Current Practice

Systemic Lupus Erythematosus

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Patients suffering from systemic lupus erythematosus are frequently demonstrated at meetings and attract great interest, consequently doctors may be led to believe that this is a relatively common disease. However, at the General Infirmary at Leeds, for every case of systemic lupus erythematosus there are six cases of pernicious anaemia and ten of leukaemia. Thus experience in managing and treating a large number of cases is not easily obtained. I have been fortunate in seeing about 80 cases in the last ten years and have been able to assess both the long- and short-term problems of management. It used to be considered that the diagnosis of this condition in a young patient implied a very poor prognosis, but since the description of the L.E. cell phenomenon by Hargreaves and coworkers in 1948 and the development of other serological techniques our knowledge of the commoner subacute and chronic varieties of the condition has been extended, and many such patients have survived for 15 or more years in comparatively good health.

Systemic lupus erythematosus is a systemic disease with pathological changes affecting the connective tissues and vascular system. Clinical features^{1,2} include fever, rashes, arthritis, involvement of the kidneys, lungs, heart, and other organs. The onset usually is in early adult life, the peak age of onset being about 30 in females and nearly 40 in males. Approximately eight women are affected for every man. This characteristic female sex predominance and age distribution of the disease suggests that only certain individuals are predisposed to the disorder, the genotype probably involving three dominant X-linked alleles and also autosomal factors.³ The initiation of the disease may result from somatic mutation in stem cells of the lymphoid series which give rise to forbidden clones of lymphocytes carrying cellular autoantibodies. An endogenous defence mechanism, which tends to inhibit the development of these forbidden clones, may be interfered with by drugs, infections, and stress, thus precipitating clinical manifestations of the disorder. Drugs which have been implicated in precipitating or activating the disease include hydrallazine, sulphonamides, certain anticonvulsants such as diphenylhydantoin, methylthiouracil, and troxidone, procainamide, penicillin, and tetracycline.

Clinical Features

The initial manifestations vary, but at some time fever occurs in 90% of patients, a rash in 80%, involvement of the kidneys in about 67%, lymphadenopathy in 50%, central nervous system manifestations in 25%, pulmonary involvement in about 20%, and abdominal symptoms in 20%. In acute cases there is usually marked loss of weight, anorexia, malaise, fever, and joint pains. A variety of rashes may be

seen, of which the commonest is erythema on areas exposed to sunlight. Classically this presents a butterfly distribution on the cheeks. Other skin manifestations include purpura, bullous eruptions, reticulate telangiectatic erythema on the backs of the fingers, on the palms, and on the lateral borders of the feet, reticular livedo, leg ulcers, gangrene, dilatation of the nail-fold capillaries, necroses around the nail-folds, and cuticular haemorrhages. The hair may be unruly or there may be diffuse alopecia. Arthritis is common and may simulate rheumatoid arthritis. Cardiac manifestations include pericarditis, Libman-Sacks endocarditis, and myocarditis. Hypertension occurs in more than a third of the cases. Pleurisy, pneumonic episodes, and radiological mottling and reticulation of the lungs are not uncommon. Renal involvement with albuminuria and casts, nephrotic syndrome, and renal failure are extremely important, particularly with regard to prognosis. There may be epilepsy or peripheral neuritis, involvement of the eyes, a myopathy, and avascular bone necrosis. Hepatomegaly and splenomegaly also occur.

Laboratory Investigations

The diagnosis depends on suspecting the disorder in a patient suffering from symptoms and signs involving several organs, in association with the appropriate laboratory investigations. About three-quarters of the patients have an anaemia as a result of a deficiency of iron or from haemolysis or renal failure. The Coombs test may be positive in the absence of haemolytic anaemia. Usually there is leucopenia, but occasionally leucocytosis can occur. Thrombocytopenia is not infrequent, and the count is usually below 40,000 in patients presenting with thrombocytopenic purpura. Although the erythrocyte sedimentation rate is raised in about 90% of patients, it may be normal even in patients in an active stage. Elevation of gamma- and α_2 -globulin, false positive serological tests, and rheumatoid factor may also be demonstrated. Cryoglobulins and cold agglutinins can be found in a small proportion of patients.

The L.E. cell test is positive in over 80% of patients, and one or more antinuclear antibodies can be demonstrated in the serum by fluorescent antibody techniques in nearly 90% of patients. The presence of antinuclear antibody in a patient suffering from a multisystem disorder should make one suspect that the patient is suffering from either systemic lupus erythematosus or systemic sclerosis, and it almost certainly excludes a diagnosis of polyarteritis nodosa or dermatomyositis.⁴ Antibodies to thyroid and precipitating antibodies to certain saline extracts of tissue can often be demonstrated. The latter are not specific to any connective tissue disease. The only characteristic pattern of antibody seems to occur in patients with chronic discoid or systemic lupus erythematosus who have erythema multiforme-like lesions. In this syn-

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drome⁵ the speckled type of antinuclear factor is found in association with a particular precipitating antibody and rheumatoid factor. It is important to realize that the various abnormalities that can be demonstrated in the serum do not occur in all patients, and for complete diagnosis in a difficult case a battery of tests should be carried out.

Prognosis

It has already been pointed out that the disorder has a variable natural history. Acute fulminating cases are relatively rare, and many patients survive for years. About half the patients will live for 10 years or more. About a third of the patients have spontaneous remissions. Patients with nephrotic syndrome do badly. However, many patients with renal involvement may live for years with albuminuria and casts in the urine, though they may eventually die from renal failure. Other causes of death include secondary infection, heart failure, and vasculitis of the nervous system. Some die from side-effects of corticosteroid therapy. The prognosis is worse in males than females.⁶ Though corticosteroid therapy improves the prognosis, this is less marked if the patient survives for two years or more. Patients with predominantly joint involvement do better than those with arteritis, haemolytic anaemia, thrombocytopenia, or with involvement of the central nervous system. The prognosis of patients with discoid lupus erythematosus and abnormalities in laboratory tests is the same as for those with uncomplicated discoid lupus erythematosus.⁷

The improved outlook for patients with systemic lupus erythematosus is not only the result of the introduction of corticosteroid therapy but also because of the recognition of the importance of rest and prevention of infection and stress. The patient should be in bed in the acute phase and also during exacerbations. In less severe cases patients can be ambulant, and many with subacute or chronic disease may be kept at work. It is important to treat the patient rather than the laboratory abnormalities, and the erythrocyte sedimentation rate is not necessarily a guide to the progress of the disease. Several of my patients have worked for up to 10 years with the erythrocyte sedimentation rate at about 80 mm. in one hour. Others in whom the L.E. cell test is repeatedly positive have never had an erythrocyte sedimentation rate over 20 mm. in 1 hour. Both physical over-exertion and mental stress should be avoided. A mild sedative may be required in certain cases. Some patients are made worse by sunshine, and they should be advised to wear broad-brimmed hats and long-sleeved garments. Sunscreens containing benzophenone, such as Uvistat, should be prescribed for use on light-exposed areas. It is important to try to avoid secondary infection, as this frequently causes an exacerbation of the disease. Though the condition has been precipitated in occasional cases by the administration of penicillin, streptomycin, or tetracycline, antibiotic therapy for infection should not be withheld. Tetracyclines are probably the safest drugs to use. Some authors consider that there is no danger in prescribing sulphonamides for urinary infections.¹ Large doses (30–50 ml.) of gamma-globulin intramuscularly have occasionally been helpful in dealing with fulminating infections unresponsive to antibiotics.

Corticosteroid Therapy

Corticosteroid therapy is required for all acute cases and for patients with haemolytic anaemia, thrombocytopenia, severe nephropathy, involvement of the central nervous system, pulmonary infiltration, pericarditis, or an abdominal

crisis. The initial dosage must be adequate. It is advisable to start with 60–120 mg. of prednisone per day, and when the condition starts to remit the dose may be reduced gradually. A maintenance dose of about 5–15 mg. a day may be required for some months or even years, but the maintenance dose should be kept to the minimum. In time patients may be maintained on a very small dose of steroids, or the drug may be stopped altogether. In one series it was impossible to stop the steroids in 46% of the patients.¹ The L.E. cell test may remain positive or become negative; despite this, antinuclear antibody can usually be demonstrated with an almost unchanged titre. Massive doses of steroids have been given for fulminating cases and those with renal involvement, but the results do not justify the serious risks and side-effects. Some authors⁸ maintain that prolonged high doses of corticosteroids—60 mg. of prednisone per day for six months—are more effective in treating the renal lesions than small suppressive doses. I think that this can rarely be justified, and Zweiman *et al.*⁹ consider that there is no real difference in prognosis with high as compared with low dosage therapy. The incidence of side-effects of corticosteroids is in direct proportion to the dose. All the well-known complications such as peptic ulceration, diabetes, oedema, muscle weakness, bacterial and fungous infections, skin purpura, ecchymoses, and atrophy must be anticipated. In patients on long-term therapy, osteoporosis is more likely than posterior polar cataracts and rupture of the tendo Achillis.

For maintenance therapy it has been claimed that single dose regimens, in which the corticosteroid is given before a meal or with milk before bedtime, reduces the incidence of peptic ulceration and helps morning stiffness. Others claim that a single dose on alternative days produces fewer side-effects without impairing the therapeutic response.¹⁰

Alternative Drugs

Chloroquine and other antimalarial substances have been given for milder cases instead of corticosteroids or in an attempt to reduce the dose of steroids required, but they are much less effective than for discoid lupus erythematosus, and ocular complications preclude their prolonged use. Though hydroxychloroquine has been claimed to have fewer side-effects than chloroquine, this has not been confirmed, though a patient may tolerate one drug better than the other. Antimalarials may be useful for patients presenting with discoid lesions or rheumatoid arthritis, or for those with actinic sensitivity.

Antimetabolites may be useful for patients not responding to corticosteroid therapy, but they should not be used for initial therapy until more is known about their value. Several drugs have been used, including nitrogen mustard, 6-mercaptopurine, chlorambucil, and cyclophosphamide, but azathioprine in a dosage of 2.5 mg./kg. body weight is probably the most suitable. This dosage may have to be continued for many months. Intravenous nitrogen mustard—mechlorethamine hydrochloride—in a dosage of 0.4 mg./kg. body weight is useful for patients with nephropathy not responding to corticosteroids and diuretics.¹¹

Thymectomy has been carried out in a few cases, but the results have not been satisfactory and occasionally systemic lupus erythematosus has followed thymectomy. Neither can renal transplantation be advocated, though it has been done in two cases which had a fatal outcome.

Haemolytic anaemia, either as a presenting or associated feature of the condition, responds to adequate doses of corticosteroids. The Coombs test may or may not revert to normal. Iron therapy is required for patients who are iron

deficient as a result of either a poor intake or gastrointestinal blood loss. For those patients with anaemia secondary to renal failure transfusion may be required. Renal failure may be a terminal problem, but little can be done in the presence of a progressively rising blood urea. Diuretics occasionally help those with nephrotic syndrome: antimetabolites may, however, be required in this condition in addition to corticosteroids. Pulmonary involvement sometimes is the predominant feature, and patients may complain considerably of dyspnoea on exertion or of pleuritic pain. Radiological infiltration of the lungs usually clears slowly with corticosteroid therapy, and two years or more may be required for complete clearance. Treatment of cardiac failure with digitalis and diuretics may be required.

Patients presenting with joint pains or with rheumatoid deformities of the hands and feet and other joints are often helped by salicylates and antimalarials as well as by bed rest. Salicylates in dosages ranging from 3.6 to 7.2 g. per day have probably been undervalued in the management of systemic lupus erythematosus. Phenylbutazone should be avoided because of the potential risk of depression of the marrow or of exacerbating the condition. Occasionally patients suffering from abdominal pain may come to laparotomy, but in general the management is essentially conservative.

Anticonvulsants may be required for patients with epilepsy, though it has already been mentioned that certain anticonvulsants, such as the hydantoins and trimethadione, are known to precipitate systemic lupus erythematosus-like syndromes.

It is sometimes difficult to distinguish the psychosis associated with lupus erythematosus from that due to corticosteroid therapy. In my experience the former association is more likely. Patients get very agitated and may be delirious. Chlorpromazine by mouth or by injection in adequate doses is the most helpful sedative.

Treatment of the Skin

Treatment of the skin depends on the extent and nature of the problem. Patients with the more florid erythematous non-scaling lesions do not need local treatment, and the condition usually settles with systemic corticosteroid therapy. Other patients with more chronic lesions, sometimes resembling discoid lupus erythematosus, are helped by topical steroid preparations, such as betamethasone or fluocinolone ointment or cream. The effect is enhanced in suitable situations by occlusion with polyethylene. Necroses around the nail-folds are very painful, and adequate doses of analgesics should be given. They heal slowly with antibiotic creams. Patients with gangrene of the extremities require the minimum surgical trimming. Vasodilator drugs do not usually have much effect. Ischaemic leg ulcers, usually about the ankles, also heal slowly. They are best treated with an antiseptic cream on a gauze pad over the ulcer itself, with bandaging of the leg from the base of the toes to below the knee with an Elastoweb bandage over stockinette. The hair is slow to regrow in patients with diffuse alopecia, and unruly hair is also slow to return to normal on corticosteroid therapy.

The liver is rarely affected in systemic lupus erythematosus, though L.E. cells may sometimes be demonstrated in hepatitis. Even with severe involvement and hepatic failure the prognosis is not hopeless. Patients can improve and even live for a long time after treatment with corticosteroids, a low protein diet, and oral neomycin. A condition badly called "lupoid hepatitis" is a disorder of young females in which a benign cirrhosis is associated with adrenal overactivity.

These patients suffer from acne, hirsutism, pigmentation, amenorrhoea, and abdominal striae, and also have fever, polyarthritis, and hyperglobulinaemia.

Pregnancy

Though it is often assumed that patients suffering from systemic lupus erythematosus are relatively infertile, this is incorrect. Pregnancy has a variable effect. In some instances the condition actually improves in pregnancy, but in more than half there is no change. Occasionally there may be an exacerbation of the condition after delivery. There is no evidence that the incidence of spontaneous abortion and the perinatal mortality are increased. In all but very acute cases there is no indication for therapeutic abortion. The dose of steroids should be increased during delivery, and excessive trauma, haemorrhage, or shock should be avoided. Although the L.E. cell factor and other antinuclear factors cross the placenta they do not harm the foetus.¹² They may be demonstrated in the newborn for up to three months. There is a potential risk that corticosteroids may cause malformation of the foetus or disturbance of its growth, but this has not been so in patients under my care.

Vaccination

Occasionally the question of smallpox vaccination and immunization arises. Though there is a potential risk of exacerbating the disease, clinical experience suggests that vaccination and immunization against poliomyelitis, influenza, typhoid with paratyphoid A and B, and tetanus toxoid can be carried out, if necessary, in patients with controlled disease, but should be withheld in those with active disease and those on large doses of steroids.

When antinuclear factor is discovered in the serum of an individual without symptoms or signs of disease, or when serological tests for syphilis occur in association with a negative treponemal immobilization test in patients attending a venereal diseases clinic or for antenatal examination, care should be taken to ensure long-term follow up. Such individuals are very likely to develop overt evidence of a connective tissue disease in the course of years.

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