The circumstances under which this communication was made available are unusual. When Dr. Sagher sent us an abstract of the article of Kooij and Pepler on "A Re-Evaluation of Tissue Reactivity to BCG, Tuberculin and Ink in Lepromatous Leprosy," published in *Dermatologica* **122** (1961) 360-372 (abstract in this issue), he said that he was sending a letter of comment to the editor of *Dermatologica* for publication. He also informed Dr. Kooij that he was doing so.

Since we do not receive that periodical, we asked Dr. Sagher for a copy of the letter to the editor, and we also asked the editor himself for permission to reproduce the letter when it should appear. Dr. Sagher's office supplied the copy requested, and the editor concerned said that it was to appear in *Dermatologica* **125** (1962) 267-269.

Anticipating that Dr. Kooij would reply to Sagher's letter to the editor, he was asked for a copy of what he would write. He replied that he had not seen Sagher's letter, but had asked the editor for permission to see it and to reply in the same issue. He had received no reply to that request. He supplied comments on Sagher's abstract, a copy of which had been sent him, and asked that they be printed if Sagher's letter should be used. They are, since it is.—EDITOR.

SIR:

After careful reading of the article of Kooij and Pepler on tissue reactivity to BCG, etc., in lepromatous leprosy, I find that it contains a number of inconsistencies. I would therefore like to offer the following criticism.

Drs. Kooij and Pepler repeated some of the experiments done independently by me and by Dr. Waaler and Dr. Richter, from which we came to the same conclusion, namely, that in lepromatous leprosy there exists a peculiar host reaction to various externally-introduced substances, similar to that in sarcoidosis expressed in the Kveim test. In their experiments Kooij and Pepler used BCG, tuberculin and India ink.

The main point of disagreement lies in the control observations of these authors. In my own examinations I found some perivascular foam cell aggregates, which I classified as of 1+ grade, in 10 out of 41 control specimens taken from 34 patients (almost all of them the same patients in whom the experiments were done). Larger lepromatous aggregates were present in only 4 additional specimens.

I do not believe that any pathologist examining lepromatous leprosy patients, elsewhere than perhaps in Africa, would confirm the finding of about 75 per cent lepromatous infiltrates in normal-looking skin well apart from overt lesions. If I am not mistaken, practically all of the biopsies in Kooij's material were from the skin of Negro patients, which may explain this high percentage. It may be that in these patients it is more difficult to recognize normal skin than in white patients. The specimens may have been taken from areas of inapparent diffuse infiltration.

Both his and my patients were for various times under sulfone treatment, but this seems not to be the main cause of the differences in our findings. It should be pointed out that the first case in which I found this peculiar reaction was a "burnt out" one in which repeated biopsies had been made over the years, without finding any lepromatous background. Then the biopsy of a tuberculin injection site revealed a picture indistinguishable from lepromatous leprosy.

If we analyze the results of Kooij and Pepler against this background, it seems strange that no lepromatous infiltrates were found in 23 out of 35 biopsies following the injection of BCG; and, furthermore, that when India ink was injected, lepromatous background was found in only 2 out of 10 biopsies. If there is a lepromatous background even in apparently normal skin, as they state, the least we might have expected is that this should also be present after any manipulation of such skin.

It is noteworthy that Kooij has actually provoked tuberculoid tissue reactions by injecting normal-tissue suspensions intradermally into patients with tuberculoid leprosy. This could be considered as a kind of "isopathic phenomenon." This only strengthens my conclusion that in leprosy there is a peculiar tissue reaction to injected foreign material; namely, that in the lepromatous type a leproma develops, while in the tuberculoid type a tubercle develops.

A further point, incorrectly stated by Kooij, is that I found only a lepromatous tissue reaction to the injection of living material such as BCG. The fact is that, after the injection of living organisms such as BCG and *Leishmania tropica,* I always observed a clinical course and histologic change typical of the respective infection. Sections revealed a tuberculoid structure following BCG, and a leishmanial granuloma following *L. tropica,* but in both cases there was also a considerable aggregation of foam cells far exceeding the number which might have been present as "background" before inoculation. It was also noted that in cases following BCG injections there were tubercles which consisted almost exclusively of foam cells and not of epithelioid cells as in tuberculosis. Furthermore *L. tropica* multiplied in foam cells and not in macrophages.

There is, further, a quantitative aspect in all my control cases in which some foam-cell aggregates were found around the blood vessels or somewhere in the cutis. The 1+ reactions were cell aggregates consisting at most of some dozens of cells. This certainly would not be apparent clinically. In the reactions following the injection of living or

nonliving materials, the background was a granuloma which clinically had shown up as an elevated papule or an infiltrated plaque. Therefore, it is difficult to accept the lepromatous-background explanation of Kooij and Pepler. I believe if they were to reexamine their slides they might find a significant quantitative difference between the biopsy specimens taken from control sites and from those in which a lepromatous reaction was evoked by the introduction of foreign substances. I further believe that they would find lepromatous material in some of their biopsies made following BCG after the lapse of 9 days.

*Summary.*—In many respects the experiments of Kooij and Pepler confirm the idea of an isopathic phenomenon in lepromatous leprosy, despite certain inconsistencies in their results and conclusions, which may have been influenced by control experiments done in patients in whom the control site could not always be recognized as normal skin.

I therefore reaffirm my findings, and those of Waaler and of Richter, in which patients with lepromatous leprosy have been shown to react in a peculiar manner to the introduction of foreign materials.

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SIR:

The abstract written by Dr. Sagher for THE JOURNAL is, in my opinion, *insufficient*, for the reader cannot judge the value of the arguments. I would propose that if his letter to the editor is published, part or all of our article should also be printed. Not knowing the content of Sagher's letter, I will confine myself for the present to a few arguments.

I was very mild in my criticism of Sagher in the article in question, but I think that he and his associates made several mistakes. (1) They did not realize that in apparently normal skin of lepromatous leprosy, many acid-fast bacilli are often found. (2) Their staining for acid-fast bacilli in histologic specimen was not always adequate. When you look at the individual cases in their tables (e.g., *Archives of Dermatology* **70** (1954) 635), there is often no concordance with the findings of acid-fast bacilli in smears and histologic specimen. I am inclined to believe that in cases with positive nasal smears, in which Sagher found lepromatous tissue histologically but without or with only a few bacilli, something was wrong with their staining. Cases with positive nasal smears are usually active cases. I may quote Jonquieres and Sanchez Caballero [THE JOURNAL **29** (1961) 327] who wrote, "It is almost always the rule in leprology that when the nasal mucus is positive, the numbers of bacilli in the skin are relatively large." This is also the experience of Davison and myself at Westfort. (3) Finally, Sagher did not know, or at least did not take into account, the fact that you cannot expect an epithelioid-cell reaction in the first 2 weeks after an injection. The existence of the "isopathic phenomenon" is still to be proved.

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[Without participating in this argument, we are constrained to remark on one phase of the matter, namely, the time at which biopsy specimens of injection sites should be taken—or, rather, the time at which they should *not* be taken—if a conclusion is to be drawn on the basis of a single examination (i.e., unless the series of changes is to be followed). The point holds for the lepromin reaction as well as other skin tests. The point is one on which Kooij touched briefly.

[The injection of any substance sufficiently irritating (or, if preferred, stimulating) to cause a tissue reaction at the site will at first cause some degree of acute inflammatory infiltration. That early reaction normally gives way in a very few days to a more chronic type of cell accumulation. It is after that when any special, specific change such as the accumulation and development of histiocytes, or the formation of epithelioid cells, will take place—if it is to take place. It is a matter of *maturation* of the lesion.

[In consideration of these factors, our advice to anyone studying, for example, the characteristic tissue changes of the lepromin reaction, is to remove the lesion for examination only after it has had time to mature.—EDITOR.]