Standardized Schemes for Steroid Treatment in ENL and Reversal Reactions

TO THE EDITOR:

Reactions in leprosy are among the most feared clinical complications of the disease. Years of clinical experience are required to arrive at the correct diagnosis and adequate treatment of such reactions.

The history of the disease, clinical symptoms and, wherever possible, histopathological examination of a biopsy should lead to the correct diagnosis of ENL (erythema nodosum leprosum, type 2 reaction) or RR (reversal reaction, type 1 reaction). I recall here Harman's statement (personal communication): "First know what is going on in the tissues and if that is understood, treatment should not be too difficult."

Clinical symptoms of reactions in leprosy have extensively been described by Jopling ([6]). Here, briefly, are my own observations: ENL reaction, resulting from a humoral antibody-antigen response comparable to a Type III Coombs and Gell hypersensitivity reaction, may last from a few months to more than six years. Some patients have a mild episode of general malaise, a few red skin nodules which may be recurrent, while other patients are severely ill with high fever, swollen hands and feet, multiple reddish, sometimes ulcerating, skin nodules particularly on the upper and lower extremities, painful nerves (neuritis), orchitis, arthritis and, occasionally, laryngeal edema. The eyes, too, may be affected and should be examined carefully; each ENL patient, if possible, should be seen by an ophthalmologist. ENL occasionally can be found in untreated BL-LLp patients with a long history of the disease but, more often, ENL occurs in BL-LLp patients after they have been on antileprosy treatment for some time.

Reversal reaction (RR), characterized by raised, red, edematous lesions at the site of inactive old lesions and, occasionally, by the appearance of new, red skin lesions and, often, by nerve involvement can occur in TTs to LLs patients during the first months of antileprosy treatment or even after the patients have been longer, i.e., as long as 1–2 years on treatment. Occasionally, RR is seen in untreated patients. In BL to LLs patients, RR may be difficult to diagnose clinically and, here, the histopathology of a biopsy could be helpful.

Both reactions can be elicited by an underlying disease, such as tuberculosis, diabetes mellitus, anemia, etc., which should be treated at once. Other factors precipitating ENL reactions have been mentioned already by Jopling ([6]). The same factors, in my opinion, for the greater part are also underlying the appearance of RR reactions. Occurrence of reactions as a result of antileprosy drug (DDS) therapy, once more, has been stressed by Anderson ([1]).

As regards the treatment of reactions, the antileprosy drug of choice in both ENL and RR reactions, in my opinion, is clofazimine (Lamprene®, B663) in the case of dark-skinned patients. Clofazimine is preferred for the following reasons: Dapsone can elicit ENL and RR in susceptible patients and, therefore, should not be used during reactions in leprosy ([2]). Furthermore, both clinically and experimentally, it has been found that dapsone is incompatible with clofazimine in ENL reactions; hence, these two drugs should never be given together to ENL patients ([5, 8]). (Dosages of clofazimine in ENL patients will be discussed below.) For RR patients, clofazimine in a dosage 100 mg three times weekly is recommended both for dark-skinned patients and for light-skinned, fair-haired leprosy patients. Such a dose does not seem to discolor or darken the skin significantly. If nerves are involved in RR patients (and they frequently are), additional corticosteroid treatment (below) is a must ([4]).

The application of corticosteroids to patients suffering from ENL or RR is well known among leprologists. In an editorial ([7]), Pearson called corticosteroid treatment the backbone of anti-reaction therapy, and mentioned that its use should be in line with the variability existing in the clinical pattern of leprosy reactions, the pattern of ENL being bouts of reactional periods alternating with periods free from ENL symptoms. RR, in treated patients, follows a short course of

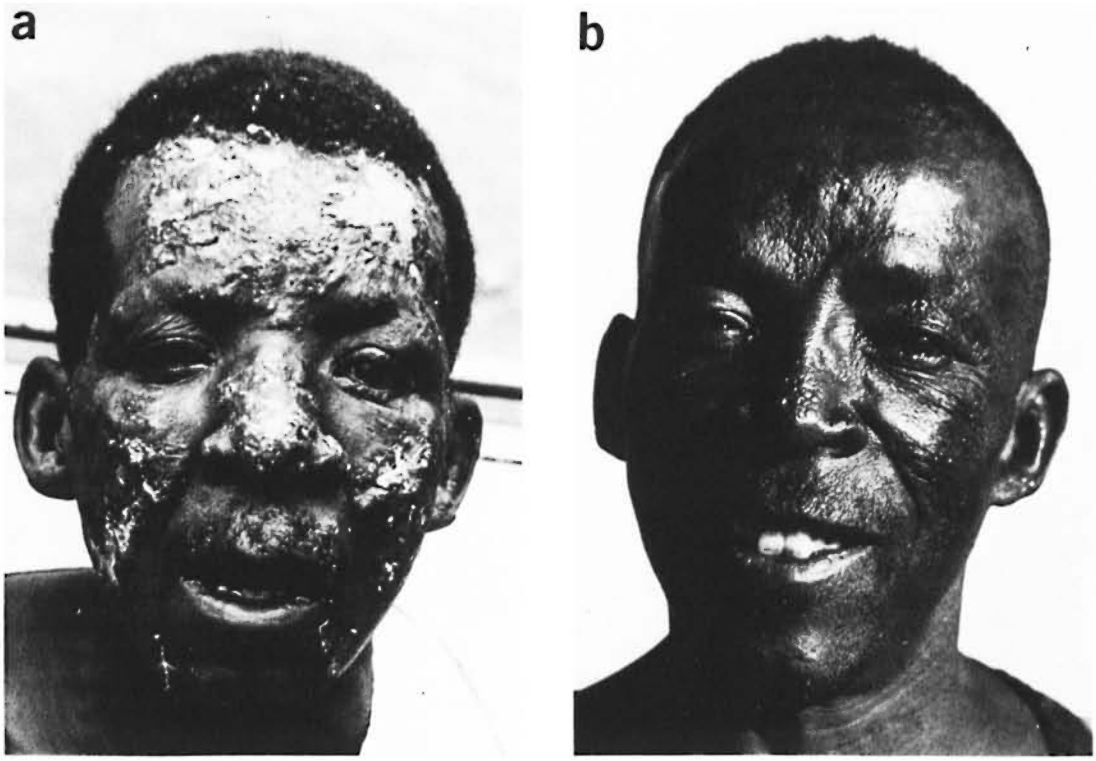

FIG. 1. Lepromatous leprosy (LL) patient with a long history of recurrent ENL reations causing ulcerations of the skin (Zambian patient): a) during DDS treatment; b) after discontinuation of DDS and following 1½ year treatment with clofazimine alone. Note that this was one of the first patients treated with B663 in 1967 in a clinical trial to evaluate the anti-inflammatory effect of clofazimine in ENL before the drug had become commercially available.

some weeks to months and, generally, is not recurrent. Hence, for ENL, Pearson advised short courses of treatment of about two weeks with a fast tapering off from the initial dose of 20–30 mg prednisone daily. For ENL patients requiring frequent courses of corticosteroids, continuous treatment with clofazimine and/or thalidomide were recommended. For RR, on the other hand, Pearson advised a continuous course of corticosteroids with an initial high dose of prednisone (30 mg daily), gradually tapering off over some weeks or months. In the same editorial, the need was expressed for a standardized scheme of corticosteroid treatment suited for field use. So far, however, no such scheme recommending dosages of corticosteroids for the treatment of leprosy reactions has appeared in the literature.

For the benefit of field workers and for doctors not yet experienced enough in leprosy treatment, I would like to describe and illustrate here the results of standardized schemes of corticosteroid treatment resulting from experiences obtained over a period of 16 years of dealing exclusively with leprosy patients in Africa (Zambia and South Africa). The treatment has proven to be very effective in these two African countries and the schemes deserve attention, particularly on the point of the weaning-off from steroids. Results obtained by the writer certainly do not mean that the schemes at once are applicable to other countries with leprosy patients. They first should be tested in such countries. Wherever thalidomide for ENL treatment is not readily available or where thalidomide is contraindicated or its use objected to, the schemes presented here may prove to be very valuable as the illustrations (Figs. 1–3) clearly show.

Before discussing the schemes, I would

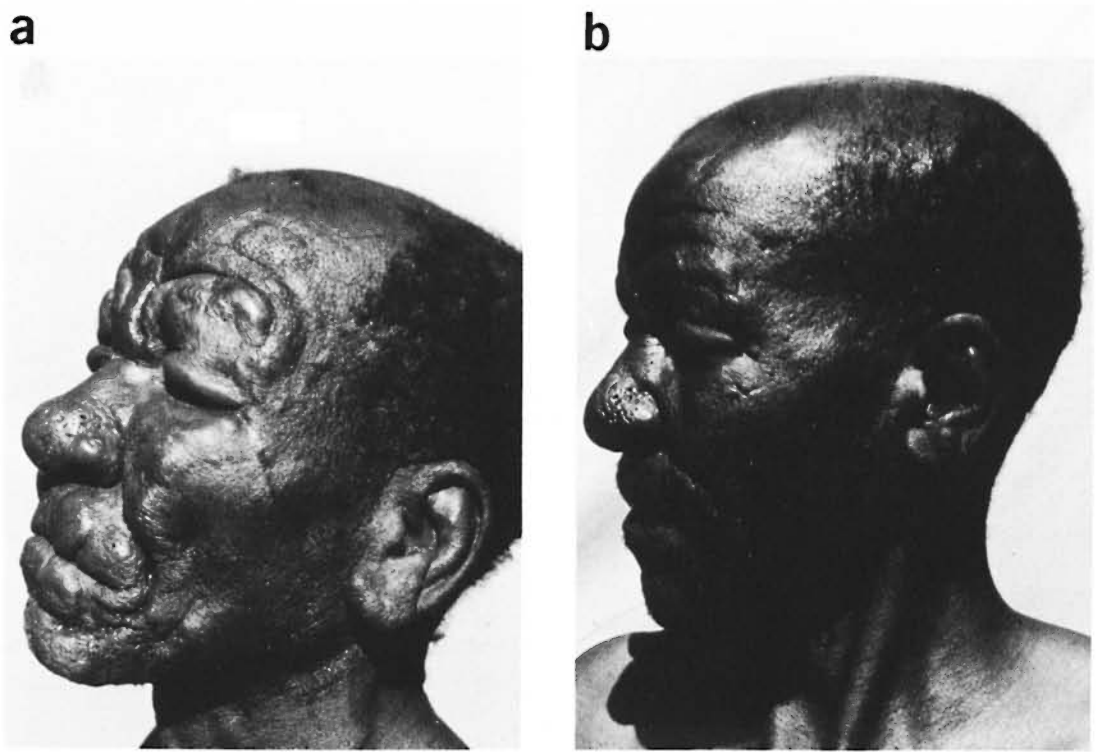

FIG. 2. Borderline tuberculoid (BT) patient in reversal reaction (RR) (South African patient): a) before any antileprosy treatment had been received by the patient; b) after treatment for 2 months with both clofazimine 300 mg weekly and with the standardized prednisone course according to Scheme 2. In addition, the patient received adequate treatment for his diabetes mellitus.

like to mention that the decision to give corticosteroids to a patient with ENL may have serious consequences. The duration of ENL is unknown and may last for many years. Once a patient has been given steroids, nothing else will do. A light-skinned patient in Zambia once compared it with morphine. "Addiction" is rapidly established. Numerous side-effects will present if ENL episodes and corticosteroid treatment stretch out over several years (i.e., decalcification of bones, stimulation of latent diabetes mellitus, suppression of general immunity and therefore increase of susceptibility to other infections, delayed wound healing, edema in the face and extremities, posterior cataract, etc.). It should also be mentioned here that the writer has been able to control severe ENL reaction which is not associated with complications (below) with clofazimine (B663) alone. In the case of mild ENL, 100 mg clofazimine daily would be sufficient. In severe ENL, one can start with 200 mg clofazimine per day and, if necessary, increase the dose to 300 mg per day. Results of such treatment are shown in Figures 1a and 1b. Other drugs, e.g., antibiotics, tranquillizers, analgesics, and sedatives, should be given when necessary. In severe ENL, patients need tranquillizers since clofazimine takes a few days to become effective clinically. (The effect of corticosteroids is much quicker.)

Corticosteroid treatment in ENL, in my opinion, should be restricted to ENL patients with one of the following complications: a) acute laryngeal edema, if there is no response to injections of epinephrine adrenaline; b) neuritis (below), or c) orchitis. In these complications, a short course of prednisone should be prescribed with adequate weaning-off, according to the following scheme.

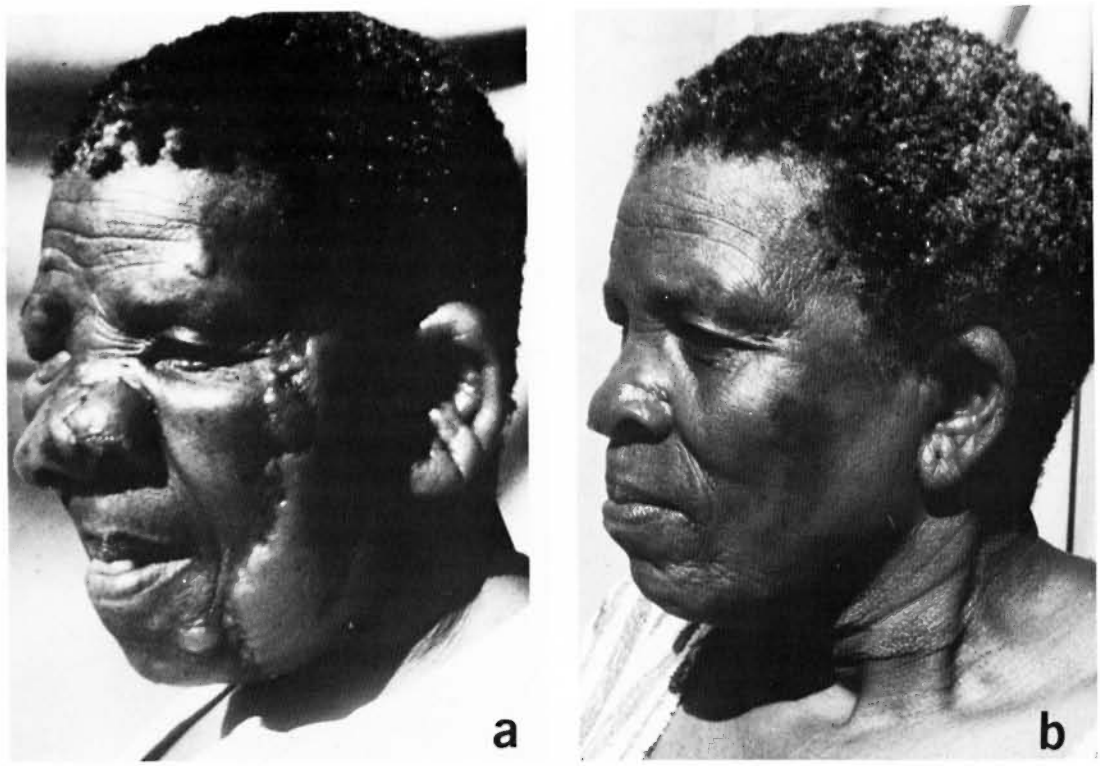

FIG. 3. Female patient suffering from BT leprosy (South African patient): a) developing a RR reaction after 3 months of treatment with DDS; b) after the patient had been taken off DDS and from then on received clofazimine 300 mg weekly and prednisone according to the standardized Scheme 2 of corticosteroid treatment, showing the result after 6 months' treatment.

Scheme 1—ENL patients with complications.

3 × 10 mg prednisone for 1 (or 2) day(s)
3 × 7.5 mg prednisone for 1 (or 2) day(s)
3 × 5 mg prednisone for 1 (or 2) day(s)
3 × 2.5 mg prednisone for 1 (or 2 day(s) or 7.5 mg stat a.m.
5 mg prednisone for 2 days
2.5 mg prednisone for 2 days
2.5 mg prednisone every other day (2 times)
2.5 mg prednisone every fourth day (2 times)

If good results have been achieved, corticosteroid treatment can be discontinued.

New ENL patients who, on admission, were shown to be corticosteroid-dependent and/or "addicted" could be weaned-off clofazimine alone ([3]). In this weaning-off process, placebos were very effective. If a patient must be weaned-off steroids, then this should be done very slowly, with a reduction of 2.5 mg every four weeks. In case new bouts of ENL occur during this weaning-off period, one should increase the dosage of clofazimine up to maximally 300 mg daily. Once the ENL reaction is controlled, one should slowly decrease clofazimine to 100 mg three times weekly. Only when the patient under the latter treatment for one whole year has not suffered from renewed ENL reactions could one attempt to (re)commence DDS treatment.

Although neuritis in ENL and RR are histopathologically quite different, the clinician should always treat neuritis in ENL with steroids because one never can be sure whether, apart from the humoral antibody–antigen reaction, a reversal reaction (no matter how slight) may be present at the same time, causing damage to nerve tissues.

It is important to mention here that ENL or RR patients on prolonged corticosteroid

treatment should be checked weekly for the possible occurrence of sugar in the urine (latent diabetes), and that in countries where pulmonary tuberculosis is endemic, additionally, INH should be given daily.

In patients with RR, the following prednisone dosages, in my experience, were very effective: 3 × 10 mg prednisone for 1 day (in severe neuritis, for 2 or 3 days); as soon as the patient has responded well to this treatment, one can change to one daily administration of prednisone (below). A satisfactory standardized prednisone scheme follows:

Scheme 2—RR.

1st day: 30 mg prednisone
2nd day: 27.5 mg prednisone
3rd day: 25 mg prednisone
4th day: 22.5 mg prednisone
5th day: 20 mg prednisone
6th day: 17.5 mg prednisone
7th day: 15 mg prednisone

From 15 mg per day, one should reduce prednisone with 2.5 mg every four weeks. The scheme, then, will be:

12.5 mg daily for 4 weeks
10 mg daily for 4 weeks
7.5 mg daily for 4 weeks
5 mg daily for 4 weeks
2.5 mg daily for 4 weeks
2.5 mg daily every other day for 4 weeks
2.5 mg twice a week every 4 weeks
2.5 mg once a week for 4 weeks

One can then stop corticosteroid treatment if no relapse of RR occurs. Results of this scheme are presented in Figures 2a and 2b and Figures 3a and 3b.

Next, one should continue with clofazimine 100 mg three times weekly for one year before changing to DDS.

If RR recurs during the weaning-off in Scheme 2, one should increase the dose of prednisone to a dose slightly higher than the one which the patient took when the relapse occurred and leave the patient on it for another four weeks, weaning off in the same way as described above.

The above standardized method has the advantage that the risk of a relapse of RR is small and that renewed damage to nerves, in this way, can be avoided.

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