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B 663 (Geigy) – Further Observations on its Suspected Anti-Inflammatory Action

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In the course of the first trials of B 663 (Geigy) at a dose level of 300 mg. daily, in a series of 26 patients with lepromatous leprosy in Eastern Nigeria, Browne and Hogerzeil (1962 a.b.) and Browne (1965) found that erythema nodosum leprosum (ENL) developed in only two patients in the course of 12 months; in both cases the condition occurred within the first four weeks of treatment, and was slight and transient. When, however, in these same patients B 663 was subsequently replaced by standard dapsone therapy, 14 of them passed, during the next two years, through episodes of acute exacerbation.

Williams *et al.* (1965) have reported that two patients receiving higher doses of B 663 (600 mg. daily) did not suffer exacerbation while receiving the drug, but did within two weeks of the drug's being suppressed, the signs of exacerbation responding promptly when the drug was readministered at the same dosage. In another patient who was also receiving dapsone throughout, B 663 appeared to exert an anti-inflamatory effect on each occasion it was given.

These findings indicated that further investigations were necessary, not only in order to confirm or refute the supposition that B 663 has an anti-inflammatory action (of indeterminate nature) but also to provide practical data for the use of the drug in treating patients with lepromatous leprosy in persistent exacerbation.

The opportunity to put this suggestion to a severe testing presented itself in Eastern Nigeria: if B 663 proved effective in suppressing persistent exacerbation uncontrollable except by continuous administration of corticosteroids in a series of such patients, then its sphere of usefulness in this regard would be established as far as lepromatous leprosy in Africa is concerned, and trials elsewhere would be indicated.

First Group – Patients with persistent exacerbation

Ten adult patients, all suffering from lepromatous leprosy, with completely negative Mitsuda reactions, volunteered to participate in the trial. They had all been suffering from persistent exacerbation for periods varying from 16 to 36 months, with an average of 24 months. Reaction had begun in these patients at different points of time in the course of treatment: from the 5th to the 9th month in five patients; from the 10th to the 19th in two, and after the 20th month in three.

The anti-leprosy drug that was in use at the onset of the acute exacerbation was in all cases dapsone, the dose of which had been subsequently reduced or suppressed for varying periods; thiambutosine had been substituted in some patients at some time or other. The exacerbation had failed to respond to the usual drug regime: sedation, antimonials, antimalarials, antihistaminics, etc., and recourse in all cases was finally had to the corticosteroids. After numerous unsuccessful attempts at weaning from corticosteroid dependence, it was regretfully concluded that each patient required a maintenance dose of the drug. Resumption of anti-leprosy therapy with small doses of dapsone or thiambutosine, under corticosteroid cover, had in some patients precipitated a return of the acute exacerbation and necessitated either suppression of the anti-leprosy drug or increasing the corticosteroid – or both these courses simultaneously.

The usual practice was then to reduce the maintenance dose of the corticosteroid used until the patient was spared the rigours and risks of severe exacerbation but was still subject to the discomfort of slight manifestations of the hypersensitive state, such as the appearance from time to time of new ENL lesions, the persistence of the more extensive and deep lesions, and the presence of some oedema and erythema and succulence of the lepromatous plaques.

While continuing the maintenance dose of the corticosteroid that had been given for the previous few weeks or months, and after suppressing the dapsone or thiambutosine that had been concurrently administered, we introduced B 663 in doses of 100 mg. daily (three of the patients having a loading dose of 100 mg. three times daily for three weeks), each oral dose being given with 5 ml. of edible vegetable oil to ensure absorption from the intestine.

In the three patients who had had the loading dose of B 663, and in three of the other seven, no more new ENL lesions appeared, and existing signs of exacerbation began to regress. These patients had been experiencing crops of ENL lesions every few days.

In the case of the remaining four patients, in whom the signs of exacerbation remained unaffected for four months while B 663 was given 100 mg. daily, the dose was empirically doubled, 100 mg. being given twice daily. Within two weeks it was apparent that the persistent exacerbation was being controlled: no new lesions appeared, and existing lesions regressed. After six months, the dose of B 663 was reduced to 100 mg. daily. ENL recurred in only one patient; it was controlled within two weeks when the dose of B 663 was doubled, and did not recur when the dose was subsequently reduced to 100 mg. daily and finally suppressed altogether.

When it would seem that all ten patients were no longer subject to acute exacerbation and were all at last showing welcome indications of improvement in their leprosy condition, the maintenance dose of corticosteroids was cautiously and progressively reduced. The rate of reduction varied with the individual patient, as did also the initial dose level. In all ten patients, it has been found possible completely to withdraw corticosteroids, though repeated attempts previously had been unsuccessful.

All ten patients are currently receiving 100 mg. of B 663 daily, in a single dose.

The *bacterial* findings in this group show certain general trends, with noteworthy exceptions. The Morphological Index (M.I.), which represents the average of the percentage of morphologically normal *Myco. leprae* at all eight skin and nasal mucosal sites smeared regularly, has remained at zero during the term of the trial, which is now 17 months. The drug has had no consistent demonstrable effect on the removal of degenerate bacilli from the tissues; in some patients, this function has continued at the same rate as before; in others the rate of removal has increased. Thus, the apparent anti-inflammatory effect in these patients is not related to any obvious factor, such as the precise height of the Bacterial or of the Morphological Index, or in the rate of removal of non-solid bacilli from the tissues.

The incidence of severe lepromatous peripheral neuritis was not high in this group, but the patients who were seriously affected have experienced a substantial and rapid improvement in the pain and tenderness in the nerve trunks.

No cases of reappearance of morphologically normal forms of *Myco. leprae* have been noted. It will be recalled that Browne and Hogerzeil (1962,c) reported that in a series of patients who had received 100 mg. of B 663 three times daily, morphologically normal *Myco. leprae* temporarily reappeared after 12 months in varying proportions at all sites smeared.

The histories of two of these patients may illustrate the therapeutic value of B 663, irrespective of the unidentified precise precipitating causes of the persistent exacerbation and failure to respond to anti-leprosy drugs. Both patients had begun treatment with methimazole (Tapazole, Lilly) (Browne and Hogerzeil 1962,d), and both had received dapsone at various dose levels, and other drugs such as thiambutosine and ditophal (Etisul, I.C.I.). Neither had shown any evidence of clinical progress for a long time. The B.I. in both patients had remained stationary for many months, at about 2.5 for one, and 1.1 for the other (maximum 4.0); but the smears from the first patient still contained nearly 10% of normal bacilli (i.e. after 41 months of treatment), whereas the second had had no normal bacilli for many months.

Both patients had a loading dose of 100 mg. B 663 thrice daily for three weeks, followed by a single daily dose of 100 mg. In the first, this dose was not initially quite sufficient to suppress all tendency to reaction, but the episodes that did occur during the first few weeks were comparatively mild and did not require corticosteroids for their control. He has improved considerably during the 16 months he has been

receiving B 663. The B.I. is falling steadily, being now 1.25. Normal bacilli disappeared finally from smears at all sites after eight months' treatment with B 663, i.e. after a total of 49 months' treatment, and have not reappeared during the ensuing seven months.

The other patient, after being in a clinically stationary condition for many months, has shown progressive improvement under B 663 therapy. Signs of acute exacerbation have disappeared; the B.I. began to fall within a month of his beginning treatment with B 663: now, after 16 months, it is zero. In this case, B 663 appears to have initiated clinical improvement in a man whose condition had been stationary for a long time. Concurrently, degenerate bacilli disappeared from skin and nasal mucosa.

Second group – patients in whom morphologically normal Myco. leprae reappeared.

The second group consists of two patients who have been under treatment for severe lepromatous leprosy for many years, and in whom there suddenly appeared numerous small succulent lesions containing innumerable viable *Myco. leprae* when skin smears had been negative for many months.

The first had had treatment for 15 years, having relapsed twice during that time. On readmission in 1958 his B.I. was 3.5 (maximum 4.0) and the M.I. 100%. By May, 1964, it seemed that the disease was completely arrested: no clinical evidence of leprosy remained, and no bacilli were seen in routine monthly smears from any site. Twelve months later, however, during the 80th month of treatment, while he was receiving 0.05 gr. dapsone twice weekly, numerous small papilliform elevations full of normal bacilli appeared in the skin. Under the impression that these bacilli were probably dapsone-resistant, the patient was given B 663. (In point of fact, it has been conclusively demonstrated by Rees (1966) that on the evidence furnished by mouse foot-pad inoculation, these bacilli are *not* dapsone-resistant).

The patient has responded well to B 663; the small papules are now flattened and level with the skin, and are replaced by striated scar tissue. The B.I. in these lesions has fallen from 2.75 to 0.7. The M.I. which was 65% when treatment started, is now zero, and much of the acid-fast debris is no longer of recognizable bacillary form. B 663 has thus acted well in this patient, who had been erroneously suspected of harbouring dapsone-resistant *Myco. leprae.*

The other patient had been under treatment for leprosy since 1952. Allegedly 'sensitive to sulphones,' she had received thiacetazone (a thiosemicarbazone) for seven years. Successive attempts at desensitization (Browne, 1963), had proved unsuccessful. Minute doses of dapsone seemed to precipitate severe exacerbation within a few hours. While continuing corticosteroid therapy, and not receiving any anti-leprosy treatment, she apparently was able to deal with and to eliminate non-solid mycobacteria and acid-fast debris. In January, 1965, and at every monthly examination subsequently, multiple smears from the skin and nasal mucosa revealed no acid-fast material.

In August, 1965, numerous small papular elevations suddenly appeared scattered over the trunk and limbs. These proved to be teeming with solid-staining *Myco. leprae*, although the intervening skin and the nasal mucosa remained bacteriologically negative. In view of the possibility that prolonged and intermittent very low-dose dapsone therapy might have induced dapsone-resistance, this patient was given B 663, 100 mg. daily. Prednisolone cover was maintained at the same dose as she had been receiving for some months. The lesions responded well, diminishing in size and elevation and eventually leaving a small thin striated scar. The *Myco. leprae* in these acute lesions rapidly showed fragmentation and irregular staining, and diminished in numbers. There has been no recurrence of exacerbation, although the dose of prednisolone given had previously been found to be insufficient to suppress all signs of exacerbation. The *Myco. leprae* inoculated into mouse foot-pads, by kind collaboration of Dr R. J. W. Rees, were shown to be dapsone-sensitive.

Pigmentation

At the dose levels of B 663 given in the 12 patients in these two groups, the red and black pigmentation of the skin was not as intense as in the series reported previously (Browne, 1962) and should not prove a contraindication in patients of similar skin hue.

DISCUSSION

In view of the vast numbers of drugs that have enjoyed but a short-lived vogue in the treatment of acute exacerbation in lepromatous leprosy, the results here recorded should be examined with caution. But because these results are so uniformly consistent, it is suggested that further investigations are indicated, particularly among patients with skin of a lighter hue, who are known to experience prolonged and intractable episodes of exacerbation. In this connection, it should be noted that Jopling (1966) has not observed similar improvement in five patients taking B 663 at dose levels os 50 mg. twice weekly or 100 mg. twice weekly, whereas Williams *et al.* (1965) found consistent ameliorstion when much larger doses (600 mg. daily) were given.

In the present series, 100 mg. daily sufficed in eight patients, but did not in four, in the latter, doubling the dose was followed by suppression of the signs of acute exacerbation.

It would appear that, B 663 in some way exerts its suspected anti-inflammatory action after absorption from the intestine and before being deposited in the tissues. After the administration of such high doses as 600 mg. for some weeks, the tissues are generally stained red with the dye and histological examination confirms that micro-crystals are present. When the drug is temporarily stopped in these patients, however, exacerbation ensues, to be suppressed again when B663 in given.

That its action in this respected is not simple, or simply bacteriocidal or bacteriostatic, is suggested by analysis of the pathological diversity of the patients in this series and the absence of complete concordance between the clinical and the bacteriological findings during the period of treatment with B 663. It will be recalled that all to patients in the larger group were practically stationary clinically because of persistent or recurrent severe exacerbation. Of these, four showed 'solid rods' in the multiple smears after 36, 39, 41, and 44 months' treatment respectively. 'Solid rods' disappeared in all four patients within 6- 12 months of beginning B663, i.e. the M.I. (which was 7%, 1%, 8%, and 12% respectively) fell to zero.

The clearance of the accumulated load of 'non-solid' bacilli proceeded at different speeds, to judge by the rate of fall of the B.I. in the individual patients. In three, all acid-fast material disappeared within 17 months, the B.I. in these patients having remained more or less stationary for many months previous to the beginning of treatment with B 663, with B.I. levels of 1.1, 0.5, and 0.4 (maximum: 4.0, on Dharmendra's notation); in one of these patients rare 'solid rods' had been encountered in the smears at the beginning of this treatment. In three other patients, the B.I. fell during the period of observation (17 months) from 1.1 to 0.2, from 1.0 to 0.5, and from 2.5 to 1.25. In one, it remained stationary.

In spite of these differences in the initial height and in the rate of fall of both B.I. and M.I., clinical progress as judged by the suppression of signs of acute exacerbation and progressive improvement in the patients' condition, was undeniably marked in all cases.

A related group of variables often suspected of playing some part in the initiation or persistence of exacerbation was represented in this small series of patients; that is, the amount of newly-formed antigen surmised to have been derived from degenerating mycobacteria, and either remaining *in situ* or in process of being phagocytosed. To judge from the varying amounts of acid-fast material found in these patients, and the fact that all patients improved when given B 663, the question of the immediate and precipitating cause of acute exacerbation still remains quite open.

The interval elapsing between the beginning of treatment with B 663 and obvious clinical amelioration was variable – from two days to two weeks. When new ENL lesions fail to make their appearance, in a patient who has experienced daily crops, the time-lag is more clearly defined than when the criterion is the diminution in existing signs of exacerbation. This aspect of the difficulty of assessing the value of any anti-inflammatory agent in leprosy, however, is not uniquely confined to the appraisal of B 663. As far as could be ascertained, psychological factors played no part in determining the persistence or the amelioration of the exacerbation in the patients under study. The criteria adopted in assessing improvement were objective.

SUMMARY

B 663 appeared to control persistent exacerbation in all ten patients, who were corticosteroid-

dependent. A dose of 100 mg. daily was sufficient in some patients, but 200 mg. daily was necessary in others. Notwithstanding numerous unsuccessful attempts at weaning from corticosteroids previously, it was found possible in all ten patients gradually to reduce, and eventually to suppress, corticosteroids while continuing to give B 663.

In two other patients, in whom dapsone-sensitive *Myco. leprae* suddenly reappeared in localised lesions in skin that had been bacteriologically negative for months, B 663 was also successful in ensuring both clinical and bacteriological inprovement.

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