Lepr. Rev. (1969) **40**, 251-253

Letters to the Editor

B I

Thank you for giving us the opportunity to reply to the letter from Dr. John H. S. Pettit regarding our paper entitled "An Open Trial of Low Doses of Dapsone in the Management of Lepromatous Leprosy".

It is because the findings were unexpected and disturbing that we felt it necessary to publish them. While it would not be proper for me to enter into a discussion with Dr. Pettit on the merits and demerits of the bacterial index (BI), I may add that most of the comments that Dr. Pettit has made in this regard would be applicable to the supposedly more sensitive parameter, namely the morphological index (MI). We are aware of very marked variation in the score given by two highly reputable laboratories in relation to the MI and, therefore, the observer's error that Dr. Pettit is pointing out, seems to be not very different from the assessment of BI, as compared to MI. I should like to state that these smears were taken and read by one senior technician with random checks by one of us (A.B.A.K.).

I would refer Dr. Pettit to page 620 of *Leprosy in Theory and Practice*, 2nd edition, 1964 (Appendix 3), where Dr. Ridley discusses the Bacteriological Indices; we have followed the definition of the positivity that Ridley gave in that paper according to his system of 0 to 6. I may add that we are not aware of "reasonable consensus of belief that in untreated lepromatous leprosy the initial BI would be above 4+". In fact this consensus (if it exists) may apply only to sanatorium-based leprosy research and certainly not to studies based on intensive domiciliary treatment programmes where it is very common to find early cases of lepromatous leprosy, the majority of which tend to have a BI below 3+ on Dr. Ridley's scale. In our domiciliary treatment programme, which has over 8000 patients, more than 50% of new registration of lepromatous leprosy patients have a BI of below 3+.

I may further add that we have been inoculating bacilli from skin biopsies from patients on low doses of DDS at periodic intervals, and data available to date suggest that the bacilli in the skin of patients treated with small doses of dapsone are viable even after 18 months of continuous treatment. I must further add that the presence of DDS in the sera of these patients has been authenticated through the courtesy of Dr. C. C. Shepard, so that there is no doubt that these patients to whom we are referring have had regular doses of DDS. The further analysis of data regarding these patients since submission of our paper is in keeping with the findings which we have already presented.

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B 663

In their paper "The effect of methylcellulose on the phagocytosis of *Mycobacterium lepraemurium*" (*Lepr. Rev.*, 1969, **40**, 83-86) Drs Wong and Gibson make some points involving B 663 (Lamprene) which require comment.

First: B 663 is not "taken up by macrophages in particulate form" as these authors state (p. 86) but rather it would appear to enter the macrophages in solution linked to a lipoprotein carrier which is then split off (Byrne, Conalty and Jina, 1969), with the consequent intracellular formation of crystals of B 663.

Second: there is no need to invoke the concept of enhancement of phagocytosis to explain the activity of B 663 as its activity

against a wide spectrum of mycobacteria is also apparent *in vitro* (Barry and Conalty, 1965). Indeed not only does B 663 not enhance phagocytosis by macrophages but in high doses it actually depresses this (Conalty, 1966; Byrne, Conalty and Jina, 1969).

Third: from their findings that methylcellulose did not alter the course of *Myco. lepraemurium* infection and that individual macrophages ingested the polymer or the bacilli preferentially they concluded (p. 86) that B 663 "must be administered either in high dosage or over prolonged periods in order to gain access to bacilli lying within cells". This extrapolation is unwarranted and is not borne out by the therapeutic findings in: experimental tuberculosis (for literature references see Barry and Conalty, 1965), *Myco. lepraemurium* infection of mice (Chang, 1962), or *Myco. leprae* footpad infection of mice (Shepard and Chang, 1962).

In conclusion we should like to express our disquiet at the publication of results based on experimental work in which no less than half of the experimental animals died from intercurrent infection.

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22 July, 1969

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B 663

It has been brought to our attention by Dr. M. L. Conalty that after submission of our paper to the *Leprosy Review* (1969, **40**, 83) evidence was presented that B 663 (Lamprene) is not taken up into the macrophages by phagocytosis and that the speculation we made about the possible sequestration into macrophages which did not contain bacilli was unjustified.

None the less, our preliminary observations showed there is evidence of preferential uptake of certain materials by particular macrophages, and this is a factor which should be borne in mind when the *in vivo* action of chemotherapeutic agents is being considered, since the uptake must be related to events at the cell surface, perhaps including pinocytosis.

I wish to emphasize that demonstration of preferential uptake would be expected to be influenced by the relative quantities of the materials administered simultaneously. When a large number of organisms is administered with a given dose of methylcellulose, some uptake of both may be observed, whereas with a smaller inoculum segregation may be more evident. So far, by the methods used, we have detected only small numbers of bacilli in cells containing large quantities of methylcellulose, whereas cells which had ingested large numbers of bacilli did not contain demonstrable methylcellulose.

Another point made by Dr. Conalty and Mr. Jina is that B 663 does not enhance phagocytosis. In our experience we found no evidence of enhancement of phagocytosis by methylcellulose, and we remarked in our paper that the action of drugs such as B 663 "cannot be ascribed to an enhancement of phagocytosis alone".

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BACTERIAL INDEX

I should like to claim a little space in your columns to consider the paper by Karat *et al.* entitled "An Open Trial of Low Doses of Dapsone in the Management of Lepromatous Leprosy" (*Lepr. Rev.*, 1969, **40**, 99-105) in which the authors admit that some of their findings are disturbing.

These are the findings connected with the Bacterial Index (BI) of their patients, and I must admit that I find equally disturbing the tendency to rely on this index as having some statistical or scientific value. It should not be necessary, Sir, to remind your readers that the skin-scraping technique is grossly inaccurate—taking, as it does, an unmeasured amount of tissue fluid and spreading it over an undefined area. It is therefore imperative to do everything possible to diminish technical variation and I should be glad to know if all the smears reported in each of their cases were taken by the same person.

I am at present engaged on an international study of the treatment of lepromatous leprosy, and scrapings taken by physicians in many parts of the world are sent to me. It is fascinating to note the difference in area that these smears cover, and to see that the size varies not only from worker to worker but also from smear to smear. It might well be that only one technician took all the smears in the paper under question, but as there is no comment on this I will not be convinced that the BI actually rose during treatment until I have been offered a little more evidence.

It is also necessary to question the authors' definition of positivity, that is to say, how they grade 1+, 2+, etc. It seems to me certain that they do not use Ridley's Logarithmic Index, as there is a reasonable consensus of belief that in untreated lepromatous leprosy the initial BI would be above 4+, and more than half the cases reported have an initial BI under 3+ (and 2 more with a BI of exactly 3.00). As Ridley took pains to show, the logarithmic index is not accurate but has simply been devised to reduce the inconsistencies of a non-scientific technique.

I should be grateful if Dr. Karat and his co-workers could tell us a little more about these matters. If all their smears were made by one worker and if their definitions of the BI have eradicated the problems that worried Dr. Ridley, it would be true that their findings needed further study. It is also possible that by now (as their paper must have been completed by March, 1969) they have further results regarding the BI in these patients; it is to be hoped that the patients continued on low dosage, as otherwise we shall never know whether the "tendency of the BI to rise" was a fact or an unfortunate combination of technical errors.

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