Systemic lupus erythematosus

A prospective analysis

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SUMMARY The spectrum of organ involvement in 50 patients with systemic lupus erythematosus has been assessed in a prospective study. All patients were admitted to hospital electively for 2 days and a complete clinical and laboratory assessment protocol completed. Subsequent hospital admissions depended on clinical status. The overall mean observation period was 29 months. Widespread multisystem involvement was found in every patient. Subclinical abnormalities of respiratory and cerebral function were common even in patients in clinical remission. A more conservative approach than has been generally recommended was used for the management of systemic lupus erythematosus and is supported by the estimated 5-year survival of 98%.

During recent years considerable change in emphasis has occurred in the clinical description of systemic lupus erythematosus (SLE). From being a rare disease, usually ending in death from nephritis, it is now regarded as a relatively common illness in which mild forms with a good prognosis are being increasingly recognised. These apparent changes in the nature of SLE have been at least partially due to a growing awareness of the disease and the addition of sensitive serological tests to the clinical and pathological diagnostic methods.

Several large series have described the clinical features of SLE (Estes and Christian, 1971; Dubois *et al.*, 1974; Fries and Holman, 1975; Lee *et al.*, 1977). The present report, a prospective analysis beginning in 1973, is the first in which the clinical diagnosis has been supported by the finding of raised levels of anti-DNA antibodies in each patient. The aim of the study was to analyse prospectively the pattern of organ involvement in SLE using all currently available techniques. All patients were admitted to hospital on at least one occasion for a complete clinical assessment, regardless of apparent disease activity. We report the findings in the first 50 patients studied.

Methods

PATIENT SELECTION

Since January 1971, 121 patients with the clinical

diagnosis of SLE confirmed by the presence of anti-DNA antibody have been seen at Hammersmith Hospital on one or more occasions. The patients were referred from local practitioners, from other centres in the United Kingdom, and from centres abroad. About half were referred directly to the rheumatology unit. Others were seen initially in other departments, particularly nephrology and haematology. A sample of 50 successive patients who were referred to the rheumatology unit after July 1973, and who have since been followed up regularly were entered into a prospective study.

A systematic collection of predefined clinical and laboratory data was made over the period of observation. The frequency of outpatient attendances was determined according to the clinical status. At each visit a detailed clinical examination was recorded and blood taken for erythrocyte sedimentation rate, full blood count including differential white cell count, anti-DNA antibodies, and complement (C3). A further aliquot was stored at -20°C . Each patient has at some point undergone a planned 48-hour hospital admission for the purpose of carrying out a comprehensive investigative profile according to a predetermined protocol (see Table 1). The patients were not necessarily symptomatic at the time of this admission. Patients who were already being followed at the rheumatology unit before the start of the study in July 1973 have also been included. Otherwise, no retrospective analysis of this study group has been performed.

In order to evaluate possible selection bias of the study sample, the major clinical features of the total

Table 1 Protocol for investigation of SLE patients during 48-hour hospital admission

(1) <i>Haematology</i> Full blood count, ESR White cell count, differential count Platelet count Coombs's test Anticoagulant screen	(4) <i>Urine</i> 24-hour urine protein Creatinine clearance Urine deposit $\times 2$ Renal biopsy (if indicated)
(2) <i>Serum biochemistry</i> Urea, creatinine, electrolytes SMA—12 profile Serum protein electrophoresis Immunoglobulin levels Creatinine phosphokinase	(5) <i>X-rays</i> Chest Hands and feet
(3) <i>Serology</i> Antinuclear antibodies Anti-DNA antibody Anti-ENA antibody (RNP, Sm) Rheumatoid factor VDRL, Wassermann reaction Complement profile Cryoglobulins Lymphocytotoxic antibodies	(6) <i>Neurological investigations</i> Brain scan Electroencephalogram Fluorescein retinal angiography
	(7) <i>Pulmonary investigation</i> Lung scan Pulmonary functions tests
	(8) <i>Cardiac investigations</i> Electrocardiogram Echocardiogram

ENA = extractable nuclear antigen; RNP = ribonucleoprotein.

Hammersmith Hospital SLE population since 1971 has been extracted from the case notes for comparison.

DIAGNOSTIC CRITERIA

Diagnosis of SLE in the study sample was established along the following principles. Each patient had a multisystem disease with clinical features typical of SLE. All had significantly raised titres of antinuclear antibodies and anti-DNA antibodies at some stage during the course of their disease. Other multisystem connective tissue diseases, particularly drug-induced syndromes, chronic cutaneous vasculitis, discoid lupus, mixed connective tissue disease, and rheumatoid arthritis with Sjögren's syndrome were specifically excluded.

SPECIAL INVESTIGATIONS

Serology

Antinuclear antibodies were assayed by an immunofluorescent technique using mouse liver as a substrate (Holborow *et al.*, 1957). Anti-DNA antibodies were detected by the Farr ammonium sulphate precipitation test using ^{14}C DNA (Pincus *et al.*, 1969; Lewkonja *et al.*, 1977). Antibody to extractable nuclear antigen and its major components was detected by counterimmunoelectrophoresis (Kurata and Tan, 1976). Lymphocytotoxic antibodies were measured using the two-stage microcytotoxicity assay (Terasaki and McClelland, 1964). Serum complement components, C3, C4, and C1q were measured by radial immunodiffusion. Total haemolytic complement (CH50) was also measured.

Pulmonary investigations

The techniques used have been described elsewhere (Gibson *et al.*, 1977). Total lung capacity was determined by plethysmography, and diffusion by single breath carbon monoxide transfer factor corrected, where necessary, for anaemia. No patient had pleuritic pain at the time of testing. Lung perfusion scanning was performed using ^{99}Tc microspheres.

Neurological investigations

A standard electroencephalogram incorporating hyperventilation and photic stimulation was performed. Where necessary, drugs which might have influenced the recording, particularly tranquillisers, were discontinued some time before. 10 mCi ^{99}Tc was used in brain scanning. 25 of the patients were also examined by fluorescein retinal angiography with accompanying fundus colour photography (Novotny and Alvis, 1961).

Statistical analysis

Statistical significance was determined by the χ^2 fourfold contingency table method using Yates's correction. Survival was calculated by the method of Merrell and Shulman (1955).

Results and discussion

GENERAL FEATURES OF STUDY GROUP OF 50 PATIENTS

Of the 50 patients, 38 (76%) were Caucasian, 10 (20%) were West Indian blacks, and 2 (4%) Asian. There were 3 males, 47 females. The age at onset, defined as the date of the first unequivocal clinical manifestation characteristic of the disease, ranged between 10 and 50 years (mean 27 years). The average duration of the disease at the time of entry to the study was 7.7 years.

The initial manifestations are summarised in Table 2. Joint manifestations were the presenting feature in 62%, and were often associated with constitutional symptoms. Presentation with haematological or neuropsychiatric features occurred in only a minority.

Table 2 Initial manifestation of SLE in 50 patients

Manifestation	Per cent
Arthritis or arthralgia	62
Cutaneous	20
Fever, malaise	4
Thrombocytopenic purpura	4
Haemolytic anaemia	4
Neuropsychiatric	4
Recurrent thrombophlebitis	2

The cumulative clinical manifestations found in the study patients are summarised in Table 3 and are compared with previous series (Estes and Christian, 1971; Dubois *et al.*, 1974; Lee *et al.*, 1977). Musculo-skeletal and skin involvement were the most frequent manifestations and occurred at some time in 49 of the patients. The percentage distribution of most individual manifestations in the 50 study patients was in general agreement with the other series. Only in the case of alopecia was there a statistically significant discrepancy.

Forty-six (92%) of the 50 patients developed 4 or more positive ARA preliminary criteria for the classification of SLE (Cohen *et al.*, 1971). The mean number of positive criteria in each patient was 6.0. The 4 patients who did not fulfil the ARA criteria had persistently raised DNA binding values.

SKIN AND MUCUS MEMBRANES (TABLE 4)

Skin and mucus membrane manifestations were recorded in 49 of the 50 patients. Varieties of cutaneous vasculitis seen included digital vasculitis, nail fold lesions, periungual erythema, palmar and plantar rashes, and erythematous and maculo-papular lesions, particularly on the elbows and breasts. Although no significant correlation could

be found between other clinical manifestations and the cumulative incidence of cutaneous vasculitis, the appearance of livedo reticularis in association with flares of cerebral vasculitis was observed in several patients.

Alopecia was a frequent and recurring feature and correlated closely with exacerbations of disease activity. Although some patients had rapid loss of large amounts of the scalp hair, mild nonscarring patchy hair loss associated with new growth on the upper forehead occurred more frequently. Mild alopecia associated with fever or corticosteroid therapy was specifically excluded from analysis. One patient with severe Raynaud's phenomenon developed chronic ulceration and digital gangrene, but in general Raynaud's phenomenon was milder than that seen in mixed connective tissue disease (Sharp *et al.*, 1972; Bresnihan *et al.*, 1977a).

Purpura was associated with thrombocytopenia in 7 of the 9 patients in whom it occurred. 11 patients developed subcutaneous nodules similar to those seen in rheumatoid arthritis. These were all less than 0.5 cm in diameter, and were found on the elbow and extensor surfaces of the forearm, the fingers, and in one patient the scalp. Discoid lesions, mainly affecting the upper portion of the body, were seen in 10 patients, and were the presenting manifestation in 3.

Table 3 Cumulative major clinical manifestations of SLE in 50 patients compared with previous series

Manifestation	This study (1978) 50 patients (%)	Lee <i>et al.</i> (1977) 110 patients (%)	Estes and Christian (1971) 150 patients (%)	Dubois <i>et al.</i> (1974) 520 patients (%)
Skin lesions	84	86.3	81	71.5
Raynaud's phenomenon	32	45.4	21	18.4
Alopecia	64	38.2	37	21.0
Oral ulcers	34	29.0	7	9.1
Arthritis	98	61.8	95	91.9
Nephritis	40	49.0	53	46.1
Pleurisy	52	30.9	48	45.0
Pericarditis	20	24.5	38	30.5
Neuropsychiatric	50	40.0	59	25.5

Table 4 Mucocutaneous manifestations of SLE in 50 patients

Manifestation	Per cent
Cutaneous vasculitis	70
Facial rash	68
Alopecia	64
Positive Shirmer's test	40
Mouth ulcers	34
Raynaud's phenomenon	32
Photosensitivity	28
Purpura	24
Subcutaneous nodules	22
Discoid lesions	20

MUSCULOSKELETAL MANIFESTATIONS (TABLE 5)

Polyarthritis or arthralgia was recorded in 49 of the 50 patients and was the presenting feature in 31 patients. Jaccoud's deformity (Bywaters, 1975) was seen in 3 patients and small radiological erosions in a further 3 patients. Avascular necrosis of bone was detected in 3 patients. One patient, with severe bilateral femoral head involvement, underwent bilateral total hip replacement. One male patient had bilateral knee joint involvement with only mild symptoms. One female had avascular necrosis of a carpal lunate. All 3 patients had been on long-term maintenance doses of prednisone, one patient having received 5 mg/day for 6 years, one 10 mg/day for 12 years, and the third 10 mg/day for 15 years.

Sixteen patients described recurrent episodes of muscular pain, particularly affecting the proximal muscles, and sometimes associated with tenderness.

Table 5 Musculoskeletal manifestations in 50 patients

Manifestation	Per cent
Nondeforming arthritis or arthralgia	88
Deforming arthritis	10
Avascular necrosis	6
Erosions	6
Myalgia or myositis	32
Tendon contractures	12

Serum muscle enzyme levels were measured frequently, but raised levels were found in only 2 patients. Varying degrees of proximal weakness in some patients were attributed to corticosteroid myopathy. 6 patients developed gradual contractures of the flexor muscles and tendons of the forearms leading to 'clawing' of the fingers. This led to considerable pain and disability in one, despite regular splinting and physiotherapy.

PULMONARY MANIFESTATIONS (TABLE 6)

Pulmonary manifestations attributable to SLE were found in 41 patients. 32 patients had had symptoms at some stage. 26 had a history of pleuritic pain which was often recurrent. 20 complained of undue breathlessness on exertion.

The most common radiological abnormality was a raised diaphragm above the level of the anterior ends of the fifth ribs (9 patients). This was associated with basal linear shadows in 2 patients, but in 6 it was the only abnormality. 5 of the 26 patients with pleurisy showed pleural shadows on x-ray. Diffuse pulmonary infiltrates characteristic of lupus pneumonitis which were unresponsive to antibiotics but cleared with systemic corticosteroids were seen in 2 patients. Only 2 of the 29 perfusion scans were abnormal, and these abnormalities corresponded with lesions seen on x-ray.

Pulmonary function tests were performed on 42 patients, 13 of whom had never had respiratory symptoms. The results from 30 patients have been previously described (Gibson *et al.*, 1977). Functional abnormalities, defined as values below 80% of predicted, were found in 37 of the patients (88%) including 8 of the 13 asymptomatic patients. Reduction of the carbon monoxide transfer factor (TLCO) was found in all 37 patients. The diffusion constant, KCO (calculated by dividing the TLCO by the alveolar volume) was reduced in 23 of these patients, but was normal in the remaining 14. Reduced lung volumes (present in 41%) appeared to account for most of the total lung diffusion

abnormalities in this latter group, as the total lung capacity (TLC) was reduced in 13 of the 14 patients with normal KCO.

Only 4 patients had abnormalities of both TLC and KCO. Overall, there was a highly significant negative correlation between KCO and TLC. All 5 patients with normal respiratory function tests were asymptomatic and had normal x-rays. In 7 of the patients with the smallest lung volumes, measurements of static pressure volume curves and of mouth pressures during maximum efforts indicated extra-pulmonary volume restriction. In 5 of these patients diaphragm function was specifically assessed and found to be grossly abnormal in 4. No correlation was found between pleurisy or lung function abnormalities and any other manifestation of SLE.

RENAL MANIFESTATIONS (TABLE 7)

Renal involvement was defined as at least one of the following: cellular casts in the urine, haematuria (5 or more red blood cells per high power field), serum creatinine $>150 \mu\text{mol/l}$, proteinuria of at least 1 g/24 h, or histological changes compatible with SLE on renal biopsy. The indications for renal biopsy generally were persistent urinary or renal function abnormalities, usually in association with hypocomplementaemia. Each biopsy was examined by light and electron microscopy and by immunofluorescence.

By these criteria, lupus nephritis was diagnosed in 20 (40%) of the 50 patients. 15 patients had abnormalities in the urine. 5 had impaired renal function. Renal biopsy was attempted in 19 patients (38%) and was successful in 18. One patient, with normal urinalysis but persistent hypocomplementaemia had normal renal histology. Two biopsies showed mesangial changes with mild hypercellularity and capillary basement membrane thickening and immunofluorescence showed immunoglobulin and complement deposition confined to the mesangium. Proliferative glomerulonephritis was present in 14 biopsies. In 5, the changes were mild and generally focal, affecting only portions of some glomeruli. 6 patients had more severe proliferative changes and these patients had the most marked abnormalities in the urine. One of these patients died in chronic renal failure. Three biopsies showed old or inactive proliferative changes with sclerosis.

Table 6 Pulmonary manifestations in 50 patients

Manifestation	Per cent
Pleurisy	52
Dyspnoea	40
Abnormal chest x-ray	38
High diaphragm	18
Pleural thickening	12
Basal line shadows	8
Diffuse infiltrates	6
Perfusion scan abnormality	6.9*
Pulmonary function abnormality	88.1†
Small volume lungs	40.5†
Diffusion defect	88.1†

*29 patients studied; †42 patients studied.

Table 7 Renal manifestations in 50 patients

Manifestation	Per cent
Proteinuria ($>1 \text{ g/24 h}$)	26
Abnormal urine sediment	30
Raised serum creatinine	10
Abnormal histology	34

Membranous glomerulonephritis with widespread basement membrane thickening, but without cellular proliferation was seen in one patient.

Fourteen of the 20 patients with lupus nephritis, including 13 of the 17 with abnormal histology, had a low serum complement (C3) recorded on more than one occasion during the period of observation. 14 of the 30 other patients who did not have lupus nephritis as defined above also had a low C3. There was no statistically significant difference in the cumulative incidence of hypocomplementaemia in the patients who developed clinically manifest nephritis at some stage during their period of observation and those who did not. It is very possible that the incidence of renal involvement in this series as in other series, has been underestimated. Abnormal histology was found in 3 patients with normal urinalysis and renal function but who had hypocomplementaemia. This has been found previously (Baldwin and Gallo, 1975; Lee *et al.*, 1977).

NEUROPSYCHIATRIC MANIFESTATIONS (TABLE 8)

Neuropsychiatric manifestations were observed in 25 patients (50%). Organic brain syndromes, characterised by impairment of orientation, perception, memory, or intellectual function of judgment (Klippel and Zvaifler, 1975), were seen in 9 patients. Additional neurological manifestations were associated in 8 of these patients. Onset was often sudden and dramatic and precipitated by stress as occurred in one patient during school examinations and another on the morning of her wedding. Corticosteroid side effects were not thought to be responsible for any of the episodes we observed. Several patients improved rapidly after an increased dose of prednisone.

Nonorganic syndromes, particularly depression, of severity such that the attending physician modified the patient's treatment for this reason, were seen in 11 patients. Lesser degrees of depression and anxiety and other symptoms which could not with

certainty be attributed to SLE were also very common.

Fourteen patients described severe, recurrent headaches, often of a migranous type. 2 patients reported transient episodes of memory deterioration. 8 patients had isolated cranial nerve abnormalities. The most common was intermittent diplopia which occurred in 5. Recurrent transient ptosis, unresponsive to intravenous edrophonium chloride (Tensilon) was observed in 3 patients. We have been unable to find previous reports of this complication. One patient had intermittent nerve deafness. 7 patients developed seizures in the absence of uraemia, hypertension, or infection. One of these patients in whom fitting was accompanied by a rapid deterioration in the level of consciousness, was found at post mortem to have a large intracerebral infarct. One of the 3 patients who developed peripheral neuropathy had a severe predominantly sensory polyneuropathy associated with a high cerebrospinal fluid protein suggestive of the Guillain-Barré syndrome. Typical cerebrovascular accident syndromes occurred in 3 patients aged 16, 19, and 46 years. 2 patients developed chorea which persisted in one for over 2 years.

A previous report from this unit pointed out that no single test or group of tests will establish a definite diagnosis of cerebral lupus (Bennett *et al.*, 1972). The electroencephalogram (EEG) was the most frequently abnormal investigation performed in this study. Of the 39 patients studied during the 48-hour hospital admission, abnormal EEGs were recorded in 10 of the 11 patients who had neuropsychiatric manifestations at that time, 7 of the 11 patients who had had neuropsychiatric manifestations 4 months to 12 years before but were asymptomatic at the time of testing, and 7 of the 17 patients who had no past or current clinical evidence of neuropsychiatric involvement. The best correlation was found in the 9 patients with organic brain syndromes, all of whom had abnormal EEGs. The most frequent pattern of abnormality was diffuse slow wave activity, but some had definite focal features or a combination of the two. Brain scan abnormalities were unusual, being found in only 3 of 37 patients tested. Fluorescein angiography showed capillary leakage in 11 of 24 patients studied, 3 of whom had no other evidence of cerebral lupus (Edmonds *et al.*, 1975).

No correlation could be found between neuropsychiatric involvement and other manifestations. The group of 25 patients with clinical neuropsychiatric manifestations also included 23 of the 41 with lymphopenia, 20 of the 35 with cutaneous vasculitis, and 9 of the 13 with thrombocytopenia, but none of these associations was statistically

Table 8 Neuropsychiatric manifestations in 50 patients

Manifestation	Per cent
All neuropsychiatric abnormalities	50
Nonorganic syndromes	22
Organic brain syndromes	18
Cranial neuropathies	16
Recurrent ptosis	6
Seizures	14
Peripheral neuropathies	6
Strokes	6
Abnormal movements	4
Abnormal EEG	62*
Abnormal brain scan	16†
Fluorescein angiography abnormalities	46‡

*39 patients tested; †37 patients tested; ‡24 patients tested.

significant. Lupus nephritis was equally prevalent in those patients with and without neuropsychiatric involvement.

HAEMATOLOGICAL MANIFESTATIONS (TABLE 9)

The lower limit of normal for haemoglobin was arbitrarily defined as 11 g/dl, leucocyte count $4.0 \times 10^9/l$, lymphocytes $1.2 \times 10^9/l$, and platelets $120 \times 10^9/l$. An abnormality was recorded if two or more measurements made on separate occasions, in the absence of drugs likely to depress bone marrow function, were below normal.

Anaemia was most commonly normochromic, normocytic. 8 patients had positive Coombs's test. Leucopenia was noted in 23 (46%) patients, but an absolute lymphopenia was found to be much more common (41 patients). Mild thrombocytopenia occurred in 13 (26%).

SEROLOGICAL MANIFESTATIONS (TABLE 10)

Serum from all patients contained antinuclear antibodies. Anti-DNA antibodies were also present in all patients at some stage during the observation period. Anti-ENA (extractable nuclear antigens) antibodies were found in 20% of patients. There was no correlation between anti-ENA antibodies, anti-ribonucleoprotein antibody, or anti-Sm antibody and individual clinical features (Bresnihan *et al.*, 1977b). Lymphocytotoxic antibodies were present in 80% of patients and correlated quantitatively with the presence of neuropsychiatric ($P < 0.001$) and cutaneous ($P < 0.004$) manifestations (Bresnihan

et al., 1978). The LE cell test was performed infrequently during the latter part of the study, but was positive in 29 of 34 patients tested (85%). Raised gammaglobulins in excess of 1.5 g/100 ml was observed in 63%. IgG was raised in 22% of patients, IgA in 13%, and IgM in 9%. 4 patients had mild reduction of one or more immunoglobulin fractions but very low levels were not recorded.

OBSTETRIC AND GYNAECOLOGICAL MANIFESTATIONS

A more detailed study of SLE and pregnancy in a larger group of patients has been reported elsewhere (Grigor *et al.*, 1977). 37 female patients were aged between 15 and 45 years at the time of the study. Secondary amenorrhoea of more than 3 months duration occurred in 10 (27%). 9 patients were taking a mixed hormone contraceptive tablet without obvious deleterious effects on the course of their SLE. In one patient onset of the disease coincided with the start of oral contraceptive therapy.

Twenty-five pregnancies have occurred in 15 patients since the onset of clinical manifestations of SLE. Of these, 7 (25%) ended in spontaneous abortion or stillbirth, while the remainder resulted in normal deliveries. Exacerbations of disease activity, sufficient to require increased corticosteroid dose, occurred in association with 10 pregnancies, most commonly during the puerperium. In 3 patients the first clinical manifestations of SLE occurred during pregnancy. 50 pregnancies occurred in 15 patients before the onset of clinical manifestations of SLE, of which 15 (30%) ended in fetal death.

PATIENT SELECTION

In Table 11 the major clinical manifestation of the 50 study patients are summarised and compared with the overall incidence. The incidence of pulmonary, cardiac, neuropsychiatric, and haematological manifestations were similar but minor differences in the incidence of skin and joint manifestations and of nephritis were seen, possibly

Table 9 Reticuloendothelial and haematological manifestations in 50 patients

Manifestation	Per cent
Lymphadenopathy	30
Splenomegaly	16
Anaemia	52
Haemolytic anaemia	12
Leucopenia	46
Lymphopenia	82
Thrombocytopenia	26

Table 10 Serological manifestations in 50 patients

Manifestation	Per cent
Antinuclear antibodies	100
Anti-DNA antibodies	100
Anti-ENA antibodies	20
LE cells	85
Lymphocytotoxic antibodies	80
Cryoglobulins	67
Hypergammaglobulinaemia	63
Hypocomplementaemia	56
Coombs's test positive	41
RA Latex	20
False positive VDRL	11

Table 11 Cumulative major clinical manifestations of SLE in 50 study patients compared with the total series of 121 SLE patients

Manifestation	Study patients (n = 50) (%)	Total (n = 121) (%)
Cutaneous	98	85
Musculoarticular	98	90
Pulmonary	64	61
Cardiac	20	18
Neuropsychiatric	50	43
Renal	40	54
Haematological	60	56

reflecting the tendency for the specialty units to attract patients whose major manifestation was related to that specialty.

INFECTIONS

Major infection producing systemic manifestations and requiring parenteral antibiotics developed in 8 patients on 10 occasions. 6 patients developed pneumonia, 2 septicaemia, and 1 a puerperal infection. Septicaemia was considered to be the cause of death in one patient. 7 of the 8 patients were on corticosteroids at the time of the infection and 3 were taking immunosuppressives.

DRUG THERAPY

One of the objectives of this study was to assess relatively conservative therapeutic regimens in SLE. Thus the average daily dose of prednisone used was 7.5 mg. 6 of the 50 patients have never received corticosteroids. The mean duration of prednisone administration in 44 patients was 22.3 months. Only 3 patients received prolonged high dose (>20 mg/day) prednisone. The benefits of low-dose steroid administration were reflected by the low incidence of steroid side effects. Serious infections were rare and aseptic necrosis of bone was seen in only 3 patients.

The most frequently prescribed nonsteroidal drug were aspirin, indomethacin, and propionic acid derivatives. These drugs usually controlled fever, arthritis, and serositis. In 3 patients transient disturbance of liver enzymes were seen during aspirin administration. Chloroquine was used for periods of up to 1 year in 6 patients. 16 patients with nephritis received azathioprine or cyclophosphamide. We did not attempt to evaluate the effect of different immunosuppressive drug regimens.

PROGNOSIS

The 50 patients were followed for a total of 1433 patient months, average 28.7 months, range 1 week (patient died) to 72 months. 3 patients (6%) died, of chronic renal failure, cerebral infarction, and septicaemia. Another 3 patients were lost to follow-up.

Survival was calculated using the time of entry to the study as the starting point (Merrell and Shulman, 1955). On this basis the overall estimated survival for the patients in the study at 5 years was 98% and at 10 years 76.7%. The average duration of disease from the time of initial manifestation until entry into the study was 7.7 years. Using the first symptom as starting point, the estimated 5-year survival was 98%, and 10 year survival 89.4%. The time of diagnosis was not used as a starting point as it had usually been made in another centre and exact

timing was difficult to determine. The indications for using various starting points for calculation of survival rates has been discussed by Fries *et al.* (1974) and Lee *et al.* (1977).

The survival figures reflect the steadily improving life expectancy that has been described in SLE since 1954. Merrill and Shulman (1955) reported 51% estimated survival for 4 years. Kellum and Haserick (1964) reported a 5-year survival of 69%, Estes and Christian (1971) 77%, and Lee *et al.* (1977) 91%.

The striking improvement in prognosis recorded in recent series may be attributed to a number of factors, of which the most important is the recognition of milder forms of the disease. This trend is continued in this study, the first prospective analysis made after the introduction of assays for anti-DNA antibody. Our observations favour a more conservative approach to the management of SLE.

Conclusions

(1) 50% of the patients had clinical evidence of neuropsychiatric involvement. Investigation showed a further 16% with clinical neurological abnormalities. The electroencephalogram was the most frequently abnormal investigation. (2) Lupus nephritis was detected in 50% of patients, but did not correlate with other clinical features, including hypocomplementaemia. There was no negative association with neuropsychiatric involvement. (3) 64% had symptoms of lung involvement. Abnormalities in pulmonary function tests, particularly volume studies, showed subclinical involvement in a further 18%. (4) The majority required either no corticosteroids or relatively low doses, and corticosteroid-induced complications were rare. (5) The estimated mean 5-year survival from the time of entry to the study was 98%.

References

- Baldwin, D. S., and Gallo, G. R. (1975). Lupus nephritis. *Clinics in Rheumatic Diseases*, 1, 639-663.
- Bennett, R., Hughes, G. R. V., Bywaters, E. G. L., and Holt, P. J. L. (1972). Neuropsychiatric problems in systemic lupus erythematosus. *British Medical Journal*, 4, 342-345.
- Bresnihan, B., Bunn, C., Snaith, M. L., and Hughes, G. R. V. (1977a). Antiribonucleoprotein antibodies in the connective tissue diseases. Estimation by counter-immunoelectrophoresis. *British Medical Journal*, 1, 610-612.
- Bresnihan, B., Grigor, R., and Hughes, G. R. V. (1977b). Prospective analysis of antiribonucleoprotein antibodies in systemic lupus erythematosus. *Annals of the Rheumatic Diseases*, 36, 557-559.
- Bresnihan, B., Grigor, Oliver, M., and Hughes, G. R. V. (1978). A prospective analysis of lymphocytotoxic antibodies in systemic lupus erythematosus. Submitted for publication.
- Bywaters, E. G. L. (1975). Jaccoud's syndrome. A sequel to the joint involvement in systemic lupus erythematosus. *Clinics in Rheumatic Diseases*, 1, 125-148.

- Cohen, A. S., Reynolds, W. E., Franklin, E. C., Kulka, J. P., Ropes, M. W., Shulman, L. E., and Wallace, S. L. (1971). Preliminary criteria for the classification of systemic lupus erythematosus. *Bulletin on Rheumatic Diseases*, **21**, 643-648.
- Dubois, E. L., Wierzbowski, M., Cox, M. B., and Weiner, J. M. (1974). Duration and death in systemic lupus erythematosus. *Journal of the American Medical Association*, **227**, 1399-1402.
- Edmonds, J. P., Hughes, G. R. V., Darvell, R., and Kohner, E. M. (1975). Brain scan, electroencephalogram and retinal fluorescein angiography in the assessment of cerebral systemic lupus erythematosus. *Scandinavian Journal of Rheumatology*, **4**, Suppl. 8, 39.
- Estes, D., and Christian, C. L. (1971). The natural history of systemic lupus erythematosus by prospective analysis. *Medicine*, **50**, 85-95.
- Fries, J. F., and Holman, H. R. (1975). Systemic lupus erythematosus: a clinical analysis. *Major Problems in Internal Medicine*, Vol. 6. Ed. by L. H. Smith. Saunders, Philadelphia.
- Fries, J. F., Weyer, S., and Holman, H. R. (1974). Estimating prognosis in systemic lupus erythematosus. *American Journal of Medicine*, **57**, 561-565.
- Gibson, J. G., Edmonds, J. P., and Hughes, G. R. V. (1977). Diaphragm function and lung involvement in systemic lupus erythematosus. *American Journal of Medicine*, (in press).
- Grigor, R. R., Shervington, P. C., Hughes, G. R. V., and Hawkins, D. F. (1977). Outcome of pregnancy in systemic lupus erythematosus. *Proceedings of the Royal Society of Medicine*, **70**, 99-100.
- Holborow, E. J., Weir, D. M., and Johnson, G. D. (1957). A serum factor in lupus erythematosus with affinity for tissue nuclei. *British Medical Journal*, **2**, 732-734.
- Kellum, R. E., and Haserick, J. R. (1964). Systemic lupus erythematosus, a statistical evaluation of mortality based on a consecutive series of 299 patients. *Archives of Internal Medicine*, **113**, 200-207.
- Klippel, J. H., and Zvaifler, N. J. (1975). Neuropsychiatric abnormalities in systemic lupus erythematosus. *Clinics in Rheumatic Diseases*, **1**, 621-638.
- Kurata, N., and Tan, E. M. (1976). Identification of antibodies to nuclear acidic antigens by counter-immune electrophoresis. *Arthritis and Rheumatism*, **19**, 574-580.
- Lee, P., Urowitz, A. M. B., Bookman, A. A. M., Koehler, B. E., Smythe, H. A., Gordon, D. A., and Ogryzlo, M. A. (1977). Systemic lupus erythematosus. *Quarterly Journal of Medicine*, **46**, 1-32.
- Lewkonja, R. M., Barth, P. T., Hale, G. M., and Hughes, G. R. V. (1977). Specificity and clinical relevance of antibodies to double-stranded DNA. *Annals of the Rheumatic Disease*, **36**, Suppl. 1, 114-118.
- Merrell, M., and Shulman, L. E. (1955). Determination of prognosis in chronic disease illustrated by systemic lupus erythematosus. *Journal of Chronic Diseases*, **1**, 12-32.
- Novotny, H. R., and Alvis, D. L. (1961). A method of photographing fluorescence in circulating blood in the human retina. *Circulation*, **24**, 82-86.
- Pincus, T., Schur, P. H., Rose, J. A., Decker, J. L., and Talal, N. (1969). Measurement of serum DNA-binding activity in systemic lupus erythematosus. *New England Journal of Medicine*, **281**, 701-705.
- Sharp, G. C., Irvin, W. S., Tan, E. M., Gould, R. C., and Holman, H. R. (1972). Mixed connective tissue disease: an apparently distinct rheumatic syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). *American Journal of Medicine*, **52**, 148-159.
- Terasaki, P. I., and McClelland, J. D. (1964). Microdroplet assay of human serum cytotoxins. *Nature*, **204**, 998-1000.