Erythema Nodosum Leprosum

To the Editor:

The article entitled "The treatment of erythema nodosum leprosum with B.663. A controlled study" by J. H. S. Pettit, which appeared in The Journal ([5]) merits a considered reply. The use of the word "controlled" in the title is open to criticism on several grounds. If the article is allowed to pass unchallenged, a disservice may be done, and a potentially valuable drug may fail to be investigated with the necessary scientific detachment.

1. In reporting the early observations on "the possible anti-inflammatory action" of B.663 in lepromatous leprosy ([1]), I suggested that the drug "may exert a suppressive effect on the development of acute exacerbation in lepromatous leprosy," and in the appraisal of the pilot trial after three years ([2]) I stated that "while taking the drug, patients seem to be much less liable to episodes of acute exacerbation." On the evidence submitted, it is difficult to see how this guarded and tentative suggestion can be characterized as not "completely logical."

2. Pettit states (p.15) that the "findings. . . show simply that as a rule ENL does not start during the first six months of the anti-leprosy treatment." But some of the patients in question had been under treatment for 12 months, and Pettit quotes (p.2) from another article in the same issue of The Journal the Carville analysis of 248 cases in which ENL "usually started six to 12 months after treatment began."

3. Our early work was concerned with reporting an apparent effect of B.663 in preventing the development of ENL. Pettit himself falls into the logical fallacy of *non sequitur* in assuming that a statement concerned with *preventing* ENL is necessarily germane to "the problem of *treatment* of ENL". It may or it may not be. We made no claim either way. At the time we had no experience in the *treatment* of established ENL with B.663; although retrospectively the two patients in our series in whom ENL appeared (and disappeared) during the first month of treatment with B.663, might have been quoted as evidence of the therapeutic effect of the drug, we did not claim that the disappearance of ENL was due to B.663, since the condition might have subsided spontaneously.

4. It is unfortunate that Pettit's patients in Malaysia did not accept the ruddiness and darkening of the skin that may follow dosages of B.663 (i.e., 100 mgm. daily) that are enthusiastically taken by the "more deeply pigmented patients participating in the trial" in Eastern Nigeria. I had already hinted that "both the red and the black coloration might prove unacceptable in the lighter-hued." That this argument may not be everywhere valid or insuperable is suggested by the fact that Caucasians, Chinese and other light-skinned patients are at present accepting treatment with the drug at that dose in Great Britain and elsewhere, despite the pigmentation. Other patients are taking smaller doses of B.663, and showing less cutaneous pigmentation than those on higher doses, and incidentally the same rate of clinical and bacteriologic improvement.

5. It is difficult to reconcile the statements (p.12) that during treatment with B.663 "the amount of anti-inflammatory hormone needed by three of the five patients diminished with surprising speed," and (p.15) "our findings show *conclusively* that B.663 . . . *has no anti-inflammatory effect* in ENL" (our italics). This sweeping generalization is not, and cannot be, deduced from the findings reported, and is another example of the logical fallacy of *non sequitur*. The conclusion may be valid for a small series of patients who received B.663 in inadequate amounts, although this is by no means deducible from the evidence submitted. It is a far cry from the dose of 300 mgm. daily that apparently *prevents* the development of ENL, to a dose of 100 mgm. daily that fails to *cure* the established severe condition.

6. No evidence is submitted in support of the statement that "it is not considered

probable that a higher dose will give more satisfactory results." In point of fact, had higher doses of B.663 been given to these Malaysian patients, it can be stated with assurance that the established and severe ENL would—on the accumulated experience in Eastern Nigeria, the United States of America ([6]), and Zambia ([4])—have yielded to this drug. I should not have expected a majority of patients with ENL of grade 4+ to improve on a dose of 100 mgm. daily of B.663.

7. The contention that the results in this small and selected group "disprove the much repeated misconception concerning the cessation of sulfones in ENL" (p.15), will not find favor with experienced leprologists who base their conclusions on larger and more representative series. While stopping dapsone may not always result in rapid improvement in ENL, it is incontestable that resumption of dapsone therapy in such patients, even in minute doses, will often precipitate a recurrence of the signs and symptoms of ENL.

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Since the publication of our earlier reports on the apparent prevention of ENL by B.663, we have had some considerable experience in treating established ENL with the drug, and conclude that when given in adequate amounts it will prevent further new ENL lesions developing and facilitate the disappearance of long-standing manifestations of the hypersensitive state.

The real value of B.663 in the treatment of patients with persistent and severe ENL, and subject to recurrent crops of ENL lesions in the skin, is indicated in a study reported in 1966 ([3]). B.663 "appeared to control persistent exacerbation in all ten patients, who were corticosteroid-dependent. A dose of 100 mgm. daily was sufficient in some patients, but 200 mgm. 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 supress, corticosteroids while continuing to give B.663." These patients were comparable with those reported by Pettit, and careful adaptation of the dose of B.663 to the individual requirements gave excellent clinical results in all the patients. The patients in the Nigeria trial had been suffering from severe ENL for, on the average, 24 months before beginning treatment with B.663 (range: 16-36 months). Pettit's patients "had been treated for severe ENL for at least six months."

More recently, a group of patients at Liteta Leprosarium, Zambia, under the care of Dr. F. M. J. H. Imkamp, has been studied. Some months ago all were bedridden, corticosteroid-dependent, and suffering from long-standing "grade 4+" ENL. Thanks to B.663, which had to be given in some patients in doses up to 300 mgm. daily, the ENL has in all cases yielded to the drug, the patients are now ambulant, and their general condition is excellent. These findings will be reported as soon as the necessary data have been critically reviewed and assessed ([4]).

The indications for the use of B.663 are now becoming clarified: it is of value in treating patients—

(1) suffering from lepromatous leprosy, particularly if they appear (on summation of clinical and perhaps biochemical indications) to be liable to severe and prolonged exacerbation;

(2) with lepromatous leprosy who are suffering from long-standing ENL of sufficient severity to necessitate continuous corticosteroids;

(3) harboring dapsone-resistant *M. leprae*;

(4) who show slow clinical and bacteriologic response to dapsone, or intolerance of or hypersensitivity to dapsone.

It is to be hoped that B.663 will be subjected to thorough investigation as an antileprosy drug having anti-inflammatory properties.

In view of the importance of the subject, I would like to call attention again to my article in *Leprosy Review* **37** (1966) 141-145, entitled "B.663 (Geigy). Further observations on its suspected anti-inflammatory

action." (Abstracted in THE JOURNAL **34** (1966) 445.)

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