Foreword

It is a pleasure to introduce and edit this Heberden supplement on scleroderma and timely that such a topic should be reviewed in a British journal. The past 10 years have seen an explosion in the number of clinicians and basic scientists exploring every aspect of scleroderma and its related syndromes, such as environmentally induced scleroderma, 'localised fibres', overlap syndromes, mixed connective tissue disease, and undifferentiated connective tissue disease.

There has been a particularly gratifying expansion in the depth of scientific investigation into possible aetiological factors and the processes which result in fibrosis and vascular damage, the two hallmarks of the disease. Much of the increased scientific interest and activity is due to an increasing understanding of immunological and genetic mechanisms and an expansion and application of the techniques of molecular biology.

The scientific work has been paralleled on the clinical front by a desire, often expressed at the international level, for collaboration to re-examine the current criteria and classification of the disease, develop indices of severity, activity, and progression and, in addition, develop a rational approach to drug treatment, with well designed, controlled multicentre national and international therapeutic studies.

It has not been possible in the space allotted to cover every aspect of the disease, to be totally comprehensive and satisfy every taste. For example, the complex interface of the immune response (both humoral and cellular), the cytokine cascade with subsequent cellular activation, and extracellular matrix protein synthesis have not been considered in detail and animal models have not been discussed.

In the clinical section an 'in-depth' examination of every internal organ has not been attempted, but each system has been outlined and, where indicated, newer methods of investigation and early detection discussed. This is particularly pertinent for pulmonary disease. The review has attempted to combine clinical aspects of current interest reflected in the chapters on epidemiology, Raynaud's phenomenon, clinical overview, treatment, and overlap syndromes with some areas of growing scientific interest. The chapters on immunogenetics, the endothelium, and control of collagen genes have permitted an in-depth examination of certain aspects of this complex disease with ideas which could be expanded into other areas of connective tissue medicine and autoimmune disease. Each contributor is an expert in his or her field and an active investigator in specific areas of research. I acknowledge with gratitude the excellence of their contributions and thank them for their efforts.

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Scleroderma, the word means 'hard skin', and it has come to be associated with, and descriptive of, a growing number of syndromes, which range from localised scleroderma (morphoes) through to chemical and drug induced disorders. It is not a new disease. The name was first coined by Gintrac in 1847, though the first written description of a case might have been 100 years earlier in 1753. Localised scleroderma, which includes limited and guttate morphoea, linear scleroderma, and generalised morphoea, is almost never associated with systemic disease but may be associated with autoimmune serology, and features prominently in the childhood form of the disease.

Generalised scleroderma is called systemic sclerosis. It is a multisystem, predominantly female disease of unknown cause. It is characterised pathologically by the overproduction of connective tissue, notably collagen, along with widespread vascular damage. Clinically, it covers a disease spectrum ranging from widespread skin thickening (diffuse systemic sclerosis) to skin thickening either limited to the face and distal extremities (limited systemic sclerosis), or absent (systemic sclerosis sine scleroderma). Classification is difficult. There are several systems in existence, and Dr Silver in his chapter has emphasised a two tier one, which in the current state of knowledge provides a useful working tool. The conclusions which may be drawn from the epidemiological data presented in Dr Silman's chapter are that the disease is uncommon, the latest incidence figures being 14.1/million population/year with a prevalence that has increased from four/million population in 1947-52 to 290/million in 1975; that it is rare in childhood but increases steadily with age; that, overall, the survival rate at 10 years is 40-50% with the diffuse subset and older patient faring much worse.

Once established in its full blown form, systemic sclerosis is a disease process difficult to stem and often impossible to reverse. The identification of a presclerotic state is therefore critical. Fortunately, almost all cases of generalised systemic sclerosis arise in the group with Raynaud's phenomenon—Raynaud's phenomenon is common and secondary Raynaud's phenomenon may be more common than previously thought. The frequency of its recognition ranges widely, depending in part on the depth and type of investigation. Two simple, inexpensive, non-invasive procedures are considered to have high predictive power for detecting patients who may develop systemic sclerosis. They are nailfold capillary microscopy and serum autoantibody determination. These tests should wherever possible be performed in patients with Raynaud's phenomenon. The cause of Raynaud's phenomenon and its relation to systemic sclerosis and other connective tissue diseases is still unknown, and there is a need for long term sequential studies on the immunogenetic aspects of this condition along with a better understanding of its systemic manifestations, such as cardiac, pulmonary, and renal vasospasm.

Apart from better documentation of hitherto inadequately
described minor organ involvement, such as that of the endocrine and reproductive organs and the nervous system, there is little to add to the clinical description of systemic sclerosis. What is changing and is of critical importance is: (a) the emphasis on the need to pinpoint the 'at risk' group and those patients in the early oedematous phase of the disease; (b) the desire to improve and standardise methods of quantifying the disease, its activity, and severity; (c) the need to anticipate impending organ involvement, its speed of progression, and to provide interventional treatment as early as possible.

Like most of the other connective tissue diseases, the cause of systemic sclerosis is unknown and, again like these related diseases, it is almost certainly multifactorial. There is, however, a gradual accumulation of knowledge about the genetic, environmental, and immunological factors which influence its development. The first two of these factors are discussed in detail in this supplement, and the role of the immune system as a stimulus to both the fibrotic and vascular damage is under intense investigation. The purported role of the immune system in systemic sclerosis has waxed and waned over the past 20 years. There is little support for a generalised derangement of the immune system, but a specific dysfunction which operates maximally at the onset of the disease is quite possible.

The clues pointing towards a specific abnormality are: (1) The activation of T cells in both the circulation and tissues of patients with systemic sclerosis as manifest by: (a) a decreased number of suppressor and suppressor inducer cells; (b) an increased number of T cells expressing deoxyribonucleic acid; (c) the possibility of a particular role for the gamma delta T cells; (d) raised concentrations of interleukin 2. (2) Activation of the complement system in systemic sclerosis. (3) The association of systemic sclerosis with certain major histocompatibility complex antigens. (4) The presence of autoantibodies with well defined target epitopes—a situation paralleled in systemic lupus erythematosus. A role for these antibodies is constantly being sought in systemic sclerosis. Recent work has shown homology between these target epitopes and retroviral proteins. This may have significance in disease pathogenesis as may the association of these antibodies with certain HLA markers.

It appears that only a certain number of well defined antibodies—for example, centromere and topoisomerase I, are important and that these may define disease subsets. They may even define the presence of the pre-systemic sclerosis state and have prognostic value.

Some of the stimuli which could induce an immune response in environmentally induced systemic sclerosis are known—for example, vinyl chloride and epoxy resin. In the idiopathic disease the situation is different, the stimuli are unknown, but the recent finding of increased expression of c-myc and c-myb proto-oncogenes in early active disease may take us closer to the primary events. The targets for the immune response in scleroderma are most likely to be the endothelial cell and the fibroblast, and both these important growth areas are reviewed in this supplement.

The intracellular signals which target the fibroblast—the primary effector cell in scleroderma for the synthesis of collagen, fibronectin, and other extracellular matrix proteins—are probably elaborated by a number of cell types, including macrophages and lymphocytes. The list of cytokines or hormones with the ability to stimulate or inhibit directly the synthesis and secretion of collagen is ever expanding and the quantity of collagen secreted by the cells is likely to be the result of a cascade or cumulative action of a number of cytokines. Therefore, a deregulation of any of these might theoretically lead to collagen over-expression. Currently, it is suggested that the expression of at least two soluble factors, transforming growth factor β and platelet derived growth factor, and the matrix protein fibronectin may represent key elements gone awry in scleroderma.

The first clue that the endothelium might be the target for injury came from the non-immune cytotoxicity work of LeRoy and colleagues in the mid 1970s. The cytotoxic factor which inhibited the growth of endothelial cells in culture has been somewhat elusive to define but soluble products of lymphocytes and monocytes have recently been shown to be capable of damaging the endothelium.

How all these complex factors interact to produce the spectrum of disease encompassed by the term scleroderma is still unknown. It is, however, conceivable that a variety of external stimuli trigger specific immunological reactions, which in a genetically susceptible host lead to extended vascular and connective tissue responses and dysregulation of normal processes, the final outcome of which is clinical disease. If the events and response are vigorous, the clinical picture may be diffuse disease, if they are more modulated, limited systemic sclerosis may occur, and it is obvious that the extent of the vascular or connective tissue damage, or both, varies between patients. The heterogeneity of the disease therefore probably represents a complex interaction of the external stimuli and the intensity and persistence of the host response. Much basic knowledge is required about all aspects of cause and pathogenesis before logical and staged treatment can be introduced—the current state of the art with respect to treatment is the final contribution to this supplement.

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Systemic sclerosis (scleroderma).

Introduction.

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doi: 10.1136/ard.50.Suppl_4.837

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