



Isopathic Phenomenon in Lepromatous Leprosy

A Reappraisal¹

C. K. Job²

Sagher and his associates (5, 8-14) have described in a series of papers an unusual tissue response in patients with lepromatous leprosy. On injecting intradermally substances like tuberculin, milk, peptone, living BCG or *Leishmania* parasites, a special foam cell reaction was noticed irrespective of the nature of the injected material. The histologic picture was indistinguishable from lepromatous granuloma, but the foam cells had no bacilli in them. This specific alteration of tissue reactivity of the host was termed "isopathic reaction" in leprosy. Later, Waaler (15) demonstrated a similar response in two of four patients which he studied using tuberculin. His attempt to passively transfer this "isopathic reaction" to his own skin, however, failed. Kooij and Pepler (4) in a re-evaluation study of the tissue response of lepromatous leprosy to BCG, tuberculin and India ink found that there was no difference between lepromatous leprosy patients and normal persons.

In view of the divergent results reported by Sagher *et al.* (5, 8-14), and Kooij *et al.* (4), a study of the histopathologic appearances of tuberculin reactions in lepromatous leprosy patients was carried out and the significance of the findings are discussed in this paper. In a few cases the histology of the lepromin reaction was also studied in an attempt to find out whether there are any inter-relationships between tuberculin and lepromin reactions in lepromatous leprosy patients.

MATERIALS AND METHODS

Tuberculin test was done using purified protein derivative (PPD) in 14 active le-

promatous leprosy patients diagnosed and classified with the aid of a skin biopsy. The antigen (1 TU in 0.1 ml.) was injected intradermally into the right forearm and the site was biopsied at the end of 48 hours. In five of these patients lepromin testing was done using 0.1 ml. of Mitsuda antigen injected intradermally into the left forearm and the site was biopsied at the end of 21 days.

The biopsies were fixed in formol Zenker fluid, processed, blocked in paraffin, sectioned at 5 μ thickness and stained with hematoxylin and eosin stain and acid-fast stain according to the modified Fite's method. In a few instances Gomori methanamine silver (GMS) stain for *M. leprae* was also done.

RESULTS

The skin biopsies in all the 14 cases showed a histopathologic appearance typical of lepromatous leprosy with macrophages in the corium separated from the epidermis by a clear area. Acid-fast stain showed a large number of bacilli inside the macrophages.

The tuberculin reaction in the 14 lepromatous patients showed a variety of histopathologic changes. In three, the tuberculin test site contained only scattered small collections of foamy macrophages with a few polymorphonuclear leucocytes in the corium (Fig. 1). Although the acid-fast stain did not show any organism, numerous bacilli were demonstrated inside the macrophages using GMS stain (Fig. 2). In one patient the macrophage granuloma was larger and more prominent than in the other three. In all these four patients the tuberculin test was considered histologically negative, the test site showing essentially a lepromatous granuloma composed mostly of bacillated macrophages.

The reaction was positive in the other 10

¹ Received for publication 27 March 1969.

² C. K. Job, M.D., Professor of Pathology, Christian Medical College and Hospital, Vellore, and Consultant Pathologist, Schiffelin Leprosy Research Sanatorium, Karigiri, South India.



FIG. 1. Photomicrograph of a section from the tuberculin test site in a lepromatous leprosy patient to show mostly foam cell collections and a few round cells. (H & E, X800).

cases of which eight had no evidence of active tuberculosis and in two tuberculous lymphadenitis was diagnosed by biopsy. The tuberculin test site showed, in addition to the foam cells that contained *M. leprae*, varying amounts of other inflammatory cells. In six of them large collections of

mononuclear cells were present around skin appendages including sweat and sebaceous glands, hair follicles and blood vessels (Figs. 3, 4). In some areas there was a mixture of mononuclear cells and foam cells (Fig. 5). In four of them there were also collections of epithelioid cells (Fig. 6). Proliferation of prickle cell layer of epidermis together with superficial tissue edema was present at the site of injection. In all the cases diffuse polymorphonuclear leucocytic infiltration was seen.

Histologic appearances of lepromin reaction in the five cases studied were very similar. The epidermis at the site of injection showed some proliferation of the epithelium. Scattered foci of foamy macrophages with vacuoles containing melanin pigment were present (Figs. 7, 8). Acid-fast stain did not show any organisms, but the GMS stain showed numerous broken-up bacilli inside the foam cells. Besides the foamy macrophages there were a few lymphocytes and occasional plasma cells. The histopathologic appearance of the lepromin reaction was essentially similar to that of the lepromatous granuloma present in the patients.

DISCUSSION

Sagher and his associates performed tuberculin tests in 14 lepromatous patients. Eighteen biopsies from the reaction sites were studied and showed, in all instances, granulomas indistinguishable from lepromas being composed largely of foam cells.

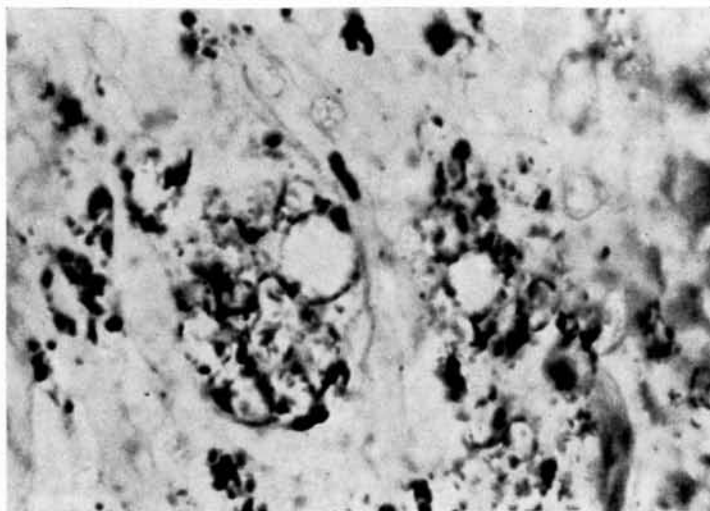


FIG. 2. Oil immersion photomicrograph of a field from the previous section (FIG. 1) to show clumps of bacilli inside foam cells. (H & E, X100).



FIG. 3. Photomicrograph of a section from the tuberculin test site in a lepromatous leprosy patient to show focal collection of mononuclear cells around blood vessels. Note the tissue edema and the few scattered inflammatory cells in the corium. (H & E, X200).

However, no bacilli were present. Therefore, they suggested that lepromatous leprosy produced a specific alteration of the skin so that the tuberculin reaction elicited a histologic response in conformity to the

altered host's tissue. They called this type of tissue reactivity of skin "isopathic phenomenon in leprosy."

In this study, biopsies of tuberculin tests from 14 lepromatous leprosy patients were examined. In four there were mainly foam cell collections and occasional round cells. The other 10 biopsies showed in addition to foam cells, a large number of mononuclear cells and in four of them numerous epithelioid cells were present as well.

Varying numbers of foam cells containing *M. leprae* were present in the test sites of all the 14 biopsies. In lepromatous leprosy foam cell granulomas are often seen, even in normal looking skin. Kooij and Pepler (⁴) found foam cells in 25 out of 31 control specimens taken from normal appearing skin of lepromatous leprosy patients, before the injection of the antigen. The bacillated macrophages could not possibly be a response to tuberculin antigen. Therefore, it is reasonable to deduce that the foam cells present in the tuberculin test site in the 14 patients of this study were part of the lepromatous infection. In four of them who showed only foam cells the test was considered negative and there was no specific tissue response to tuberculin.

In the other 10 cases, apart from the lepromatous background the test site showed a typical positive response with numerous mononuclear cells and epithelioid cells and this is in agreement with the findings reported by Kooij and Pepler (⁴). Therefore, according to this study, there is

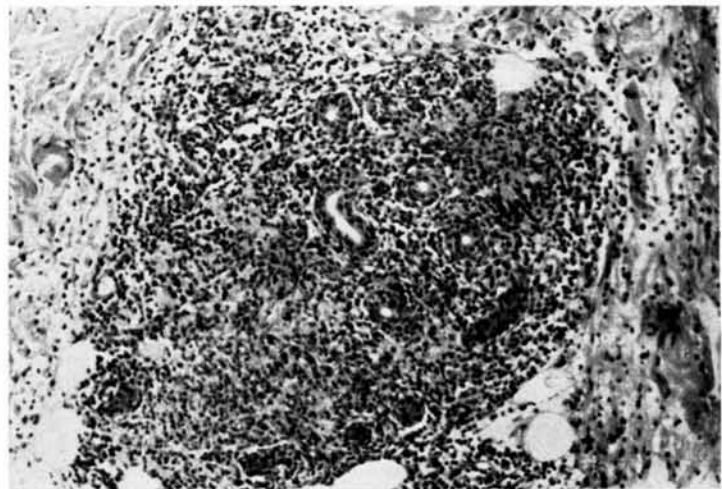


FIG. 4. Another field from a section of the tuberculin test site showing inflammation around sweat glands. The cells are mostly mononuclear cells, but several foamy macrophages can also be seen. (H & E, X200).

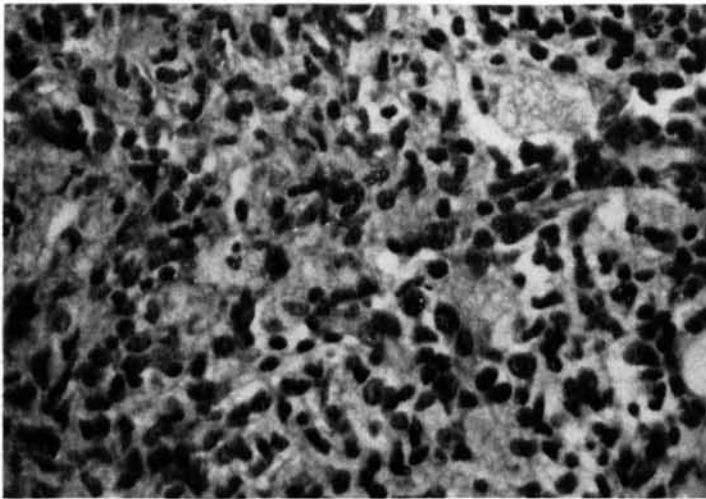


FIG. 5. High power photomicrograph of the previous section (FIG. 4) to show clearly the few foamy cells among the numerous mononuclear cells around sweat glands. (H & E, X800).

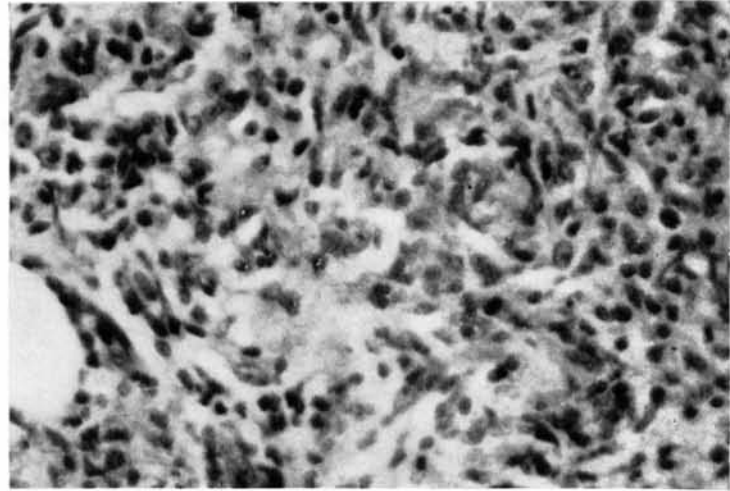


FIG. 6. Another field from the same section of the tuberculin test site (FIG. 4) to show the collection of well formed epithelioid cells. (H & E, X200).

no difference in the tissue response to tuberculin between lepromatous leprosy patients and normal individuals and isopathic reaction reported by Sagher and his co-workers in lepromatous leprosy patients is not confirmed.

A positive lepromin test is characterized by the formation of epithelioid cells and occasional giant cells (⁷), and according to most leprologists indicates a certain amount of "resistance" to the leprosy infection (⁶). The lepromin test was negative in all the five lepromatous patients who received it and the histopathologic appearance of the test site was identical and showed collection of foam cells containing *M. leprae*.

Most workers agree that the lepromin reaction, though nonspecific, is a hypersensitivity reaction (⁶). There are others who suggest that lepromin serves only as foreign body material (^{3,4}). In lepromatous leprosy strangely enough the lepromin test is negative and is said to be due to anergy of the patient to *M. leprae*. In the lepromin negative group of five patients the tuberculin test was positive in all except one. The mononuclear cell infiltration was pronounced in four and epithelioid cells were present in three of them. A positive tuberculin test indicates that a person has at some time been infected by tubercle bacilli; but does not tell us whether the infection



FIG. 7. Photomicrograph of a section from the lepromin test site in a lepromatous leprosy patient. Note the dark staining histiocytes scattered among the collagen bundles containing melanin pigment. A small collection of foam cells and round cells are seen superficially in the corium. (H & E, X200).

is healed, latent or active. It is quite possible that these four patients had a tuberculous infection before they contracted lepromatous leprosy and developed hypersensitivity to tuberculin which persisted even

after the patient contracted lepromatous leprosy. In that case positive tuberculin reactivity did not seem to have conferred any tissue immunity, not even hypersensitivity to *M. leprae*. These patients developed the anergic form of leprosy in spite of the presence of tuberculin reactivity. Or it may be that they contracted a tuberculous infection after developing lepromatous leprosy. The fact that, except for two patients, no patient had active tuberculosis indicates that most of them were able to effectively develop immunity to tuberculosis even though they were anergic to lepra bacilli.

The study of the histology of tuberculin and lepromin reactions in lepromatous leprosy patients reveals that there was no cross immunity between the two diseases. It may be wrong to assume that reactivity to one would confer immunity or even hypersensitivity to the other.

SUMMARY

In 14 lepromatous leprosy patients the histopathologic appearances of tuberculin test were studied. The tissue response to tuberculin in lepromatous patients is not different from that of normal persons and the "isopathic phenomenon," as described by Sagher and his associates, was not confirmed. In five of the patients the histology of the lepromin test was also studied and compared with that of the tuberculin reaction and there was no evidence of cross immunity between tuberculosis and leprosy.

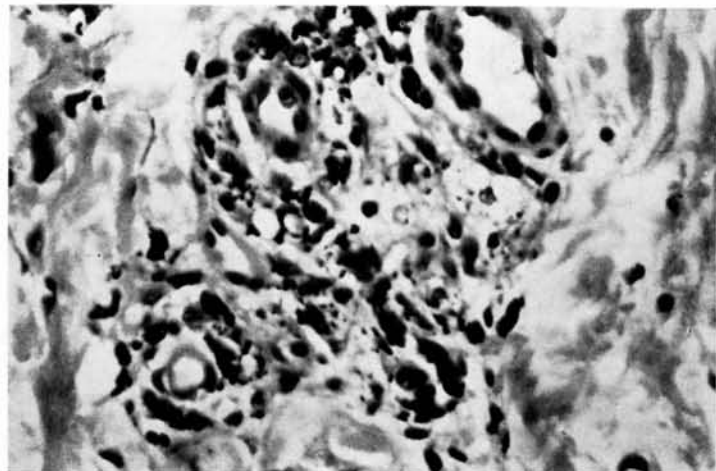


FIG. 8. High power photomicrograph of the previous section to show the melanin granules inside the foam cells. (H & E, X800).

RESUMEN

Se estudió la histopatología de la prueba tuberculínica en 14 enfermos le lepra. La respuesta tisular a la tuberculina en enfermos lepromatosos no es diferente a la de las personas normales y el "Fenómeno Isopático" descrito por Sagher y col. no fué confirmado. En cinco de los enfermos, la histología de la prueba de lepromina también se estudió en comparación con la reacción tuberculínica, y no se observó evidencia de inmunidad cruzada entre tuberculosis y lepra.

RÉSUMÉ

Chez 14 malades atteints de lèpre lépromateuse, les manifestations histopathologiques du test tuberculínique ont été étudiées. La réponse tissulaire des lépreux est identique à celle des sujets sains, et le "phénomène isopathique" décrit par Sagher et ses collaborateurs n'a pas été confirmé. Chez 5 des malades, l'histologie du test à la lépromine a été effectuée et comparée à celle de la réaction tuberculínique; il n'a pas été observé d'immunité croisée entre tuberculose et lèpre.

Acknowledgments. I am grateful to Dr. A. B. A. Karat and his associates for the biopsies. The technical assistance from Mr. S. Jesudass and Mr. A. Ebenezer Davie and the secretarial assistance from Mr. K. George William are gratefully acknowledged. Funds for this study were made available by The Leprosy Mission, London, and American Leprosy Missions, Inc., New York.

REFERENCES

1. AZULAY, R. D., CESAR DE ANDRADE, L. M., SILVA, C., NETTO, A. V., AZULAY, J. D., NEVES, R. G. and ALONSO, A. M. Comparison of the macroscopic readings and microscopic findings of the lepromin reaction. *Internat. J. Leprosy* **28** (1960) 38-43.
2. DHARMENDRA and JAİKARIA, S. S. Studies of the lepromin test. Results of the test with various antigens in non-contacts. *Leprosy in India*. **15** (1943) 40-45.
3. KLOKKE, A. H., BHAKTAVIZIAM, A. and SUBRAMANIAM, B. The isopathic phenomenon in infiltrated tuberculoid and macular tuberculoid leprosy. A comparative histologic study of the tissue response produced by cotton pellet implantation and lepromin injection. *Internat. J. Leprosy* **35** (1967) 477-487.
4. KOIJ, R., and PEPLER, W. J. A re-evaluation of tissue reactivity to BCG, tuberculin and ink in lepromatous leprosy. Absence of isopathic phenomenon. *Dermatologica (Basel)* **122** (1961) 360-372.
5. LIBAN, E., ZUCKERMAN, A. and SAGHER, F. Specific tissue alteration in leprosy skin. VII. Inoculation of *Leishmania tropica* into leprosy patients. *Arch. Dermat. & Syph.* **71** (1955) 441-450.
6. LOWE, J. and McNULTY, F. Tuberculosis and leprosy. Immunological studies. *Leprosy Rev.* **24** (1953) 61-90.
7. OGATA, T., FUKUSHI, K., ISHIHARA, S., KOBAYASHI, S., ARAKAWA, I. and NARITA, M. Histopathological studies of the lepromin reaction: Studies of leprosy based upon fundamental investigation into tuberculosis. Published by Japan Lep. Res. Comm. (1963) 147-161.
8. SAGHER, F. The isopathic phenomenon in lepromatous leprosy. *Internat. J. Leprosy* **25** (1957) 270-271. (*Correspondence*).
9. SAGHER, F. Isopathic phenomenon as an expression of specific tissue alteration in leprosy skin. Mem. VI. Cong. Internat. Leprol Madrid, 1953: (1954) 488-490. (*Abstract in Internat. J. Leprosy* **21** (1953) 612-613.
10. SAGHER, F., KOCSARD, E. and LIBAN, E. Specific tissue alterations in leprosy skin. I. Transformation of the tuberculin reaction in leprosy patients into leproma-like lesions. *Internat. J. Leprosy* **20** (1952) 341-346.
11. SAGHER, F., KOCSARD, E. and LIBAN, E. Specific tissue alteration in leprosy skin. II. The histology of the tuberculin reaction in leprosy. *J. Invest. Dermat.* **19** (1952) 499-508.
12. SAGHER, F., LIBAN, E. and KOCSARD, E. Specific tissue alteration in leprosy skin. III. Specific reaction due to various agents. *J. Invest. Dermat.* **20** (1953) 343-352.

13. SAGER, F., LIBAN, E. and KOCSARD, E. Specific tissue alteration in leprous skin. VI. "Isopathic phenomenon" following BCG vaccination in leprous patients. *Arch. Dermat. & Syph.* **70** (1954) 631-639..
14. SAGER, F., LIBAN, E., ZUCKERMAN, A. and KOCSARD, E. Specific tissue alteration in leprous skin. V. Preliminary note on specific reactions following the inoculation of living microorganisms ("isopathic phenomenon"). *Internat. J. Leprosy* **21** (1953) 459-462.
15. WAALER, E. The isopathic reaction in leprosy. *Internat. J. Leprosy* **25** (1957) 207-212.