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Treatment of Leprosy with a Phenazine Derivative (B 663 or G 30 320)—Clofazimine*

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A report of good results obtained in 35 leprosy patients treated with B 663 (clofazimine)

The phenazine compound known as B 663 or G 30 320 (clofazimine) is a rimino compound obtained by progressive manipulation of a molecule of aniline aposafranine. It can be administered orally and if given in large doses is deposited in the principal organs and especially in the reticulo-endothelial cells. Like many other anti-leprosy drugs, it was first tried out in the treatment of tuberculosis. The Therapy Committee of the Eighth International Leprosy Congress at its meeting in Rio de Janeiro in 1963 advised a continuation of the trials started a short time previously, after noting its beneficial effects in the treatment of leprosy patients.

Browne and Hogerzeil (1962*a*) reported the results in 16 patients with lepromatous leprosy and concluded that B 663 had a beneficial clinical and bacteriological effect; this effect was enhanced by later adding DDS or, in some cases, ditophal. Browne (1966*b*) also drew attention to the anti-inflammatory effect of B 663 as seen in 10 patients with reactions controllable by steroids; he was able to eliminate steroid treatment gradually, by replacing it with B 663. This author also noted a suppressive effect on the lepra reaction in 26 lepromatous cases. Together with Hogerzeil (1962*b*) he described 5 cases in which after 12 months of B 663 administration a bacteriological resistance apparently developed but disappeared again as treatment was continued.

Pettit and Rees (1966) described 3 cases of DDS resistance which, when treated with B 663 for one year, showed clinical, bacteriological and histological improvement. They also noted the intense red coloration of the skin and the blue-black pigmentation of lepromatous lesions which had already been described by Browne (1966*a*). These authors, together with Ridley, Pettit *et al.* (1964), gave B 663 for 5 months to lepromatous patients previously untreated and obtained results comparable to those obtained with sulphone treatment.

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PERSONAL OBSERVATIONS

Number of patients, clinical type, dose and duration of treatment

The present study was carried out on 35 selected leprosy patients, of whom 30 had lepromatous leprosy, 5 with reactions, 3 were tuberculoid cases without skin lesions but with residual nerve involvement, one dimorphous case, and one indeterminate case. Of these 35, 10 of the lepromatous patients and the patient with indeterminate disease were previously untreated. Out of the remaining 20 lepromatous cases which had been treated previously (with sulphones or thiambutosine or long-acting sulphonamides) 5 had undergone intense reactions of erythema-nodosum type whatever the drug used. The other 15 and the dimorphic case had all shown resistance to these drugs.

Following the modern practice of using low doses of sulphones in treating leprosy, which results in equal effectiveness with a lower incidence of reactions, we gave 25 of the patients 100 mg of B 663 by mouth daily, the other 5 lepromatous cases acting as a control group

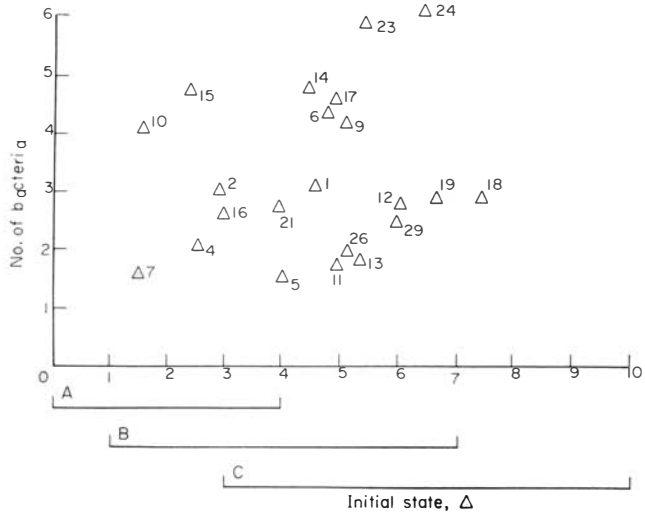

FIG. 1

Bacteriology. Morphological Index: A, typical agroupic bacteria (1); typical aislic bacteria (2-4); B, fragmented bacteria (1-7); C, granular bacteria (3-10).

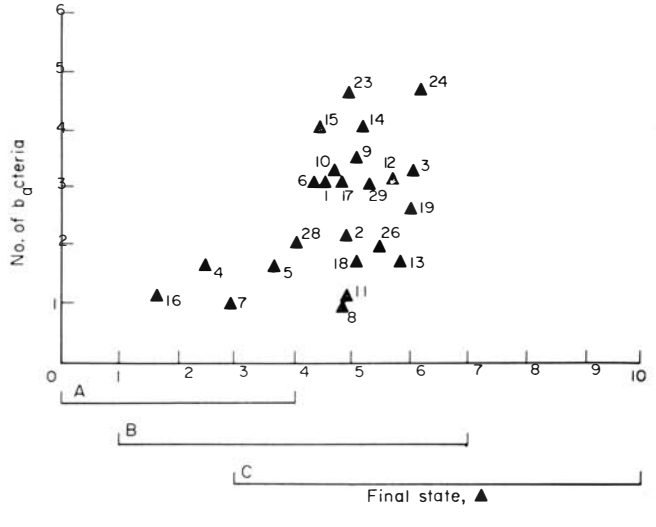

FIG. 2

Bacteriology. Morphological Index: A, typical agroupic bacteria (1); typical aislic bacteria (2-4); B, fragmented bacteria (1-7); C, granular bacteria (3-10).

on 300 mg daily. The 3 patients with tuberculoid leprosy, residual neural damage, and lepromatous reactions were also given 300 mg a day. The drug was administered for between 4 and 13 months. Of the 30 lepromatous patients, 2 have almost completed one year of treatment and 22 a period of 6 months.

RESULTS

Subjectively the patients were all content with the results of treatment and in general were not particularly disturbed by the red coloration of the skin. The objective clinical findings were as follows:

(a) The general condition of the patients remained unchanged, with no variation in body weight or appetite.

(b) In all cases, after one month of treatment the skin lesions showed less infiltration together with flattening, and this was very evident towards the sixth month. The lepromatous lesions mostly became frankly atrophic, with folds upon the surface and usually taking on a blue-black colour upon a skin which appeared xerodermic especially in the distal areas of the limbs. In 2 patients the skin became obviously ichthyotic; in the patient with an indeterminate condition the lesions disappeared completely by the sixth month.

(c) In the 3 tuberculoid patients with residual nerve damage and in 4 lepromatous patients who also had intense neuritis, the lesions improved after the second week of administration of B 663; the lightning pains disappeared, as also did the aching in the elbow and the sensations of formication and paraesthesia.

(d) In one patient with lepromatous leprosy and obvious lesions of the rhino-pharynx and larynx it was observed that after 6 months the nose became less congested, there was obvious healing in the pharynx and larynx, and the epiglottis was less infiltrated and more mobile.

Bacteriologically, within a month there was a fall in the bacillary count in most cases, with an increase in granulation in the bacilli. Fig. 1 shows a high bacillary index at the beginning

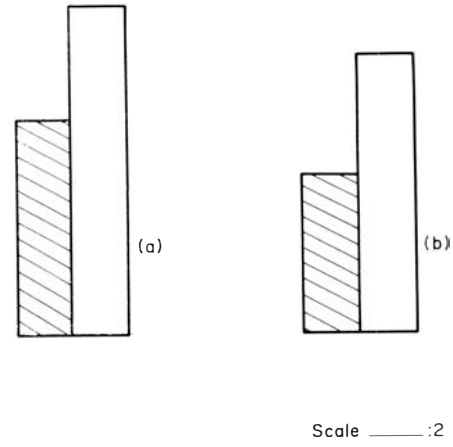

FIG. 3

Bacteriology—absolute values. (a) Initial, (b) final. The bacteriological index is shown shaded and the morphological index open.

of treatment with most of the bacilli lying within the range of morphologically normal grouped and isolated bacilli. Fig. 2 on the other hand, which represents a stage after treatment, shows that the bacillary index has fallen and the morphological index has stabilized within the middle range. Fig. 3 summarizes the findings in Figs 1 and 2 and demonstrates a significant change in the number of bacilli and a fall in the morphological index, with 3 negative cases. In the 2 lepromatous patients treated for one year no bacterial resistance has developed.

Histologically, the biopsy specimens taken during the early months of treatment showed favourable changes, consisting in a diminution in Virchow cells, and the appearance of fibroblasts in lepromatous cases with accentuation of tuberculoid structures; in the dimorphic case there was a diminution in lepromatous structures. Although there were changes in the number and morphology of bacilli, this was not so evident as the cellular change. Where the histological change was not very obvious, the patient had usually been treated previously with other drugs which had produced an improved and more or less stable histological and bacillary picture.

There were no significant changes in the lepromin reaction.

Tolerance, complementary studies

Tolerance of B 663 was good in all cases. The one notable secondary effect due to the drug was a red pigmentation of the whole skin, especially in exposed sites, which appeared after 15 days and was more obvious in those given 300 mg daily. After 4 or 5 weeks of treatment, it was found that the skin had become xerodermic and in 2 cases frankly ichthyotic.

No significant changes during treatment were detected at any of the 3-monthly laboratory examinations which included liver function tests and serum electrophoresis.

B 663 coloured the urine a yellowish-red and after 3 or 4 days of treatment there was a level of 0.005 to 0.015 mg of the drug per 100 ml of urine. No trace of the drug was detected in the cerebrospinal fluid. These studies were carried out on 13 patients receiving 100 mg of B 663 daily.

Reactions

None of the patients given 100 mg of clofazimine daily underwent a reaction, and on this dosage one steroid-dependent patient lost his dependency on steroids.

Out of 5 lepromatous patients given 300 mg of clofazimine daily, 4 had had an erythema nodosum reaction and one of these showed a typical Lucio phenomenon; reactions subsided in all cases with thalidomide administration. When treatment was resumed with 100 mg daily, the reactions did not reappear.

Comments

In spite of the short period of study and the small number of patients involved, which does not permit of a definite statement, we can say with certainty that B 663 has a clinical effect comparable with that of the sulphones and indeed acts even more rapidly. During the period of observation there was histological and bacteriological improvement, and a definite effect on nasal and laryngeal lesions and on specific neuritis was also observed.

The finding that patients in whom a leprosy reaction had been overcome did not have further reactions when the drug was resumed in the lower dosage of 100 mg, endorsed our view that B 663 should be used in small doses, since these will produce as good a therapeutic effect with a lesser incidence of reactions. Another argument in favour of this lower dosage is that patients who are attending as out-patients will have less skin pigmentation.

SUMMARY

Thirty-five leprosy patients with various clinical forms of the disease were treated with B 663 (clofazimine) for 4 to 13 months. An excellent clinical result was obtained, together with both histological and bacteriological improvement, on a dosage of 100 mg a day. Reactions were absent on this dose and the drug was tolerated perfectly.

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