymphocytes and the extent of the disease. To what is this deficiency of T lymphocytes due? We do not know, but it may be due to a redistribution of lymphocyte populations, a secondary effect of the disease or the result of chronic antigenic stimulation such as that seen in 'host versus graft' disease. Studies of T-cell subsets by other workers have shown that helper cells are increased[48] and suppressor cell function is decreased in systemic sclerosis. Whiteside and her colleagues have reported that depressed suppressor cell function is not related to severity of the disease or to other immunological abnormalities[49]. Unlike T cells, B cells are not reduced even in severe disease.

Reduced lymphocyte cytotoxicity can also be demonstrated in systemic sclerosis. There are several possible lymphocyte tissue damaging mechanisms, first, T lymphocytes with specific cytotoxicity to target cells, second, a combination of non-T lymphocytes, or killer (K) cells, and antibody to target cell tissue antigens (so-called antibody-dependent cytotoxicity) and third, spontaneous lymphocyte-mediated cytotoxicity produced by natural killer (NK) cells which are mainly T cells; NK cells may take part in immune surveillance. Patients with systemic sclerosis with extensive disease, according to our grading system, and low T cells have both reduced antibody-dependent cytotoxicity and reduced PHA-induced T cell cytotoxicity to Chang liver cells when compared with mildly-affected patients and with controls[50]. We do not know the cause of this defective cell-mediated cytotoxicity but circulating factors capable of blocking or inhibiting these two types of cytotoxicity have been demonstrated in some of our patients and these could be lymphocyte toxins, immunosuppressive globulins or immune complexes.

We have also demonstrated decreased NK cell cytotoxicity to Chang liver cells in severe systemic sclerosis, but not in mild cases compared with controls[51]. It has been impossible to substantiate the claims of Trayanova *et al.*[52] and Currie *et al.*[53] that lymphocytes from patients with systemic sclerosis have increased cytotoxicity to cultured muscle, fibroblasts and epithelial cells, but this may be due to technical reasons, i.e. to differences in the time of incubation of the lymphocytes with the target cells[54].

Dr Hughes and colleagues have allowed me to present some results on antibody-dependent cellular cytotoxicity to human vascular endothelium[55]. Serum from about a quarter of our patients with systemic sclerosis produces cytotoxicity of human umbilical vein endothelium when co-cultured with human peripheral blood mononuclear cells. Sera from normal controls and patients with atherosclerosis or diabetes do not show similar cytotoxicity. The serum factor(s) in patients with systemic sclerosis is present in IgG fractions and the effector cells have all the characteristics of K cells. There is some evidence that these serum factors may be immune complexes, but antinuclear antibodies could also be involved. This antibody-dependent cellular cytotoxicity to vascular endothelium was found particularly in patients with circulating immune complexes, anti-nuclear and ENA antibodies, and more severe disease. Only one serum causing cytotoxicity had anticentromere antibody, which is normally associated with the mild CREST variant of systemic sclerosis. Kahaleh *et al.*[56] have reported direct cytotoxicity of vascular endothelium which they attributed to a circulating protease-like factor in serum from patients with systemic sclerosis. This non-immunological cytotoxicity has not been confirmed by others. Serum from our patients, with or without added complement, did not cause direct cytotoxicity.

We have also studied immune complexes in systemic sclerosis using three techniques: Raji cell radioimmune assay, C_{1q} binding and K cell inhibition[57]. The Raji cell test is the most sensitive but immune complexes were found in 58 per cent of patients by at least one technique, an incidence similar to that found in systemic lupus erythematosus. Complexes were associated with elevated IgG and IgA levels, a high incidence of auto-antibodies and severe visceral involvement. They occurred in 41 per cent of mild cases compared with 76 per cent of severe cases. Other workers have produced some evidence that C_{1q} binding immune complexes seem to be associated with lung involvement[58].

More recently we studied the mean finger temperatures during a standard vasodilating stimulus in patients with systemic sclerosis[59] and showed that patients with the disease have cooler hands than the controls, with more variation in temperature between digits than in controls. Patients with circulating immune complexes have much lower resting temperatures than those without complexes, and the rate of vasodilation under stimulation was also slower in patients with immune complexes. These two features suggest that immune complexes could be a factor in the production of ischaemia in the hands of some patients with this disease. Other workers, using a different technique, have shown a relationship between the presence of immune complexes and Raynaud's phenomenon[60].

How do immune complexes work? We do not know, but they could have a direct action on blood vessel walls, although we have been unable to demonstrate immune complexes in arteries by immunofluorescent techniques in autopsied cases. They are more likely to arm K cells with antibody-dependent cytotoxicity. They could increase platelet aggregation or they could inhibit the release of prostacyclin from vascular endothelium.

Widespread vascular changes of intimal hyperplasia and endothelial damage occur in systemic sclerosis, and there is considerable evidence to indicate that the microvasculature may be the prime target in the disease[61, 62]. It has been suggested that ischaemia or the release of vasoactive substances may initiate the excessive collagen synthesis which leads to the characteristic fibrosis of the disease. Circulating antibodies to collagen Types I and IV occur in systemic sclerosis[63], and Type IV collagen is found in blood vessel walls. It is interesting, however, that anticollagen antibodies appear to be inversely related to the severity of the disease.

Genetic Aspects

That there is a genetic predisposition to systemic sclerosis has been suggested by the occasional familial cases, by the finding of abnormalities of serum proteins and by the increased incidence of ANF in first-degree relatives of patients. The United Kingdom Study Group studied 50 British patients and their blood relatives and found antibodies to collagen in 49 per cent of patients and in at least one relative in 87 per cent of families, whether or not the patient had anticollagen antibody. Various chromosomal abnormalities have also been found in the disease[64, 65].

HLA typing has been done in several studies. In 71 of our patients with systemic sclerosis no significant alteration in the incidence of HLA type was found when the

group was considered as a whole. However, further analysis showed that the incidence of HLA-B8 was greatly increased in the severe cases with extensive visceral involvement. Patients with B8 had more rapidly progressive and extensive disease than B8 negative patients[66]. Moreover, the more severely involved patients had a higher mean ESR, decreased circulating T cells and depressed lymphocyte responses to PHA. This association of impaired cell-mediated immunity and genetic factors has been confirmed by Kallenberg and colleagues[67], who found an association between haplotype B8/DR3 and impaired cellular immunity. Recently Black and her colleagues[68] reported an increase in DR2, DR3 and DR5 and a reduced incidence of DR2 in systemic sclerosis. The increased incidence of DR3 was attributed to an increase in the A1, B8, DR3 haplotype. Mild cases, i.e. those with the CREST syndrome, had an increased incidence of DR1 and DR5 and decrease of DR2 when compared with the severe cases. They noted that patients with anticentromere antibody were mainly DR1 or DR5 but there was no relationship between HLA and Scl 70 antibodies. They found no association with any specific organ involvement in their series, but Lynch et al.[69] noted an increase of DR3 and a decrease of DR4 in a subset of patients with systemic sclerosis and pulmonary fibrosis.

A Unified Concept

One of the most neglected aspects of a disease is the interpretation of its age and sex distribution. The age at onset of Raynaud's phenomenon in our patients is shown in Table 6. The onset in males is later than in females.

Table 6. Age at onset of Raynaud's phenomenon in 131 patients with systemic sclerosis (Leeds).

Age (yr)	Females	Males
0– 9	2	0
10–19	14	2
20–29	19	4
30–39	20	5
40–49	17	11
50–59	17	6
60–69	2	1
70–79	1	0
	92	29

Professor Burch carried out a mathematical analysis of age and sex specific incidence rates as a function of age on my original cases over 20 years of age[70]. Plotting the age-specific incidence rates for each sex versus age at onset on log/log scales results in curves which rise to a peak and then fall steeply to zero. The meaning of these curves, which are similar in type but not in detail to those found in other autoaggressive diseases like systemic[71] and discoid lupus erythematosus[72], is that the disease in question is confined to genetically predisposed individuals and that each disease is characterised by one or more specific genotypes. The characteristic female sex pre-

dominance in systemic sclerosis, about 3–4 females to every male affected, together with other evidence, suggests that the genotype involves one dominant X-linked allele as well as autosomal factors.

Mathematical analysis of these curves indicates that the disease appears to be initiated in predisposed individuals by a small number of random events; the average rate of such events is effectively constant throughout life and is independent of secular and geographical factors. These random events, Burch and I suggest, are somatic mutations in predisposed lymphoid stem cells. How does one, or a small number of mutations cause widespread disease? We believe that forbidden clones of lymphocytes synthesising cellular autoantibodies develop and, after a proliferative phase or latent period which is longer in females, attack the primary target tissue, which, in the case of systemic sclerosis, is possibly vascular endothelium. The body appears to have an endogenous defence mechanism, probably involving both immunoglobulins and cell-mediated immunity, which can be modified or inhibited by environmental factors which, in the case of systemic sclerosis, could include exposure to vinyl chloride or silica.. This defence mechanism, partly dependent on genetic factors involving the X-chromosome, is thus more effective in females, which accounts for the slower progress of the disease and the better prognosis in females than in males. Other factors, for example HLA B8 and DR3, seem also to govern prognosis. That genetic factors may be concerned in the progression of disease can also be seen in other conditions. For example, alcoholic cirrhosis occurs more rapidly in patients with HLA B8 and DR3[73]. Defective humoral and cell-mediated immunity may allow forbidden clones to proliferate. The former would account for the high incidence of autoaggressive disease in agammaglobulinaemia.

Clinical and immunological subsets are probably genetically determined, and this could be confirmed by studies of the onset patterns of precisely defined groups. The pattern of organ involvement in a particular patient may depend on several factors, for example on particular forbidden clones, on genetic differences in the antigenicity of target tissues, on local defence antibodies or on local vascular factors. Antinuclear antibodies arise as the result of release of nuclear material by damaged tissues. They may themselves enhance tissue damage, as can be demonstrated in animal experiments[74, 75]. The fact that they are not present in all patients may, in part, be due to the genetic inability of certain individuals to produce these antibodies. Patients with overlap syndromes probably have the genetic factors for more than one disease or, alternatively, certain alleles may be pleiotropic and predispose to more than one disease.

This unified concept (Fig. 1) though obviously controversial, is consistent with the sex and age distribution, the spontaneous onset in many cases, environmental factors, clinical and immunological subsets, multiple immunological abnormalities, differences in prognosis between males and females and overlap with other autoaggressive diseases. Our theory, however, is much less controversial but perhaps not so startling as Sir Fred Hoyle's concept of disease being due to viruses, bacteria and genes descend-
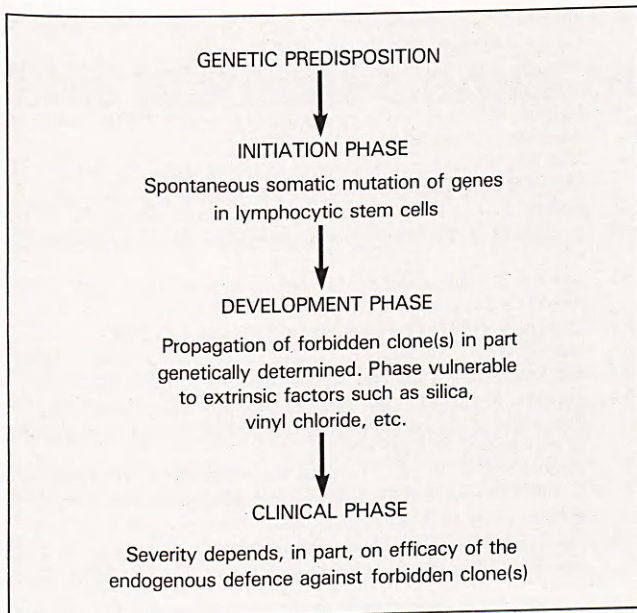
Fig. 1. *General scheme of autoaggressive disease.*

ing on the earth from outer space[76]. But Hoyle does, however, point out that 'old style genetics . . . failed to give proper emphasis to stochastics . . .' which we have endeavoured to correct in our consideration of age and specific incidence rates in the disease.

At present there is no specific or effective treatment but what of the future? Recombinant DNA technology and drug- or virus-induced gene switching could modify genetic aspects, and in time it may be possible to develop antibodies to specific forbidden clones which will allow a more rational approach to therapy. These aspects highlight the need for more precise definition of clinical and immunological subsets. The outcome of a disease depends on the balance between attack and defence. Attacking factors have attracted most attention in the past. Perhaps we should now concentrate more on enhancing defence mechanisms. The pace of advance is now so rapid that I can see all these developments occurring in my lifetime.

Wulff has discussed two philosophical concepts of disease—the nominalistic and the essentialistic (or demonic)[77]. In the first concept a disease consists of patients with similar clinical, immunological or pathological features, that is, a disease is a collection of sick people. In contrast, the essentialistic concept suggests that, like demons, diseases actually attack people. I recognise both concepts in systemic sclerosis, which is not a homogeneous condition but consists of several groups or subsets of patients. Demons also exist and possibly attack primarily the endothelial tissue of blood vessels.

Acknowledgements

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