diverse as branding cattle and treating warts. Oils from some species—for example, croton—were formerly used as over-draught purges.

Even if the offending plant is eventually identified, as in the American cases, the exact nature of the reaction may remain a puzzle, for plants attack the animal kingdom in a variety of ways. The possibilities that have to be considered include mechanical or chemical irritation, phototoxic reactions, and true allergic sensitisation.

Mechanical irritation from spines, thorns, and specialised bristles is usually obvious. Some plants combine this with chemical irritation. *Mucuna pruriens*, for example, the itch plant, is a member of the bean family whose seed pods are covered with short barbed spicules: these are the main ingredient of itch powder so popular with practical jokers. The itch is actually caused by a proteolytic enzyme, mucunain, studies of which have greatly advanced our knowledge of the physiology of itching.²

Phototoxic reactions are caused by contact with a photosensitising compound, usually a psoralen similar to those used in the photochemotherapy of psoriasis, followed by exposure to sunlight. The mechanism is not immunological, so that reactions can occur on first exposure. Blisters may form, and the residual pigmentation may last many months. Notorious offenders include the Umbelliferae (which cause reactions among celery harvesters, carrot processors, and those in contact with giant hogweed) and the Rutaceae, such as the gas plant and the bergamot orange. Although the creeping spurge eruptions were bullous and mainly on exposed parts, phototoxicity seems to be unlikely with the Euphorbiaceae.

An allergic contact dermatitis is by far the most common reaction to plants. In the United States the rhus group (poison

ivy and poison oak) causes more sensitisation than all the other plants put together. The oleoresin content of their sap is such a powerful sensitiser that allergy may follow a single exposure, and over a quarter of North Americans are thought to react to it. In Europe, *Primula obconica* heads the list: about 5% of all women patchtested to it in Copenhagen gave positive reactions. Both rhus and primula eruptions usually consist of linear streaks or patches of erythema and vesication. Reactions to pollen give a quite different picture, with chronic erythema and scaling on the exposed parts, such as the face, neck, and hands, which may mimic a chronic photodermatitis or neurodermatitis, but with exacerbations occurring during the pollen seasons. The pollen of chrysanthemums needs prolonged contact to sensitise, so that allergy often affects florists and horticulturists, with exacerbations occurring in the autumn.

The punishment inflicted by creeping spurge has served to highlight the problems of plant reactions in general. Mechanical irritation and phototoxicity seem unlikely mechanisms, and chemical irritation is the most likely cause, although a contact allergy is still possible, as the authors admit¹—especially as other members of the Euphorbiaceae can cause true sensitisation.³ The patients who reacted to creeping spurge were not patchtested to the plant or its extracts, but that is the only way in which allergy and irritation can be separated. Even by using this technique, however, allergic and irritant reactions may look very similar and control patients have to be tested also. Until such testing has been done the mystery of the creeping spurge must remain unsolved.

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Regular Review

Systemic lupus erythematosus: treatment and prognosis

GRAHAM R V HUGHES

A 33-year-old schoolteacher had presented at the age of 28 with a two-year history of intermittent joint pains and stiffness in the hands. In addition she had suffered for several years from intermittent migrainous headaches. Some eight years previously she had been investigated for epilepsy and depression.

The only abnormal physical finding was mild flexor tendonitis. Investigations showed a sedimentation rate of 80, a strongly positive antinuclear antibody test, DNA binding values of 80% (Farr technique), a low total haemolytic complement, and high-titre circulating complexes. There was no evidence of renal disease. Systemic lupus erythematosus was diagnosed.

For the next five years she was treated intermittently with non-steroidal anti-inflammatory drugs. She has remained well and at work and has married and had two normal pregnancies. There has been no evidence of renal disease. During that time her DNA binding values have

never fallen below 70%, serum immune complex titres have remained high, and total complement levels have fluctuated.

Traditions die hard. The diagnosis of systemic lupus erythematosus (SLE) all too often evokes a set of medical reflexes that include treatment with high dosages of steroids, advice against pregnancy, an assumption that nephritis is an inevitable sequel, and a gloomy prognosis.

During the past two decades the development of sensitive antinuclear antibody tests has contributed to a recognition that SLE is a far commoner and in most patients a milder disease than was once thought.

Present statistics suggest a prevalence of up to 1 in 2000 for women.¹ Nevertheless, in some communities such as black women in the United States, the West Indies, and South Africa the prevalence may be as high as 1 in 250^{1 2} and similar

epidemic figures are being described from Hong Kong, Singapore, and even mainland China.

The prevalence in Britain is unknown. In 1970 a lupus clinic was instituted at the Hammersmith Hospital, in which some 300 patients have been seen. The number of cases seen with mild or fluctuating disease suggests that every general practitioner, rheumatologist, psychiatrist, or physician may be seeing undiagnosed patients with SLE masquerading as "seronegative arthritis," tendinitis, migraine, depression, or epilepsy.

The case for conservative treatment—In severe SLE the value of corticosteroids is undoubted and frequently lifesaving. Nevertheless, some of the currently accepted clinical and serological indications for steroid treatment (such as mild neuropsychiatric disease, arthritis, high titres of DNA antibodies, or circulating complexes) are being reassessed.³ One aim of a prospective study of SLE in progress in this unit since 1970 has been to assess the outcome of a more conservative approach to treatment using, where possible, low doses of prednisolone daily or on alternate days.³ Even in the presence of active renal or neuropsychiatric disease doses of over 50 mg of prednisolone daily have been the exception. This approach, requiring as it does a continuous "fine tuning" of treatment, is laborious but already appears to have reduced overall morbidity.

A preliminary report has been published.⁴ The main conclusions agree with those of other recent studies. The estimated five-year survival was 98%. The mean prednisolone dosage was 7.5 mg daily in 1433 patient-months of study, and most patients could ultimately be weaned off prednisolone altogether or managed by doses of 7.5 mg-15 mg on alternate days. Apart from the presence of severe renal or cardiac disease, there was no medical contraindication to pregnancy.⁵ Infection in SLE was almost totally confined to those patients receiving corticosteroids. No new cases of aseptic bone necrosis were seen in patients entering the study. Neuropsychiatric disease waxed and waned in severity. No fatal central nervous system disease could be attributed to an over-conservative approach to patients with psychiatric features alone.⁶ The presence of abnormal serological findings was not itself an indication for treatment. With the possible exception of diffuse renal lesions, the severity of disease at presentation did not necessarily preclude subsequent remission, and in several patients the disease took a "one-shot" form. An interesting, though as yet unrecognised, concept is that of "transient lupus." Several patients have been seen in whom SLE (positive serologically and fulfilling American Rheumatism Association criteria) has presented with acute "viral" symptoms, pursued a transient course of several weeks or months, and subsequently gone into apparent total remission. (These cases are not included in the present discussion.)

Routine management—We have devised a two-day "protocol" for investigation of new referred patients. This includes full serological testing, as well as full tests of respiratory, renal, and cerebral function. Our indications for renal biopsy in SLE are as inconsistent as those of most others treating this disease. For patients wishing to learn more of the disease, a British Lupus Society has now been formed.*

Drug reactions and allergies are common problems. Ultra-violet light converts DNA into thymine dimers, which are highly antigenic.⁷ While this may occur in skin exposed to sunlight, attempts at measurement of ultraviolet DNA antibodies in the serum have not been successful, and there is

no way of forecasting which of the patients (around half) will develop photosensitisation. There has been a resurgence of interest in hormonal effects in SLE and in immune responses in general.⁸ The 9:1 female-to-male ratio and the occasional association of Klinefelter's syndrome with SLE in men all point to a hormonal influence. Although the vast majority of patients with SLE tolerate oral contraceptives, exacerbations of the disease have been reported in patients given oestrogens of any kind.^{8,9}

Sulphonamides frequently cause exacerbations of SLE and are best avoided. Penicillin may be used with circumspection. Drugs such as hydralazine known to cause a lupus-like syndrome (also including penicillamine, anti-epileptics, and antituberculous agents) are not, on present evidence, contraindicated in idiopathic SLE.¹⁰

Aspirin may cause problems in higher doses because of hepatotoxicity. Seaman and Plotz¹¹ found raised activities of liver enzymes in seven of 16 patients and in a retrospective study noted that 13 out of 14 patients developed raised concentrations of transaminase within three weeks of beginning aspirin. In our clinic five patients were found to develop raised transaminase concentrations while receiving 1.8 to 3.6 g aspirin daily.¹² The concentrations returned to normal within two to seven weeks of stopping aspirin. Rechallenge with diflunisal (which does not contain the *o*-acetyl moiety of aspirin) caused no signs of hepatotoxicity.

A further effect of aspirin in SLE is a mild reduction in the glomerular filtration rate.^{12,13} Kimberly¹⁴ observed that the rise in creatinine concentration was more appreciable in patients with mild renal impairment and suggested that the cause might be interference with a prostaglandin-dependent compensatory mechanism related to renal blood flow.

Non-steroidal anti-inflammatory agents may similarly affect the glomerular filtration rate¹⁴ but they are both widely used and valuable. Occasional idiosyncrasies including fever, rash, and abdominal pain have been described in patients with SLE on ibuprofen.^{15,16}

The pendulum has swung firmly back towards the use of antimalarials in SLE,¹⁷ particularly in patients with arthritis and skin lesions. Though they have been used in treating discoid LE since 1894, their mechanism of action is unknown. In a comprehensive review Dubois has suggested that retinal toxicity is not a problem with the smaller doses (such as hydroxy-chloroquine 200 mg daily) now recommended. None the less the eyes should be checked every six months.

Corticosteroids—How much individual variation there is in steroid prescribing was shown recently by Wasner and Fries,¹⁸ who surveyed prescribing practices among 200 clinicians given eight hypothetical patients with SLE. Rheumatologists and nephrologists showed several differences in practice, the latter using immunosuppressive agents twice as frequently in early disease. A reflection on current medical practice was the size and duration of corticosteroid doses used—for patients with disease in the central nervous system all those questioned used 60-80 mg daily as a matter of course, tapering to a mean of 33 mg daily after three months.

Corticosteroids contribute to morbidity figures. Sergeant *et al*¹⁹ looked at the management of brain lupus retrospectively and concluded that death rates from steroid-associated opportunistic infection were probably higher than from the underlying condition. There is an almost linear relationship between the dose and duration of steroid dosage and incidence of aseptic necrosis of bone.²⁰ Despite the number of immunological and other reasons²¹ for the tendency to infection in SLE, corticosteroid treatment seems to be the main factor in

*The Lupus Society, c/o British Rheumatism and Arthritis Association, 6 Grosvenor Crescent, London SW1X 7ER.

most cases^{22 23}; the incidence of infection rises steeply at doses over 30 mg prednisolone daily.²³

There is still some disagreement about the use of immunosuppressives in SLE.²⁴ Though cyclophosphamide is more rapid in action azathioprine is less toxic and is now the drug of choice.²⁵ Most authors advocate combination of azathioprine with steroids in active (especially diffuse proliferative) nephritis.²⁶⁻²⁹ Perhaps the main value of azathioprine is as a "steroid-sparing" drug. In a 12-year follow-up of 47 patients with SLE and with severe renal SLE treated with combination treatment Barnett *et al*³⁰ reported an 82% survival at five years and 74% at 10 years. Of the eight deaths, five were due to infection, and they concluded that the lower doses of steroids that can be used with azathioprine "cover" contributed to the good survival—a view supported by Cameron *et al*²⁹ in their analysis of management of lupus nephritis.

The place of plasmapheresis in SLE was discussed at a recent workshop,³¹ which concluded that its clinical effect is unpredictable. The most consistent benefit has been with vasculitis and arthritis, though improvement has been temporary. The optimum regimen seems to be four-litre exchanges in combination with immunosuppressive drugs. DNA antibody and complexes are removed by plasmapheresis; but the extent is influenced by many factors, one of which may be the degree of "saturation" of the reticuloendothelial system.³²

Though the procedure is expensive, it is relatively safe. Despite the number of studies reported,³²⁻³⁵ however, the data are still largely anecdotal and the value of the treatment cannot be said to be proved for any single manifestation of SLE. Nevertheless, from a practical point of view, the temporary improvement seen in vasculitis suggests that it might prove a "time-buying" manoeuvre in the patient with fulminant generalised vasculitis or vasculitis affecting the central nervous system.

Management of renal lupus—Analysis of nine recent series of patients with lupus nephritis (reviewed by Cameron²⁹) showed the histological distribution to be focal glomerulonephritis (31%), membranous (13%), and diffuse proliferative (53%). Baldwin³⁶ has suggested that immunosuppressive treatment is of value only in the last group, with the caveat that mild SLE nephritis may occasionally transform into more severe forms.^{36 37}

Most reports of renal SLE have been based on follow-ups of fewer than five years. The recent study by Cameron *et al*²⁹ reported on 71 patients with SLE and nephritis seen during a 15-year period and followed for a mean of seven years. There was no mean difference in survival in the different histological groups, neither was there a prognostic difference between those who presented with nephrotic syndrome and without.

Most patients with mild lesions were treated with steroids alone, while most of those with histological evidence of moderate or severe disease were given combination treatment (usually azathioprine with prednisolone). Using azathioprine for its steroid-sparing effect (perhaps earlier than had been favoured by previous authors), Cameron *et al*²⁹ reported a far lower mortality and a lower infection rate. Their data provided an impressive argument for more conservative steroid treatment, if necessary under azathioprine cover.

Management of brain lupus—This is one of the most difficult problems of SLE. As with other aspects of the disease, there is a wide discrepancy between the teaching of older textbooks and current experience. Up to five years ago, disease extending to the central nervous system was universally regarded as a grave feature, and even patients with SLE psychosis were

generally treated with 80 mg, 160 mg, and even higher daily prednisolone doses. While these heroic regimens were occasionally effective, possibly the tendency developed to overtreat all aspects of central nervous system lupus. In the patient with widespread vasculitis, convulsions, and focal signs there is little choice other than to "try anything." The problem is, however, more difficult in the patient with mild neuropsychiatric illness.

Conventional neurological investigation and serological tests are of limited value^{4 38 39} though the recent finding of an antineuronal IgG antibody in SLE⁴⁰ suggests that new serological guides may be available before long. Recent studies⁶ have indicated that neuropsychiatric lesions, especially mild forms, may be one of the most common features of SLE. Certainly, neuropsychiatric symptoms fluctuate widely, and in some episodes improvement occurs spontaneously given time (the figure is unknown). For the patient with non-focal neuropsychiatric disease massive increases in steroid dosage are probably unwarranted.

Pregnancy—About two-thirds of the patients referred to the lupus clinic at Hammersmith have been advised against pregnancy. That this advice is wrong has been reiterated in many studies.^{6 41-43} In our own cases⁵ even the presence of mild renal impairment has been no contraindication to pregnancy, and the fertility rate has been higher than the national average. Two recurring problems, however, are a tendency to spontaneous abortion (the finding that antilymphocyte antibodies cross-react with placental trophoblast may have pathogenetic implications⁴⁴) and an increased incidence of lupus "flares" in the puerperium.

Serological tests—DNA-binding activity^{45 46} has proved one of the most valuable diagnostic tests in the connective tissue diseases. Nevertheless, though raised titres may predict SLE flares, this is not a universal finding—indeed, we are currently following several patients with several years' continuous high DNA binding values in the absence of significant clinical disease. Thus DNA binding values are less than accurate guides to the pattern of disease in the individual patient and may be oversensitive as an index of disease activity.^{3 47}

Despite the importance of immune complexes in the understanding of the pathogenesis of SLE,⁴⁸ their kinetics are complicated, and too much value should not be placed on static measurements using a single test.⁴⁹ Thus high C1q binding values, for example, do not necessarily indicate renal disease. Indeed, recent studies of C1q binding values in our patients (unpublished) have shown a similar scatter in patients with and without renal lesions.

Prognosis—Prognosis hinges on the definition of the disease. Even by using the ARA criteria,⁵⁰ which have been widely criticised as including only more severe or "classical" disease, the prognosis has clearly improved dramatically in the past two decades (see figure). Recent series from Toronto⁵¹ and

Hammersmith,⁴ both of which included all patients referred to different departments (including those of rheumatology, haematology, and nephrology), quoted five-year survival figures in the 90% range. If the milder (and transient) forms of lupus had been included these figures might have been even better. Even in patients with proved nephritis (which is currently reported in roughly half the cases, though this figure will fall as milder cases are increasingly recognised) the survival figures have improved from less than 10% in 1957⁵² to 80% and 76% five-year survival in the series of Morel-Morager *et al.*²⁶ and Cameron *et al.*²⁹

In individual patients the role of prognostic markers is still uncertain, though the efforts at defining subsets of cases, pioneered by Dubois⁵³ and Fries and Holman,⁵⁴ may be of

value. The disease may be milder in children⁵⁵ and in patients over 40,⁵⁶ though, as always, selection of cases may influence the figures.

The overall improvement must be ascribed mainly to a wider recognition of the disease. Possibly a further improvement in prognosis will occur when more clinicians appreciate that most patients with SLE do not have fulminant disease and that prolonged high-dose corticosteroid treatment is far from mandatory.

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