

CURRENT METHODS OF TREATMENT

Management of Systemic Lupus Erythematosus

By WILLIAM D. ROBINSON

THIS DISCUSSION will reflect certain concepts concerning the nature of systemic lupus erythematosus and the influence of agents used in its management. First, the diagnosis must be based on adequate clinical and laboratory evidence of multiple system involvement, rather than any single manifestation or test. Secondly, the disease is a chronic one with fluctuations in the level of activity. In the not too distant past, it was usually recognized only in its acute, fulminating and often fatal form. With the development of more precise methods of diagnosis it has become apparent that such fulminating stages are nearly always episodes in a long-term illness with subacute or chronic low grade manifestations, and that systemic lupus erythematosus often is characterized only by such subacute or chronic activity. In the third place, the agents used in management of the disease are essentially suppressive. The dramatic effect of adrenal corticosteroids in essence depends on their ability to convert the acute fulminating form of the disease to a subacute or chronic level of activity.

The program of management must be highly individualized. There is great variation from one patient to another as to the organs and systems which are involved, and a fluctuation in the level of activity of the disease in the same patient from time to time. Assessment of the activity of the disease must depend on careful evaluation of various clinical and laboratory findings, as there is no single specific and reliable index of activity.

Before administering adrenocortical steroids or their analogues to patients with systemic lupus erythematosus, the physician should attempt to define those manifestations of the disease which he intends to suppress with these agents. In general, the corticosteroids are effective in suppressing the inflammatory manifestations of the disease, and particularly those that can be attributed to exudative inflammation. Fever and general toxicity can usually be adequately controlled. The erythematous skin rash usually responds in a few days. The heat, swelling and redness of involved joints are usually promptly controlled, although muscle aching and stiffness may persist to a considerable degree. The serosal involvement, manifested as pleuritis, pericarditis, or—less commonly—peritonitis, also responds to steroids. The number of granulocytes and platelets in the peripheral blood, if initially depressed, usually returns to a normal level. Anemia, when present, often does not respond to corticosteroid administration unless there is a significant hemolytic element. With the possible exceptions noted below, "lupus nephritis" is not influenced by steroid therapy. The effect of these agents on laboratory

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findings is variable. It is quite clear that an elevated sedimentation rate, a persistently positive L.E. cell test, or an elevation in the titer of antinuclear factors or of globulin concentration in the serum do not constitute an indication for corticosteroid therapy. The effects of corticotropin, adrenal corticosteroids and the synthetic analogues are essentially the same. It is usually advisable to avoid the preparations which profoundly influence water and electrolyte metabolism.

Antimalarial drugs were introduced into the treatment of systemic lupus erythematosus after it had been demonstrated that these compounds were effective in chronic discoid lupus erythematosus. Preparations most frequently used are chloroquine, 250 mg. two to three times daily, or hydroxychloroquine, 200 mg. two to three times daily. The mode of action of these drugs is unknown. Experience indicates that they usually are not immediately effective, and they certainly cannot be relied upon to suppress acute activity of the disease. They are chiefly of value in dealing with the subacute or chronic levels of activity. Some workers have felt that the administration of an antimalarial drug resulted in a significant reduction of dosage of corticosteroids required; however, the known spontaneous fluctuations in level of disease activity make it difficult to establish this point. If chloroquine or hydroxychloroquine are used, a significant effect should not be anticipated until they have been taken for at least 1 to 2 months, and a period of 6 months' administration is recommended before concluding that these drugs are not of value in the particular patient concerned. Side reactions to these antimalarials include dermatitis, gastrointestinal disturbances, dizziness, psychosis or convulsions, corneal opacities and, rarely, bone marrow depression or adenopathy.

General measures which may be useful in the management of the patient with systemic lupus should not be overlooked. Sponging with water or alcohol may lower dangerously high fever. Salicylates induce prompt defervescence in some patients, and are helpful in relieving the joint symptoms. Not only may salicylates be helpful in the acutely ill patient, but their administration can control some patients with chronic low grade activity and permit reduction in the maintenance dose of corticosteroids. Complicating infection should be recognized and treated with appropriate antibiotics. Development of cardiac insufficiency is an indication for limitation of activity, digitalization, sodium restriction and diuretics as necessary. Severe anemia may require blood transfusions.

The basic principle in treating acute fulminating lupus is to use as large a dose of corticosteroid as is necessary to suppress the life-threatening manifestations of the disease. In the critically ill individual, the effective initial dose may be 60 mg. a day or higher of prednisone, or its equivalent with other steroid analogues. In individual patients, much larger doses have been required to control "acute lupus crises." After maximal benefit has been achieved, the daily dose is gradually reduced. The rapidity with which this is done depends on the general condition of the patient, with particular attention to the functional status of the vital organs involved. Once the acute fulminating manifestations are suppressed, subsequent management is similar to that of the subacute or chronic forms of the disease.

The most important precaution in this situation is the necessity for a diligent search for a complicating infectious process. Such intercurrent infection is not a contraindication to the use of steroids, *if the intercurrent infection is recognized and it can be effectively controlled by antibiotics or chemotherapy*. This fact has been particularly well demonstrated in patients with both tuberculosis and systemic lupus erythematosus.

In the seriously, but not critically, ill patient, treatment is initiated with a dose of 30 to 40 mg. of prednisone daily, or its equivalent. In less seriously ill patients, the initial dose may be in the range of 20 mg. of prednisone daily. If after a few days there is no response, this dose is increased in a stepwise manner until control of the predetermined manifestations is obtained. After maximal benefit has been achieved, the daily dose is gradually reduced, with decrements not exceeding 2.5 mg. at each step and with an interval of 5 to 7 days between steps. Additional measures are brought into play according to the individual patient's manifestations. Every effort is made to keep the steroid dosage at the minimal level which will provide reasonable suppression of the disease activity. Since many patients manifest a sensitive balance between dosage and suppression of disease activity, the decrease in corticosteroid dosage is best carried out more slowly than in patients with rheumatoid arthritis.

Particularly when dealing with chronic low-grade activity should the physician consider whether or not corticosteroids are necessary to control the disease manifestations. Many of these patients can be controlled with other measures, including antimalarial drugs. Regular use of salicylates is indicated for patients in whom musculoskeletal complaints predominate, and physical medicine measures may be helpful. Even in patients with chronic low grade activity it is important to avoid fatigue and regular afternoon rest periods should be advised. The patient should avoid exposure to the sun, since further systemic as well as dermal manifestations may develop after such exposure.

The untoward reactions in the course of corticosteroid therapy are well known. Since the dosage of steroids required for the control of systemic lupus erythematosus is often higher than in rheumatoid arthritis, such undesirable effects may present considerable difficulty. At times the physician must decide whether some degree of activity of the lupus is a greater risk to the patient than the potential untoward reaction to the hormones. Particularly troublesome problems are presented when new symptoms develop in the patient with systemic lupus erythematosus under treatment with corticosteroids. These may be due to an untoward reaction to the hormone, indicating a reduction in dosage; or due to an increased activity of the lupus, suggesting the need for increased dosage; or attributable to an intercurrent process, perhaps masked to some extent by the corticosteroids. Careful appraisal of all features of the patient's illness is required at this point. Sometimes cautious reduction in steroid dosage will help to clarify the picture, as the manifestations of the primary disease which have just barely been suppressed will usually flare if this is done. In other patients, the potential danger of such a flare precludes the reduction in dosage.

The renal complications of systemic lupus erythematosus, when present, re-

quire special consideration. Kidney involvement in this disease may simulate either the nephrotic syndrome or subacute or chronic glomerulotubular nephritis, and renal failure is the most common cause of death. There is general agreement that the use of adrenal corticosteroids in suppressive dosage, as described above, does not influence the course of "lupus nephritis." Although other manifestations of the disease may be suppressed by appropriate doses of the corticoids, once renal impairment is established it appears to be progressive and these patients usually die in uremia. Recently, however, Pollak and his associates have reported that improvement of the renal lesion may result from large doses of prednisone, 50 to 60 mg. daily, given for a period of 6 months. These investigators relied heavily on serial renal biopsies as evidence of improvement, but also noted improved survival in a small group of patients as compared with a previous group of patients who had received only suppressive doses of adrenal corticosteroids. It may be significant that such improvement of survival was not seen in patients whose blood urea nitrogen exceeded 30 mg. per cent at the time of initiation of the large-dose therapy. These favorable results have not as yet been confirmed by other observers.

Until further information is available, the following recommendations can be well supported. When systemic lupus erythematosus presents as the nephrotic syndrome, the therapeutic program should be directed accordingly and include the use of adrenocortical steroids in large doses for at least several weeks. The use of large doses for several months, as recommended by Pollak, Pirani and Kark, appears justified in patients with established kidney disease in whom renal function is not severely impaired, provided the patient and physician are willing to accept the risks of the induced hyperadrenal cortical state over this period of time. If renal function is already severely impaired, such large dose therapy is useless, and may appear to be disastrous.

In summary, the management of systemic lupus erythematosus is a highly individualized proposition. It is not dependent on any single method of treatment. It is carefully adapted to the needs of the individual patient, taking into account the organs and systems involved and the level of disease activity at any given time. It requires close medical supervision and the intelligent cooperation of the patient, as well as alertness on the part of the physician to the changes in disease manifestations, to intercurrent complications, and to complications of the program of management itself.

REFERENCE

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Discussions

THE DECISION to label a patient "SLE" is a serious responsibility based on clinical judgment. Unfortunately, many pieces are missing from the jigsaw puzzle which makes up the whole clinical picture. It is difficult to be sure about "early" cases or bizarre

ones—such as those which involve the CNS (e.g., pseudo-tumor cerebri or psychiatric symptoms) or large blood vessels (e.g., aortitis). Often one has to temporize until new symptoms and signs develop which give criteria more acceptable for diagnosis. In

many, however, only a presumptive diagnosis may be made even after prolonged study.

This conservative attitude is proper, but there is always the nagging thought that if one had been willing to "stick one's neck out" a little earlier, the disorder might have been managed better in some patients by a simple regimen involving small doses of steroids and avoidance of possible precipitating factors. These are: all unnecessary drugs (such as penicillin, sulfanilamide, and phenylbutazone), exposure of the hands to cold and the body to sun, contact with sensitizing cosmetics and hair dyes (especially those containing *para*-phenylenediamine), and household and garden chemicals.

Patients who wish or expect to become pregnant would be told to report as soon after conception as possible for frequent visits throughout pregnancy and into the 3rd month of the puerperium. This would allow one to catch and vigorously treat with large enough doses of steroids the fulminating cases which are precipitated during the 4th to 8th week post-partum and during the first trimester of pregnancy. These acute flare-ups related to pregnancy should be treated promptly and effectively with steroids to minimize the danger to the health of mother and fetus. Other very acute flare-ups of SLE may on occasion require heroic treatment with up to 1-3 Gm. of hydrocortisone intravenously every 24 hours. Too frequently the acutely and very severely ill patient with SLE may die suddenly after a short period of debilitating illness. Such deaths often occur from undertreatment and may be prevented by the prompt administration of large doses of hydrocortisone intravenously. When these cases are brought under control the dosage must be slightly reduced by small decrements until a small standard dose is reached—the crisis being over—or until the symptoms begin to recur, at which time the dosage must be quickly increased to a sufficient level to suppress activity. Activity still has to be gauged by trial of therapy. Osler indicates that his measurements of serum complement levels and antinuclear factors may provide a laboratory method of gauging activity, and hopefully we look for confirmation of this by others. In our experience, antinuclear factors have not provided a reliable enough index for the individual patient.

All too often, as in lupus myocardopathy,

large doses of hydrocortisone or prednisone do not work, or if the activity is suppressed, the patient dies of disseminated aspergillosis of the lungs or some other fungal, viral, or bacterial infection. As we get to know more about the natural history of the disease, we recognize that many patients with SLE have a comparatively long life span; and the more fortunate ones, a full and useful life. The prognosis is particularly good in those who develop an SLE-like disease associated with exhibition of Apresoline or other drugs, provided that the drugs are stopped. On the other hand, unless treated, lupus glomerulonephritis is usually fatal.

As response to treatment is most favorable when the blood urea nitrogen has not yet climbed to very high levels, it is important to recognize the disease early and to treat it vigorously when found. Thus, in patients who have no evidence of renal disease, the urine should be tested each month for protein and red blood cells. The patient can conveniently test it herself with dipsticks. If and when persistent proteinuria develops, if the laboratory findings indicate lupus glomerulonephritis and if the BUN is not higher than about 30 mg/100 ml, then the patient should be treated with 50-60 mg. prednisone each day for 6 months, as the observations of Pollak et al. have now been confirmed by Schreiner in Washington, and Mackay in Melbourne, Australia. It is still difficult, however, to assign definite clinical and laboratory criteria which in the individual patient will distinguish non-progressive lupus glomerulitis from progressive lupus glomerulonephritis. Thus renal biopsy is valuable in deciding who should be treated with large doses of prednisone. When this is done, close attention must be paid to the dietary management. It is important to work with the patient and dietitian to insure a high calcium, high protein intake each day while patients are on this regimen. This type of dietary regimen is also important in all situations where large amounts of steroids are being used.

It is also important to see that patients with lupus, who are debilitated, consume a high calorie, high protein diet to prevent them going into nutritional bankruptcy. It is seldom that one sees lack of absorption of foodstuffs in SLE, but this does occasionally occur; and at times, even steroids may not be absorbed by mouth as evidenced by lack of development of cushingoid features

| E. S. | ADM. 1956 | 38 W. F. |
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| AGE (Year) | EVENT | |
| AGE 21 (1939) | BARTHOLIN GLAND INFECTION, STS + (AND ALL SUBSEQUENT TESTS POSITIVE) | |
| AGE 36 (1954) | AFTER PENICILLIN, POLYARTHRITIS 6 MONTHS | |
| AGE 39 (1956) | ARTHRALGIA, PE 0, STS +, TPI 0, LE CELLS +, JOINT X-RAYS NORMAL | |
| AGE 39 (1957) | PE 0, STS +, TPI 0, LE CELLS + | |
| AGE 43 (1961) | ASYMPTOMATIC, PE 0, LE CELLS + | |

Fig. 1.

in patients on large doses of prednisone.

We make the above comments as supplements to Dr. Robinson's statements, which we regard as admirable.

ROBERT M. KARK AND VICTOR E. POLLAK

IT IS A PLEASURE to have the opportunity to comment on this excellent description of the management of systemic lupus erythematosus by Dr. Robinson. I was pleased to see that he titled the article "management" of SLE rather than "treatment." The term treatment implies the use of specific therapeutic agents while the term management embraces the total problem of the handling of the patient. SLE serves as a prototype of a chronic disease of many years duration which may involve almost any structure and is punctuated by episodes of acute illness interspersed with periods in which the process may be relatively quiescent. It is important, under these circumstances, to give consideration to the patient's understanding of the disease process and the best plan for adapting to it. It encompasses preventive measures as well as the forms of treatment which may be required for the various clinical reflections of activity of the process.

In the management of patients with this syndrome, it seems to me important to take a somewhat broader concept of diagnosis. One possible approach is to consider that these individuals have a genetically determined immunologic abnormality which may lead to the formation of auto-antibody and delayed sensitivity not only against

unaltered or relatively slightly altered non-foreign antigens but also against substances which are not "good" antigens.¹ As has been pointed out, in SLE one may find a battery of antibodies against erythrocyte, leukocyte and platelet antigens, some of which are "poor" antigens; in other individuals, against proteins of the clotting complex as well as nuclear constituents which also are "poor" antigens. In addition, there is delayed sensitization to some of the same cellular elements. Our studies in the follow-up of a large series of healthy individuals with a biologic false-positive test for syphilis (BFP) have indicated that this is more than a theoretical concept. We have seen individuals who have developed, in addition to the BFP reaction, L.E. cells and in whom there has been no clinical illness except following the administration of certain therapeutic agents. In particular, we have seen two such individuals whose only clinical evidence of the underlying abnormality has been the development of a polyarthritis of several months duration following, in one instance, penicillin, (fig. 1) and in the other, aureomycin. After recovery from the polyarthritis, these patients have remained clinically well although they continue to show the BFP reaction as well as L.E. cells. This implies that it is important to recognize the "latent" state of this syndrome, if one may use that term, in order to prevent as far as possible those situations which may precipitate disease activity, such as the administration of drugs and exposure to sunlight.

In any chronic disease which runs an intermittent course of activity, such as SLE, it is important to recognize that when an acute episode of illness occurs it may be 1) due to activity of the underlying disease process, 2) represent a complication of therapy, or 3) may be a totally unrelated illness. In a disease such as SLE in which tissue damage in almost any structure may develop and mimic almost any other disease process involving that area, this concept becomes of practical importance in management.

In regard to the use of steroids in the treatment of SLE, I would agree entirely with Dr. Robinson's approach that significant involvement should be present before embarking on the administration of steroid hormones. I think it is important for the physician to pick one hormone which does not have striking effects in terms of salt and water retention and become thoroughly familiar with the clinical use of that hormone in the management of these patients.

In regard to certain specific points in the discussion, I believe that caution should be exercised in the use of chloroquine. In most instances the potential benefit from the use of this drug is not great enough to run the risk of the serious toxic effects which may ensue after long-term, high-dosage administration. We have seen irreparable ocular damage occur from the administration of 500 mg. of chloroquine over a period of 6 months. It is our feeling that this dosage should not be given for longer than 1 month, following which the maximum daily dose should be no greater than 250 mg.

In terms of general measures useful in the management of the patient, I think it is important to point out that many physicians do not explain the nature of the disease process in the proper fashion to the patient and as a result many of them have very serious emotional reactions. This is particularly true since on their own they often consult some of the past literature which states that the disease is inevitably fatal. There is one other comment under general measures in regard to transfusions. Since these patients do respond immunologically to exposure to "poor" antigens, there is a greater risk than in the normal individual of transfusion reactions to some of the

erythrocyte iso-antigens which do not ordinarily evoke an antibody response.

Although there has been considerable discussion in the literature of the need for extremely high dosage of steroids in acute fulminating lupus, we have rarely seen an individual in whom the important manifestations of the disease could not be controlled with 60 mg. of prednisone as the initial dose. High dosage of steroids over prolonged periods should certainly be avoided because of the serious catabolic effects of these hormones.

In terms of preventive measures, Dr. Robinson mentions avoiding exposure to the sun. In our experience, even more important is the avoidance of any unnecessary medications because of the wide variety of drugs whose administration has been followed by acute activity of the disease.

The problem of management of the renal involvement is difficult, but it has been our feeling for many years that any evidence of renal involvement should be aggressively followed and treated. We have seen evidence of improvement in patients started on steroid therapy when their BUN was above 30 mg. per cent. We have also seen patients who had clear evidence clinically and on biopsy of renal involvement and who, for one reason or other, were not treated with steroids and whose disease process seemed to remain static from the functional point of view over several years. Since the renal lesions are so uniformly progressive, however, and end fatally, I think they should be treated in most instances with steroids, even though there is evidence of renal functional impairment. The untoward effects of the steroids in terms of their catabolic effect can be counterbalanced to some degree by regulating the dietary intake of protein and by the use of anabolic steroids. We have recently seen a patient who was followed in another hospital for 3 years with biopsy proof of renal lupus without significant evidence of advancing renal insufficiency even though no steroids were administered over this period of time. Following a pregnancy, she had an acute exacerbation of the nephritis with complete suppression of urine flow. Renal biopsy showed extensive changes in the glomeruli with widespread fibrinoid deposits and hematoxylin bodies. During 3 weeks she was anuric and two dialyses were

necessary. With the use of anabolic steroids and other measures during this period the BUN did not rise more than 10 mg. per cent daily, even though the patient was receiving 40-60 mg. of prednisone. After 3 weeks she began to secrete urine and a second biopsy showed striking improvement in the glomerular lesions. There is no doubt that one of the important needs is a better means of evaluating the degree of activity of the renal lesions. Dr. Stevens, working in our laboratory, has some preliminary data suggesting that in the active period there may be a greater amount of gammaglobulin in the urinary protein. Dr. Townes and Dr. Osler are also studying this problem from the point of view of quantitation of anti-nuclear antibody in the serum along with complement determinations.

Also important in the follow-up of these patients is frequent examinations of the urine so that the early evidences of renal nephritis may be recognized, and the care-

ful follow-up of these patients during and in the period following pregnancy. In this way the onset of fulminating activity, which may occur particularly in the post-partum period, may be recognized early and proper steroid therapy outlined.

One other thing that is of importance in the following of patients with SLE and which may relate to their proper treatment is to be on the look-out for the development of other auto-immune diseases. We have seen several instances of the gradual onset of hypothyroidism with the typical changes in the thyroid of Hashimoto's disease.

In summary, it is our feeling that if this syndrome is recognized early and the patients are carefully followed with all of the available preventive measures being taken, the results of their management can, in a large percentage of instances, be quite successful and the patients enabled to lead a full and useful life.

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