"LEPROMIN" REACTIONS WITH NORMAL—TISSUE PREPARATIONS

TO THE EDITOR:

We have read with interest the paper by Doctors Kooij and Gerritsen on positive "lepromin" reactions with suspensions of normal tissue particles in THE JOURNAL [**24** (1956) 117-181], particularly since reference was made to their work by Dr. A. R. Davison of the Westfort Institution at the East African Conference on Leprosy and Tuberculosis, held in Dar-es-Salaam in January of this year. Since then we have been able to examine their conclusions more closely.

It has been generally recognised that, although lepromin is the only antigen for leprosy work available, it is not ideal, and the authors have successfully drawn attention to some of the difficulties. At the same time there are gaps in the evidence for their conclusions that they may have already recognised, and which we hope will prompt them to continue their interesting investigations.

In the majority of tests based on reactions to allergens or antigens, there are sufficient variations in the normal host response to make it difficult to fix absolute standards of positivity. There is also the influence of sensitization (or "conditioning") by members of the same or other groups of microorganisms which, for our purpose, may be labelled "nonspecific." These factors do not necessarily invalidate a test if due allowance is made for them. The tuberculin test with PPD gives negative results in certain circumstances, even when bacilli are present and active, and there are geographical variations in the standard of positivity which may depend on the host or on the influence of other antigens. There are, in addition, the practical difficulties of accurately measuring infiltrations 3 mm. or less in size, which we assume have been taken into account. These are good and sufficient reasons for thinking that comparisons based on very small infiltrations should be treated with some degree of caution.

Our main difficulties in accepting the authors' argument can be summarised as follows:

1. Their Table 1 is based on the late results in 10 tuberculoid patients who had previously reacted strongly to lepromin. Although it is not clear from the table (which gives details of only 4 cases), only 1—not 4—of the 10 gave a positive late reaction with the normal skin preparation by the criteria employed by the authors (i.e., 3-4 mm. = doubtful, 5-7 mm. = 1+), and that reaction had a diameter of only 5 mm. as against 18 mm. with lepromin. One weak positive out of 10 is hardly convincing.

2. Their Table 2 shows the late results in another 10 tuberculoid patients each of whom had received injections of three skin preparations. One was a ten-times concentrated whole-skin preparation, and despite this high concentration only two cases gave positive reactions to it. One of these cases and 3 others gave positive results with the watery fraction after extraction of the lipids. The measured responses of the same patients to normal lepromin and to ten-times concentrated lepromin, which are fundamental, were not shown. (One lepromatous case gave a positive early reaction with one of the fractions.)

3. Their Table 3 shows that only 2 of 10 tuberculoid patients gave late positive reactions by the authors' standards to any of the three fractions of normal tissue, and neither was positive to more than one fraction. The measured reactions to normal lepromin are again not given. (One lepromatous case gave a positive late reaction with one of the fractions, and another case had a positive early reaction with another fraction.) Incidentally, below the table the lipid fraction is designated B, in the text, C. We assume B is correct.

Comparison of the late results in the only 5 tuberculoid patients common to Tables 2 and 3 (Nos. 12467, 12484, 12492, 12498, 12506) shows that only one (No. 12492) gave a positive reaction in both experiments.

4. Their Table 4 shows that among 10 tuberculoid patients there were 4 positives and 2 doubtfuls in the 28-day results to various lepromin

preparations, whereas the normal liver suspension produced only 1, and this in the only patient (No. 12492) who appeared in the three Tables 2, 3 and 4. This individual's response was consistently greater than that of any other, whatever the preparation. Allowing for his greatest nonspecific reaction of 10 mm., he still responded by another 15 mm. when tested with the bacillus, a difference which is surely significant (25 mm. in Table 4, minus 10 mm. with normal liver or the ten-times concentrated water fraction of normal skin).

5. A conclusion that a reaction to a bacillus is a foreign body reaction can hardly be based on the biopsy of a single papule following an injection from which the bacillus had been excluded.

6. We find it difficult to understand the reason for adding together the measurements of a series of small reactions many, or the majority, of which were negative by the authors' standards. Adding them together does not give them any more significance.

We have concentrated on the late reactions because, as the authors say, it is the Mitsuda reaction that is prognostic. Like the authors, we would prefer a more absolute test. A purified protein derivative would be useful for comparisons with tuberculin. An antigen containing the whole killed tubercle bacillus, and one containing the killed leprosy bacillus from which all tissue detritus had been removed, would be the ideal. It may be useful to be able to find out how an individual has reacted previously to the challenge of infection, but it would be of greater practical value to know how someone will behave the first time infection is encountered. We also agree, as we showed at Dar-es-Salaam, that evidence based on the lepromin and tuberculin tests alone by no means proves a universal immunological relationship between leprosy and tuberculosis. Sir Harold Himsworth said in his summary that the differences may be more important than the similarities. On the other hand, one can hardly reject a long-established test out-of-hand, unless the evidence is based on facts which are statistically incontrovertible.

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The foregoing letter was submitted for comment to the authors of the article referred to. Their reply follows.—EDITOR.

TO THE EDITOR:

We are pleased with the interest taken by Dr. Kinnear Brown and his associates in our article, and we hope that the following reply will remove their doubts. The numbered paragraphs correspond to those of their letter.

1. We did not mean that the reactions were positive according to the Madrid criteria, but were pointing out that reactions do occur to injections

of normal skin preparations. Most workers who have carried out experiments with extracts of normal skin did not obtain any reactions.

2. In this experiment we, too, had expected stronger reactions with the ten-times concentrated preparation A. However, this does not mean that this preparation was 10 times as strong as the skin preparation referred to in Table 1, because the method of this preparation is very inaccurate. Although the measured responses of the same patients to normal lepromin were not shown, it was stated that the patients with tuberculoid leprosy had previously reacted strongly to lepromin. In the following tabulation the measurements of the reaction to normal lepromin (L) are shown in comparison with those to the concentrated skin preparation (A).

Case No.	Type	48-hour readings		28-day readings	
		L	A	L	A
8962	L	0	2	0	0
9759	L	0	5	1	2
12175	L	0	4	0	0
12176	L	1	3	0	0
12220	L	1	2	0	0
11458	L	1	2	1	0
12286	L	2	3	0	4
12290	L	2	2	3	3
12304	L	5	7	2	0
12312	L	0	3	0	1
12435	T	13	3	12	0
12448	T	10	5	17	3
12467	T	10	2	7	1
12498	T	8	2	5	3
12506	T	24	9	20	5
12424	T	15	2	10	—
12427	T	15	5	12	2
12471	T	12	2	9	2
12484	T	10	2	8	0
12492	T	20	10	16	7

3. The designation B for the lipid fraction is the correct one.

4. We agree that the responses to normal tissue preparations are weak.

5. Because of the weak responses, and because of the fact that after concentration and centrifuging the activity of the preparations seemed to decrease, we came to the *hypothesis* that probably the presence of particles and their size might be of importance, and that in the late lepromin reaction we are dealing with a kind of (sarcoid-like) foreign-body reaction.

6. Because of the poor response to our preparations of normal tissue, we wanted to know if there was a difference in response between the two *groups* of patients, lepromatous and tuberculoid. In this way one may detect small differences. For scientific purposes it is better to compare millimeter readings than personal conclusions regarding positivity

and negativity. Furthermore, one must bear in mind that we were not dealing with a preparation ready for clinical use, but that we were experimenting.

From the last paragraph of the letter of Dr. Kinnear Brown and associates we get the impression that they assume that we think the lepromin test is of no use. That is not the case. In our mind it is of great use for classification and prognosis. However, we need a better standardized preparation, and we must know more about the nature of the lepromin reaction. In the Wade-Mitsuda lepromin the bacilli are still for the most part responsible for evoking the reaction, but with a concentrated preparation of normal liver we can equal it.

We have continued our studies and obtained stronger preparations from normal liver. For particulars we may refer to our article on "The nature of the Mitsuda and the Kveim reactions" in *Dermatologica* (Basel), in press. In that article are reported results of experiments with bacterial filtrates of lepromin and of normal tissue preparations, and the reactions to lepromin and Kveim antigen in leprosy patients are also compared.

After the publication of the article which is the subject of this correspondence there appeared one by Floch [THE JOURNAL **24** (1956) 292-296] in which our results are confirmed.

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