Connective Tissue Diseases

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THIRD EDITION

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Preface to the third edition

In the third edition I have made numerous additions to the text, and have concentrated especially on providing up-to-date references, especially reviews.

Two new sections have been added—one on the newly described anticardiolipin syndrome, and one with a more detailed characterisation of extractable nuclear antigens and 'overlap' syndromes.

Throughout the book I have kept to the central thesis that clinical descriptions remain the most important source of detail in these complex diseases.

London 1986 *G. R. V. Hughes*

Preface to the second edition

In preparing the second edition, I have again attempted to provide up-to-date (including 1979) references and reviews.

I am especially grateful to Dr Peter Ryan, Hammersmith Hospital, for his criticisms and help at the proof-reading stage.

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Preface to the first edition

The connective tissue diseases present some of the most taxing clinical problems in medicine. Although recent advances, particularly in immunology, have contributed to a finer definition of some of these diseases, their diagnosis and management rely heavily on clinical criteria.

The emphasis of this book is towards diagnosis, though current theories regarding aetiology are discussed and recent references are included.

The reputation of the Hammersmith Hospital as a referral centre for patients with connective tissue diseases has been largely due to the work of Professor E. G. L. Bywaters. His help and advice in the writing of this book have been invaluable. I am also grateful to Dr Charles Christian, Cornell University, New York, for his advice, to Dr R. Travers for proof-reading and indexing, and to Mrs J. Andrews and Mrs O. Wong for typing the manuscript.

London 1977 *G. R. V. Hughes*

Contents

CHAPTER ONE

Introduction

Implicit in the term connective tissue disease is the assumption that members of the group have a common pathogenesis or aetiology. Although the generally accepted members of the group of diseases, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis and the various vasculitides, have enough features in common to ensure their acceptance as a clinical family they differ in many aspects and do not have any consistent pathological or immunological features. A negative common feature of the group is the lack of a proven aetiological agent. Rheumatic fever, known to be a hypersensitivity reaction to streptococci is now excluded, though other members still included may have similar aetiological mechanisms. For similar reasons, the genetically determined connective tissue diseases such as Ehlers-Danlos syndrome—perhaps the only 'true' connective tissue diseases, are excluded.

Aetiology

Three headings appear repeatedly in the aetiology sections of this book—immunological, viral and genetic. All of the diseases discussed demonstrate immunological abnormalities, particularly the presence of humoral autoantibodies. In some cases, such as the haemolytic anaemia of SLE, these autoantibodies clearly have a direct pathogenetic role. For the most part, however, they may merely be epiphenomena, reflecting a more basic defect of the immune system such as loss of T-cell suppressor activity. Considerable knowledge has accumulated of immune complex disease mechanisms, where pathological change, particularly in renal glomeruli and blood vessels, is brought about by complement-mediated inflammatory processes, secondary to the deposition of antigen–antibody complexes. A separate chapter is devoted to this subject at the end of the volume.

Immune complex tissue damage is a secondary phenomenon. The initiating factors leading to altered immunity in these diseases are unknown, though evidence for both infective and genetic mechanisms is increasing. Perhaps most attention, in terms of aetiological factors, has been given to SLE, and for this, as well as other reasons, more space is devoted to this than to the other diseases.

None of the diseases has clear inheritance patterns, yet evidence from family and twin studies, as well as inferences made from animal models suggests that genetic factors may play an important pathogenetic role. The concept that a disease pattern of response to an infection might be genetically deter-

mined has received impetus from the work on immune-response genes in mice, and the finding of strong associations of spondylitis and sacroiliitis with HLA-B27, including those examples following gastroenteric infection. An increasing number of examples of genetic deficiencies of various complement components has been recognised. A significant number of these patients have subsequently developed one or other of the connective tissue diseases, in particular SLE. In more recent studies, evidence for an increased prevalence of a C4 null allele on the 6th chromosome in SLE provided further support for a genetic hypothesis.

Diagnosis

In the majority of cases, a clear diagnosis of one or other connective tissue disease can be made. However, undoubted examples of 'overlap' do occur. The finding of a serological marker for 'mixed connective tissue disease' has demonstrated that the use of immunological tests may contribute further to 'splitting'. During the past few years, the development of tests for studying 'extractable nuclear antigens' has played a useful role in the definition of subsets of lupus-like diseases.

To fall into the temptation of making the all-embracing diagnosis of 'connective tissue disease' or 'overlap syndrome' is to put the clock back on the development of this subject. It is salutary to remember that until relatively recently ankylosing spondylitis was considered by some to be a variant of rheumatoid arthritis—a view that may well have delayed the discovery of its relationship to HLA antigen.

An intelligent approach to classification has been in the drawing up of criteria for classification. While these cannot be used for diagnosis, the use of statistical analysis must play a part in assessment of such complicated disease patterns and their prognosis. Such an approach has been made in SLE by Fries and Holman (Systemic lupus erythematosus, 1975) to whose volume the reader is referred.

Nevertheless, at the bedside, initial diagnosis is made largely on clinical grounds and the emphasis of this volume is directed towards clinical diagnosis, exemplified where possible by case reports.

It is becoming increasingly clear that a spectrum of severity is seen in each of these diseases. Thus what might appear to be rapidly progressive scleroderma might be benign eosinophilic fasciitis, or a young woman with SLE psychosis and DNA binding values of 100% may yet have a very good prognosis. Indeed with the development of serological tests, the concept of 'minimal lupus' might be extended to other members of the group, leading to a recognition of milder variants of these diseases, and offering, if nothing else, more hope to the patient.

CHAPTER TWO

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), because of its widespread clinical manifestations, and because of rapidly increasing knowledge concerning its pathogenetic mechanisms, has achieved an importance among the connective tissue diseases out of all proportion to its clinical frequency. During the past 2 decades, the prevalence of lupus appears to have increased—indeed in some countries in the Caribbean and in the Far East, it is overtaking rheumatoid arthritis in importance.

It is predominantly a disease of young women and, until relatively recently, was widely regarded as having an almost uniformly poor prognosis. The introduction of sensitive immunological tests, particularly antinuclear antibodies, antiDNA antibody and complement estimations, has led to the recognition of milder forms of the disease, which in turn has contributed to the apparent increase in prevalence.

SLE may affect any organ of the body, though for some reason the liver is rarely clinically affected (the confusing terminology of 'lupoid hepatitis' is now being abandoned). The characteristic pattern of disease is one of exacerbation and remission. While it was once thought to lead to death in the majority of cases, it is now recognised that permanent remission may occur and indeed may be common in mild cases.

SLE characteristically affects the vasculature (leading to renal, cerebrovascular, pulmonary, and widespread organ involvement) as well as serosal surfaces (leading to pleurisy, pericarditis and peritonitis). In particular it is characterised by a profound and widespread disturbance of immune mechanisms, leading to the formation of antoantibodies and immune complexes. While renal, central nervous system (CNS) and cardiac lesions are prognostically most important, the most frequent manifestations of SLE are of skin and of joint disease, and in a proportion of patients the disease appears to be confined to these parts of the body. For a number of reviews of developments in SLE, the reader is referred to Hughes (1982b).

HISTORICAL

While SLE has probably been recognised for a number of centuries as one of the causes of facial 'lupus', it was not until the 19th century that Cazenave, Hebra & Kaposi (1875) recognised the distinct systemic form of the disease, and separated it from discoid lupus. Kaposi associated the facial 'butterfly' eruption with 'more or less fever of an irregularly remittant type ... attended

by general prostration and disturbed consciousness, resulting in coma or stupor or complicated with pleuro-pneumonia and ending in death'.

It is William Osler (1895) who deserves the credit, however, for describing the disease in the form in which we currently recognise it: '... polymorphic skin lesions ... arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastrointestinal crisis, endocarditis, pericarditis, acute nephritis and haemorrhage from the mucous surfaces. Recurrence is a special feature of the disease and attacks may come on month after month or even throughout a long period of years.'

Over the ensuing decades, various morbid anatomical and clinical features were described but in 1948, the next major advance came with the discovery of Hargraves, Richmond & Morton (1948) of the LE cell in bone marrow preparations of patients with SLE. This led to the recognition both of milder forms of lupus and of the widespread immunological disturbance present in the disease.

PREVALENCE

Epidemiological studies have been limited until recently by the lack of agreed classification criteria.

SLE in the male is extremely rare, and most series agree on a female:male ratio of 9:1. The disease is commonest in the childbearing years, and especially in the later teens and early 20's (Fig. 2.1).

Although it has been difficult to analyse ethnic prevalence differences, the disease does appear to be commoner in Negro populations, particularly in the USA and the West Indies. The author, during 1 year in Jamaica, saw 81 new

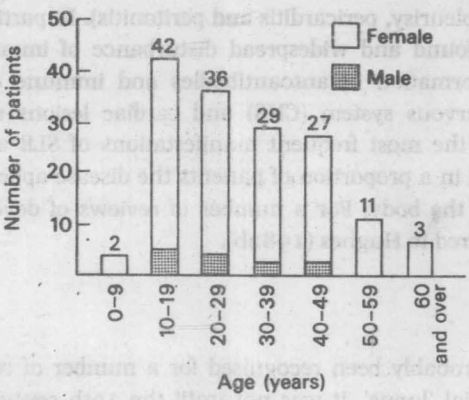

Figure 2.1 The age distribution of patients at the onset of multisystem disease. The number at the top of each bar refers to the total number of patients in each decade. (From Estes & Christian 1971.)

cases of SLE, and the prevalence of the disease on this island may approach 1 in 250 women. In one 10-year study (Siegel, Holley & Lee 1970) the age-adjusted mortality prevalence rates were three times greater for black females than white females in New York City, and 4·3 times greater in Jefferson County, Alabama—a close agreement for such widely separated communities. Further difficulties have arisen because of differences in diagnostic interpretation in some studies, for example, inclusion of 'rheumatoid arthritis and LE'. The widespread use of diagnostic criteria such as those suggested by the American Rheumatism Association (see below) may lead to further clarification, as will the development of more specific diagnostic tests such as measurement of antiDNA antibodies.

The epidemiology of SLE has been extensively reviewed by Siegel & Lee (1973). The highest incidence reported at that time was in New York: 14 new cases per 100 000 were reported in black females between the ages of 15 and 44 in 1960. The prevalence (i.e. number of people suffering from the disease at any one time) in this group on July 1st 1965 was 80·9 per 100 000 or just under 1 in 1000. Fessel (1974) in an extensive survey of residents of San Francisco noted a prevalence in women (aged 15–64 years) of 1 in 2000. The prevalence in black women rose to 1 in 245. Thus SLE is not a rare disease—indeed in parts of South East Asia, prevalence figures may exceed those of rheumatoid arthritis. In London, in the decade since the lupus clinic was instituted, one thousand new SLE patients have been seen.

PATHOLOGY

Table 2.1 summarises the main pathological features. Despite the long list, surprisingly little diagnostic help in SLE is obtained from histology. The most striking histological feature is the so-called 'fibrinoid necrosis' which affects particularly the small arteries, arterioles and capillaries (as distinct from polyarteritis nodosa which affects predominantly medium sized vessels such as the coronary and mesenteric arteries). Fibrinoid necrosis also affects the interstitial collagen and membranes such as the pleurae and joint capsules. It occurs in a number of well-defined stages. First increased amounts of mucopolysaccharide cause the swelling of collagen ground substance. The collagen fibres then swell and become fragmented, finally dissolving into a homogeneous hyaline or finely granular periodic acid-Schiff (PAS)-positive substance. Immunofluorescent studies have shown that this fibrinoid contains large amounts of gammaglobulin, with fibrin or ground substance, together with complement and fibrinogen.

The other feature highly suggestive of SLE is the haematoxylin body, the tissue counterpart of the LE cell, that represents the pyknosis of nuclei, with resultant coalescence or phagocytosis.

Table 2.1 Principal pathological changes in SLE

General
Fibrinoid necrosis
Haematoxylin bodies ('tissue LE cells')
Deposition of immune complexes along basement membranes
Skin
Discoid—follicular plugging and scarring
Systemic—immune complexes in dermal/epidermal junction
Kidneys
Immune complex deposition ('lumpy-bumpy' immunofluorescence)
Focal or diffuse glomerulonephritis
Fibrinoid necrosis of arterioles or arteries
CNS
Microinfarcts
Choroid plexus complexes
Heart
Pericarditis
Myocarditis
Libman-Sachs endocarditis
Blood vessels
Arteriolitis & capillaritis
Major arteries less frequent
Micro-thrombi
Spleen
'Onion-skin' thickening
Joints
Fibrinoid deposition
Lungs & pleura
Fibrinoid. Adhesions. Effusions
Interstitial pneumonitis
Recurrent atelectasis. Infections

Kidney There are no pathognomonic changes, though a number of features are regularly seen. The 'classical' change—the *wire loops*; eosinophilic thickening of the basement membrane of some capillary loops—is seen only in more advanced cases. Other light microscopic changes include a local or generalised focal glomerulitis—with or without crescent formation, capsular adhesions and glomerular fibrosis—haematoxylin bodies and interstitial infiltration by plasma cells and lymphocytes. In other (rare) patients, the predominant lesion is a diffuse membranous glomerulonephritis. Fibrinoid necrosis may develop, especially in afferent arterioles (Fig. 2.2).

Electron microscopy has revealed that the main lesion in lupus nephritis is the deposition of electron-dense material on the endothelial aspect of the membrane, either in linear or 'lumpy bumpy' distribution. Immunofluorescent

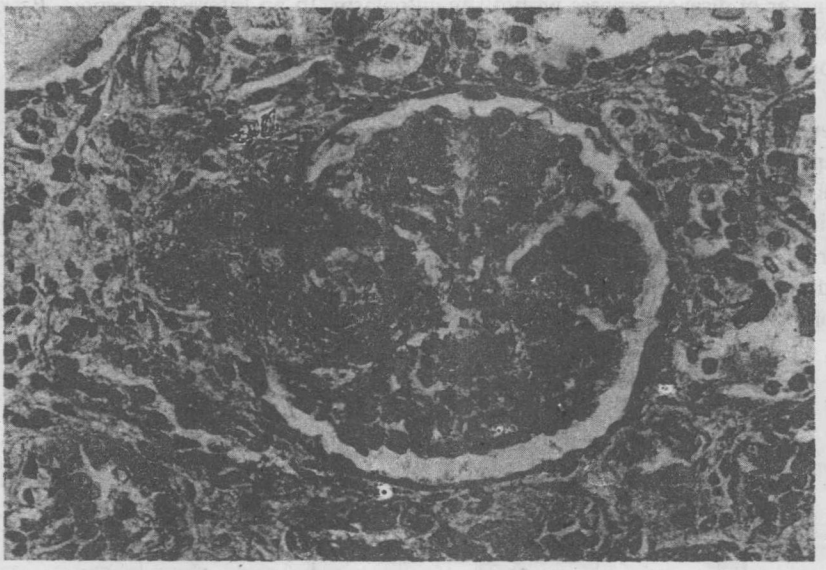

Figure 2.2 SLE nephritis. Glomerulus showing marked fibrinoid necrosis of afferent arteriole. (H & E × 340. Dr Shirley Amin, University Hospital of the West Indies.)

examination, which has now largely replaced light microscopy as an investigative tool in SLE, has shown this material to consist largely of gammaglobulin (particularly IgG), complement and fibrinogen. The globulin has antinuclear activity, particularly against DNA. The distribution of complement is generally similar to that of immunoglobulin suggesting that both are deposited in the form of immune complexes. Demonstration of the antigen has proved far more difficult though DNA has been localised histochemically. The pathological features of lupus nephritis have been extensively reviewed by Baldwin & Gallo (1975).

Skin The more benign discoid lupus has the more florid clinical and pathological changes, with hyperkeratosis, follicular plugging, vacuolisation of basal cells, perivascular infiltrate with lymphocytes and plasma cells and fibrinoid necrosis in the dermis. Immunofluorescent studies of skin have proved diagnostically useful, especially in SLE, showing deposition of gammaglobulin and complement along the dermal–epidermal junction (reviewed by Shrager & Rothfield 1975). This finding may be present in clinically uninvolved skin. Further findings of interest, to be discussed later (p. 11) are virus-like particles, or more precisely cytoplasmic tubular aggregates (CTA). These have been seen in the skin, kidney, synovial membrane, lung, muscle and liver of patients with SLE. While not confined to this disease, they are not found in normal cells. They are now thought not to be virus particles as such, but to represent a

marker of disease process within the cytoplasm. In an interesting report, Berk & Blank (1974) noted that ultraviolet irradiation of skin in patients with SLE doubled the incidence of CTA in normal skin.

Central nervous system Very little is known about the neuropathology of CNS lupus. In the study of Johnson & Richardson (1968) the predominant lesions related to small blood vessels where destructive and proliferative changes were found, associated with scattered microinfarcts. In retrospect, perhaps the most striking finding of this 'classic' study was the notable *absence* of vasculitis—micro-thrombi being more a feature. Likewise, evidence that cerebral immune complex deposition (including choroid plexus immunoglobulin and lowered CSF

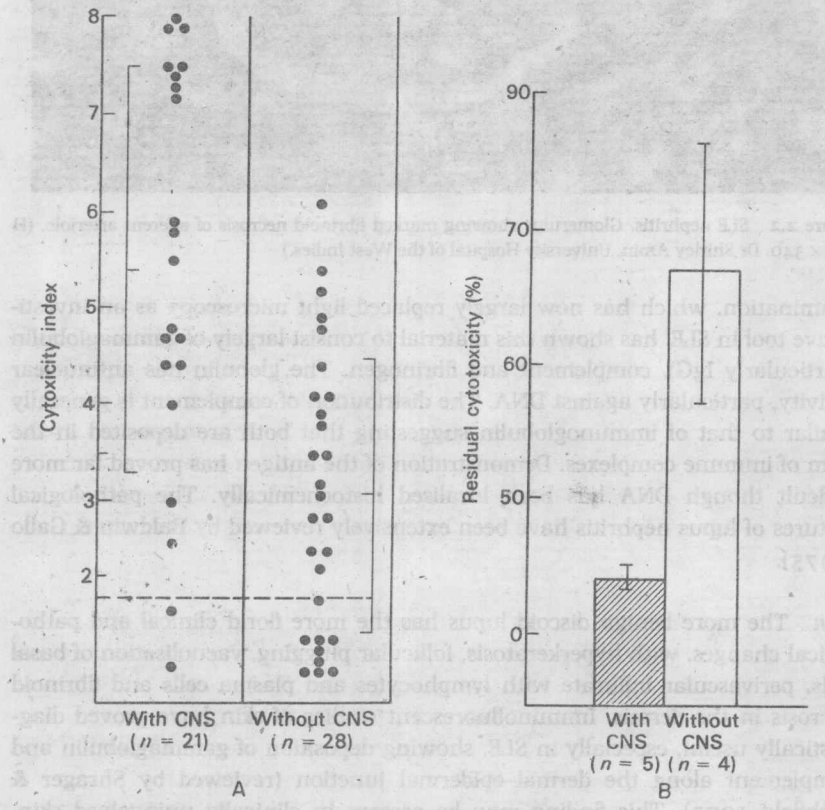

Figure 2.3 A. Maximal cytotoxicity index of SLE patients with and without CNS involvement. The titres of lymphocytotoxic antibodies were significantly higher ($P<0{\cdot}001$) in those with CNS disease.

B. However, comparison of lymphocytotoxins from CNS and non-CNS patients showed that only those from the CNS group could be absorbed out by incubation with brain homogenates. (From Bresnihan *et al* 1977.)

C_4 levels), is a major cause of CNS lupus is scanty (reviewed by Hughes 1978), though the choroid plexus and glomerular basement membrane do have striking morphological and functional similarities, and share common antigenic determinants. IgG antigen and C_3 have been demonstrated in the choroid plexuses of animals with acute serum sickness (Koss *et al* 1973) and, in the New Zealand mouse (Lampert & Oldstone 1973).

An alternative mechanism of neuropsychiatric involvement is suggested by the observations that human brain shares antigens with lymphocyte membranes and cross-reacts with antilymphocyte antibodies (Bluestein & Zvaifler 1976). Cold-reactive antilymphocyte antibodies are found more frequently in those patients with neuropsychiatric disease (Fig. 2.3a) (Bresnihan *et al* 1977). Furthermore, only those seen in the CNS group of patients are absorbable by brain (Fig. 2.3b). Further studies have shown that a subgroup of antineuronal antibodies exists which are warm-reactive IgG and probably directed against the neuronal cell membrane (Bresnihan *et al* 1979). Their presence correlates broadly with clinical CNS involvement.

Other organs The commonest cardiac lesion is fibrinoid deposition on the pericardium. Mild myocarditis, with focal fibrinoid change in the walls of small arteries and fibrinoid deposition in the septa and near blood vessels is the second most frequent finding. The well known endocardial ('Libman–Sachs')

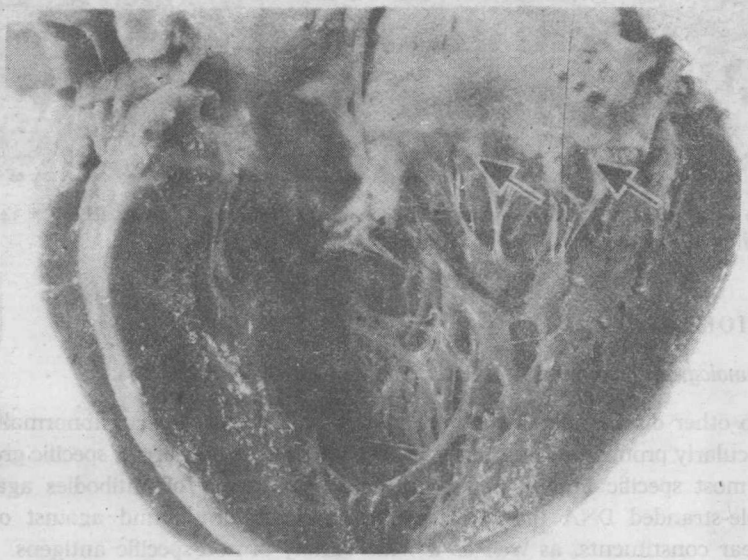

Figure 2.4 Heart showing non-infective (Libman-Sachs') vegetations on and below the line of closure of the mitral valve.

vegetations (Fig. 2.4)—dry granules on either surface of any of the valves—are found only rarely, and in patients with severe generalised disease.

The spleen may show a very characteristic 'onion-skin' lesion, said to be one of the most pathognomonic histological findings in SLE, and due to marked perivascular fibrosis around the central and peripheral arteries (Fig. 2.5).

In the lungs, recurrent pleurisy and adhesions may lead to progressive elevation of the diaphragm and a restrictive lung pattern on respiratory function tests. An interstitial pneumonitis may be seen and wire-loop lesions of pulmonary capillaries have been described.

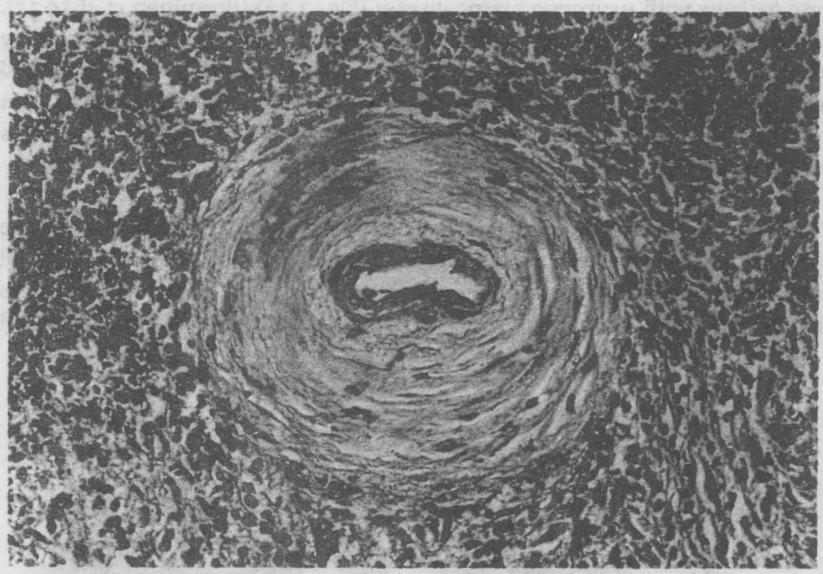

Figure 2.5 Spleen in SLE, showing concentric 'onion-skin' periarterial fibrosis. (H & E × 340. Dr Shirley Amin, University Hospital of the West Indies.)

AETIOLOGY

Immunological changes (see *Arthritis and Rheumatism* 1982 25 (7).)

In no other disease are there more widespread immunological abnormalities. Particularly prominent are humoral antibodies of the non-organ specific group. The most specific finding appears to be the presence of antibodies against double-stranded DNA (p. 259) though antibodies are found against other nuclear constituents, as well as a wide variety of non-specific antigens. Less prominent are antibodies against organ-specific antigens such as thyroid and gastric parietal cells. The wide range of serological abnormalities has led to the suggestion that there might be a general defect of 'self tolerance' or in more

current terminology, in T-cell suppressor function (Alarcon-Segovia 1982; Searles & Williams 1982). While this is almost certainly the case in the New Zealand mouse (see later), the evidence for a defect in cell-mediated immunity in human SLE has been less clear-cut (reviewed by Hahn 1975) (Table 2.2). Messner, Lindstrom & Williams (1973) reported that absolute numbers of circulating T cells were reduced in patients with active SLE. Titres of antilymphocyte antibodies in SLE tend to correlate with fever, leucopenia, anaemia, CNS involvement and arthritis (Butler *et al* 1972). Other factors, such as a reduced level of thymic hormone (Bach, Dardenne & Bach 1973) may also contribute.

Table 2.2 Evidence for reduced cell-mediated immune responses in SLE (from Hahn 1975)

In humans	*In New Zealand mice*
Reduced delayed hypersensitivity*	Reduced *in vitro* lymphocyte transformation to allogeneic cells
Reduced *in vitro* lymphocyte transformation to specific antigens*	Reduced *in vitro* lymphocyte transformation to non-specific mitogens
Reduced *in vitro* lymphocyte response to non-specific mitogens*	Circulating antibodies against T cells present during active disease
Reduced CMI response to DNA in face of enhanced antibody response	Reduced ability of lymphocytes to produce GVH reactions
Reduced numbers of circulating T cells during active disease	Reduced ability to reject allografts
Circulating antibodies against T cells present during active disease	Resistant to induction of immune tolerance*
	Reduction of T-cell helper effects on antibody formation
	Reduction of T-cell suppressor effects on antibody formation
	Acceleration of autoantibody formation and nephritis by reduction of T-cell function

* Conflicting results are reported in the literature.

Whatever the cause, defective T-cell function is, at the present time, a useful unifying concept linking some of the immunological changes seen in SLE, including the possible failure to eliminate extrinisic antigen such as viruses, and the failure to suppress B-cell activity, with the resultant gross overproduction of humoral antibodies (Bresnihan & Jasin 1977; Landry 1977) (reviewed by Searles & Williams 1982).

Some of the various theories of 'autoimmunity' have been reviewed by Rabin & Winkelstein (1975). Current views on the aetiology of SLE are reviewed in *Arthritis and Rheumatism* 21 (No. 5) (Suppl.) 1978 and in Hughes (1982b).

Virus infection

In 1975 De Horatius and Messner published a paper in which they demonstrated lymphocytotoxins in 68% of close household contacts of SLE patients.

This finding, confirmed in other studies (Folomeeva *et al* 1978), provided support for the participation of a transmissible agent in the aetiology of human SLE.

Direct attempts at virus isolation in SLE have failed (Phillips 1975) though the recognition that persistent or slow virus infection may lead to chronic disease with autoimmune features (Levy 1974), has led to a concentration of effort to demonstrate slow virus infection in SLE.

Most of the evidence supporting a virus infection in SLE has come from observations on animal models, in particular the New Zealand mouse, and a colony of dogs which develop SLE-like features (see below). In both animal

Table 2.3 Summary of serum virus antibody levels in SLE patients compared to controls (from Phillips 1975)

	RNA		*DNA*	
Mean antibody level in SLE	*Virus*	*Group*	*Virus*	*Group*
Usually high	measles	paramyxo		
	rubella	toga		
Variably high	parainfluenza	paramyxo	Epstein–Barr	herpes
	mumps	paramyxo		
	reo	reo		
Usually normal	influenza	myxo	adeno	adeno
	Newcastle disease	paramyxo	cytomegalo	herpes
	OC43	corona	papova	papova
	respiratory syncytial	paramyxo	hepatitis B	?
			herpes simplex	herpes

groups, type-C virus infection has been implicated. These particles contain a virus core, surrounded by an outer envelope, acquired as the virus buds down from the cell membrane. They also carry the virus enzyme reverse transcriptase. Two further observations have linked this finding to human SLE:

Schwartz *et al* (1975) using conjugated rabbit antiserum against C-type particles demonstrated adherence to lymphocytes, using immunofluorescent staining, in 10 out of 12 patients with SLE, and none in controls; secondly, using a sensitive radioimmunoassay, Strand & August (1974) demonstrated type-C antigen in preparations of spleen, placenta and kidney in three SLE patients. Mellors & Mellors (1976) demonstrated type-C proteins in the glomerular immune deposits of a fatal case of renal SLE. The role of type-C virus in SLE has been reviewed by Pincus (1976) and in considerable detail in *Arthritis and Rheumatism* 21 (No. 5) (Suppl.) 1978.

Three other findings have, during recent years, also stimulated interest in a viral aetiology: