

THE ISOPATHIC REACTION IN LEPROSY

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In 1876 Heinrich Köbner (5, 6) showed that the skin of patients suffering from psoriasis often reacted in a special way to stimuli of various kinds. Trauma, or insignificant, nonspecific, inflammatory processes, produced typical localized psoriatic efflorescences at the place of irritation. The reactivity or irritability of the skin appeared to be modified in a special direction.

Those observations were confirmed by other authors, and similar conditions have been observed in other dermatological diseases, as for instance lichen ruber, eczema, erythema nodosum, erythema multiforme, and dermatitis herpetiformis (1, 3, 4, 7). The phenomenon has been called Köbner's symptom, or the "isomorphic" reaction, and its mechanism and importance from the point of view of pathogenesis has been discussed extensively (2, 8). The so-called Kveim reaction in Boeck's disease is regarded by some authors as an isomorphic reaction due to a special sarcoid mode of reaction of the skin (9), although this has been contradicted by other authors, for example Refvem. (10).

In cases of leprosy Sagher and co-workers have described, in a series of papers (11-16), a reaction of similar type which they call an "isopathic" phenomenon. Intradermal injection of tuberculin, milk, peptone, or leishmanin, or of living BCG or leishmania parasites, caused a special foamy-cell reaction typical of lepromatous leprosy. A similar reaction was seen in patients bitten by the sand-fly. The interesting feature of these reports is the histological studies. In some cases the authors found what they called "leproma-like" reactions, in others a "prelepromatous" reaction, and in some only "foam-cell nests." The intradermal injections were made in normal-looking skin, and biopsy specimens were taken from 2 days to 2 weeks, in some instances several months, after the inoculations.

By the courtesy of Dr. R. S. Melsom I have had the opportunity to make a histologic study of tuberculin reactions in four patients in the Bergen leprosy hospital. The intradermal Mantoux test with 1 mgm. of old tuberculin 1/100, 0.1 cc.) was performed, and biopsy specimens were removed 5 to 10 days later. The injections were placed in areas of completely normal-looking skin, without any traces of active or old leprosy lesions.

CASE REPORTS

CASE 1.—J. N., male, born 1890. He was admitted to a leprosarium in the United States in 1939, 10 years after his first symptoms began, and was transferred to the Bergen hospital in 1954. The condition at the time of the test was typical lepromatous leprosy, still active.

The tuberculin reaction was positive. A biopsy made on the 8th day showed a marked lepromatous reaction with numerous nodules in the corium. The infiltrating cells were mainly of the foamy type, cells with a clear cytoplasm and small dark nuclei, although some few giant cells were present as well as some plasma and lymphoid cells (Figs. 1-3). Acid-fast bacilli were not found.

CASE 2.—T.L., female, born 1882. Since 1892 she has had the maculoanesthetic form of leprosy with numerous anesthetic areas.¹ There have been no active symptoms for at least 30 years; the condition is purely residual.

A positive tuberculin-reaction lesion was removed for study on the 5th day. In the corium there was a definite prelepromatous reaction, with small nodules containing mainly foam cells and a few lymphoid cells but no giant cells (Figs. 4 and 5). No acid-fast bacilli were found.

CASE 3.—M.B., female, born 1885. Since 1916-1917 she has had maculoanesthetic leprosy, with numerous anesthetic spots and deformities. Admitted to the leprosy hospital in Bergen in 1919, she has shown no activity of the disease for approximately 25 years; another residual case.

A positive tuberculin-reaction lesion, removed on the 7th day, showed a nodular reaction with plasma and lymphoid cells, but no foamy cells. The histologic picture was therefore rather noncharacteristic.

CASE 4.—S.M., male, born 1925. His disease started as of the maculoanesthetic form, with anesthesia and deformities; but nodular lesions developed later, 6 years ago. Admitted to the hospital in 1951, the clinical picture then was "lepra mixta" but mainly with neurological findings. In 1951 and 1952 he suffered some rather severe lepra reactions, and another about a year ago. Sections of one of the residual skin lesions examined recently show only scar tissue, but bacilli were found in the skin nerves.

In spite of two previous BCG vaccinations the tuberculin reactions of this patient were persistently negative. He was then given BCG vaccine percutaneously, and one lesion was removed for examination on the 7th day. The histological picture was that of a subacute inflammation, with many polymorphonuclear leukocytes and a few lymphoid cells and macrophages. Some of the macrophages had a clear cytoplasm, and there were a few foam-cell nests more or less covered by the polymorphonuclear leukocytes, but there was no real leproma-like lesion.

Four months later a new Mantoux test was carried out, and this time the reaction was weakly positive. A specimen removed on the 10th day showed only noncharacteristic inflammation, with lymphoid and plasma cells, a few macrophages, and some polymorphonuclear leukocytes.

DISCUSSION

The findings in these four cases are summarized in Table 1. Two of them showed significant histological pictures in the tuberculin-reaction lesions, definitely lepromatous in Case 1 and prelepromatous in Case 2,

¹ The term "maculoanesthetic" is employed in this report in the classical sense of Hansen and later Norwegian workers.

according to the designations of Sagher and associates. In the other two cases the tissue reaction to the tuberculin tests did not differ from what is found in nonleprous individuals, although in Case 4 a few foamy-cell nests were found in the sections of a BCG lesion. One of these patients (Case 1) had lepromatous leprosy; two (Cases 2 and 3) were residual maculoanesthetics with no sign of activity for many years; the other (Case 4) had had nodules several years ago and reactional episodes more recently, but the lesions had subsided with bacilli found only in the skin nerves of a lesion scar examined.

TABLE 1.—*Summary of the cases tested and of the histological findings in the reaction lesions.*

No.	Age and sex	Duration (years)	Clinical type	Histology of the tuberculin reaction
1	65, M.	25	Lepromatous, active	Lepromatous
2	73, F.	63	Maculoanesthetic, residual	Prelepromatous
3	70, F.	40	Maculoanesthetic, residual	Noncharacteristic
4	30, M.	15	Lepromatous, subsided	Noncharacteristic ^a

^a A few foamy-cell nests were found in sections of a BCG-vaccination lesion of this patient, four months before the tuberculin test.

The "isopathic phenomenon" described by Sagher and associates occurs in leprosy, and apparently these patients often have a "stereotypic" skin reaction. There is a specifically altered reactivity of the skin which causes tuberculin to induce a histological picture characteristic of the host's tissue response. Sagher's cases were mainly lepromatous; only a few of them were classified as indeterminate, and one was tuberculoid.

My small material does not indicate any relationship between this altered tissue response on the one hand and the clinical form of the disease or its duration or treatment on the other hand. The conspicuously leproma-like lesion in the first case, the only active lepromatous one, is apparently in accord with Sagher's usual experience. The most striking result, however, was obtained in the second case, because the disease had been very mild, never other than maculoanesthetic, and had shown no signs of activity for 30 years. Nevertheless, there was a prelepromatous skin reaction to tuberculin with well-developed foamy-cell nodules, as shown in Figs. 3 and 4. Activity of the disease does not appear to be of any importance to this peculiar change in tissue reaction.

Conversely, it is strange that the youngest patient, Case 4, who had once had lepromatous nodules and reactions more recently, gave a completely negative, noncharacteristic reaction to tuberculin. However, his tuberculin reaction had been negative for many years, although he had

been vaccinated twice with BCG; a third BCG inoculation was followed by a weakly positive tuberculin reaction. The BCG inflammation showed microscopically a few nests of foam-cells, but the tissue reaction to the Mantoux test carried out four months later did not differ from what is seen in normal individuals. Apparently in this patient the leprosy bacillus had not produced a "parallergy" toward the related microorganism, the tubercle bacillus, and the positivity that was achieved after the third BCG vaccination seemed to be an ordinary positive Mantoux reaction.

There is reason to suppose that the isopathic reaction in leprosy patients may be connected with the living cells which, through the influence of the leprosy bacilli, have acquired this peculiar characteristic. It is also possible, however, that the leprosy skin, after several years of disease, may contain substances which—in connection with tuberculin or other stimuli—may produce the isopathic reaction.

In an attempt to elucidate this question I have tried to transfer passively the isopathic characteristic from a leprosy patient to the skin of a normal, tuberculin-positive subject (myself). A piece of normal-looking skin from the first patient was ground, suspended in normal saline, and after a few hours the preparation was heated twice at 60°C for one-half hour to kill any pyogenic germs. This "leprosy extract" was used in the following experiment by injections into the skin of the arm.

1. Tuberculin diluted 1/10 with leprosy extract.
2. Tuberculin diluted 1/10 with normal saline.
3. The leprosy extract alone.

In each case an intradermal papule approximately 2 mm. in diameter was produced. These were removed 8 days after the injection for histological examination. The findings after these three injections, in order, were as follows:

1. Edema, diffuse infiltration of lymphoid and plasma cells, and a few macrophages. No leproid reaction.
2. Almost identical with No. 1. The cellular reaction was possibly somewhat less marked (Fig. 6).
3. Practically no reaction.

Passive transfer of the isopathic ability from the leprosy patient to the normal subject did not take place. The results thus lend support to the theory that the living cells are the carriers of the ability. However, the injections caused a slight general reaction with chills and malaise some 7-8 hours after the inoculation and of 5-6 hours duration.

SUMMARY

Histologic examinations were made of tuberculin-reaction lesions in four patients with leprosy. The specimens from two of these patients showed the typical "isopathic phenomenon" described by Sagher and co-workers. The histologic picture was leproma-like, with nodules of foamy

cells. In the other two cases the tissue reaction to tuberculin was non-characteristic, although a BCG-vaccination lesion from one of them showed a few foamy-cell nests.

The isopathic phenomenon in leprosy appears to be due to a peculiar change in the reactivity of the tissue. This acquired reactivity of the skin may be present many years after leprosy has "burned out."

An attempt was made to induce the isopathic reaction in my own skin by adding a suspension of skin from one of the leprosy patients to tuberculin and injecting the mixture intracutaneously. Passive transfer of the isopathic ability did not occur. Apparently the isopathic reaction depends upon the living cells and is not due to a humoral factor, at least not a heat-stable one.

RESUMEN

Se hicieron exámenes hisotológicos de las lesiones producidas por la reacción a la tuberculina en 4 leprosos. Los ejemplares obtenidos de 2 de éstos revelaron el típico "fenómeno isopático" descrito por Sagher y colaboradores. El cuadro histológico fué lepromatideo, con nódulos de células xantomatosas. En los otros 2 casos, la reacción del tejido a la tuberculina fué atípica, aunque una lesión causada por la vacunación con BCG en uno de ellos reveló unos pocos nidos de células xantomatosas.

El fenómeno isopático parece deberse en la lepra a una alteración peculiar en la reactividad del tejido. Esta reactividad adquirida de la piel puede estar presente muchos años después de "extinguirse" la lepra.

El A. ha tratado de inducir la reacción isopática en su propia piel agregando a la tuberculina una suspensión de piel de uno de los leprosos e inyectando la mezcla intracutáneamente. No se observó pase pasivo de la capacidad isopática. Al parecer, la reacción isopática se basa en células vivientes y no se debe a un factor humoral, a lo menos a uno termoestable.

REFERENCES

1. BETTMANN. Über Umbauvorgänge als Ausdruck spezifischer Reaktionsfähigkeit bei Hautkrankheiten (die Reizbarkeit der Haut bei der Darierschen Krankheit). Arch. Derm. u. Syphil. **135** (1921) 65-76.
2. BIZZOZERO, E. Sur la phénomène de Koebner dans le psoriasis (Psoroasis factise). Ann. Derm. et Syph. **3** (1932) 510-529.
3. FISCHER, K. Das Köbnersche Symptom. (Der isomorphe Reizeffekt.) Arch. Derm. u. Syphil. **153** (1927) 318-325.
4. GALEWSKY, E. Beiträge zur Aetiologie des Lichen ruber. Familiärer Lichen ruber, Lichen ruber unter Ehegatten, Lichen ruber und Reizung. Arch. Derm. u. Syphil. **129** (1921) 484-490.
5. KÖBNER, H. Zur Aetiologie der Psoriasis. Vierteljahress. f. Derm. u. Syph. **3** (1876) 559-561.
6. KÖBNER, H. Künstliche Hervorrufung von Psoriasis. Berliner klin. Wochenschr. **15** (1878) 631-632.
7. KREIBICH, C. Der isomorphe Reizeffekt. Wiener klin. Wochenschr. **76** (1926) 904-906.
8. LEVI, I. Fenomeno di Köbner e patogenesi della psoriasis. Giorn. italiano Derm. Sif. **72** (1931) 661-712.
9. NELSON, C. T. Kveim reaction in sarcoidosis. Arch. Derm. Syph. **60** (1949) 377-389.
10. REFVEM, O. The Pathogenesis of Boeck's Disease. Nationaltrykkeriet, Oslo, 1954.

11. SAGHER, F., KOCSARD, E. and LIBAN, E. Specific tissue alterations in leprous skin. I. Transformation of the tuberculin reaction in leprous patients into leproma-like lesions. *Internat. J. Leprosy* **20** (1952) 341-346.
12. SAGHER, F., KOCSARD, E. and LIBAN, E. Specific tissue alteration in leprous skin. II. The histology of the tuberculin reaction in leprosy. *J. Invest. Derm.* **19** (1952) 499-508.
13. SAGHER, F., LIBAN, E. and KOCSARD, E. Specific tissue alterations in leprous skin. III. Specific reaction due to various agents. *J. Invest. Derm.* **20** (1953) 343-352.
14. SAGHER, 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. SAGHER, F., LIBAN, E. and KOCSARD, E. Specific tissue alteration in leprous skin. VI. "Isopathic phenomenon" following BCG vaccination in leprous patients. *A.M.A. Arch. Dermat. & Syph.* **70** (1954) 631-639.
16. LIBAN, E., ZUCKERMAN, A. and SAGHER, F. Specific tissue alteration in leprous skin. VII. Inoculation of *Leishmania tropica* into leprous patients. *A.M.A. Arch. Dermat. & Syph.* **71** (1955) 44-450.

DESCRIPTION OF PLATES

PLATE No. 11

FIG. 1. Reaction to tuberculin in Case 1, 8th day. Definite nodular cellular reaction. Hematoxylin and eosin, 90X.

FIG. 2. Same case as in Fig. 1. The nodules in the cutis contain mainly foamy cells, with some lymphoid cells and giant cells. Hematoxylin and eosin. 105X.

FIG. 3. Same case as Figs. 1 and 2, showing details with foamy cells, lymphocytes and giant cells. Hematoxylin and eosin, 350X.

(Note that the giant cell containing a giant globus, seen in the upper edge of this field, is the same as the one near the lower edge of Fig. 1.)

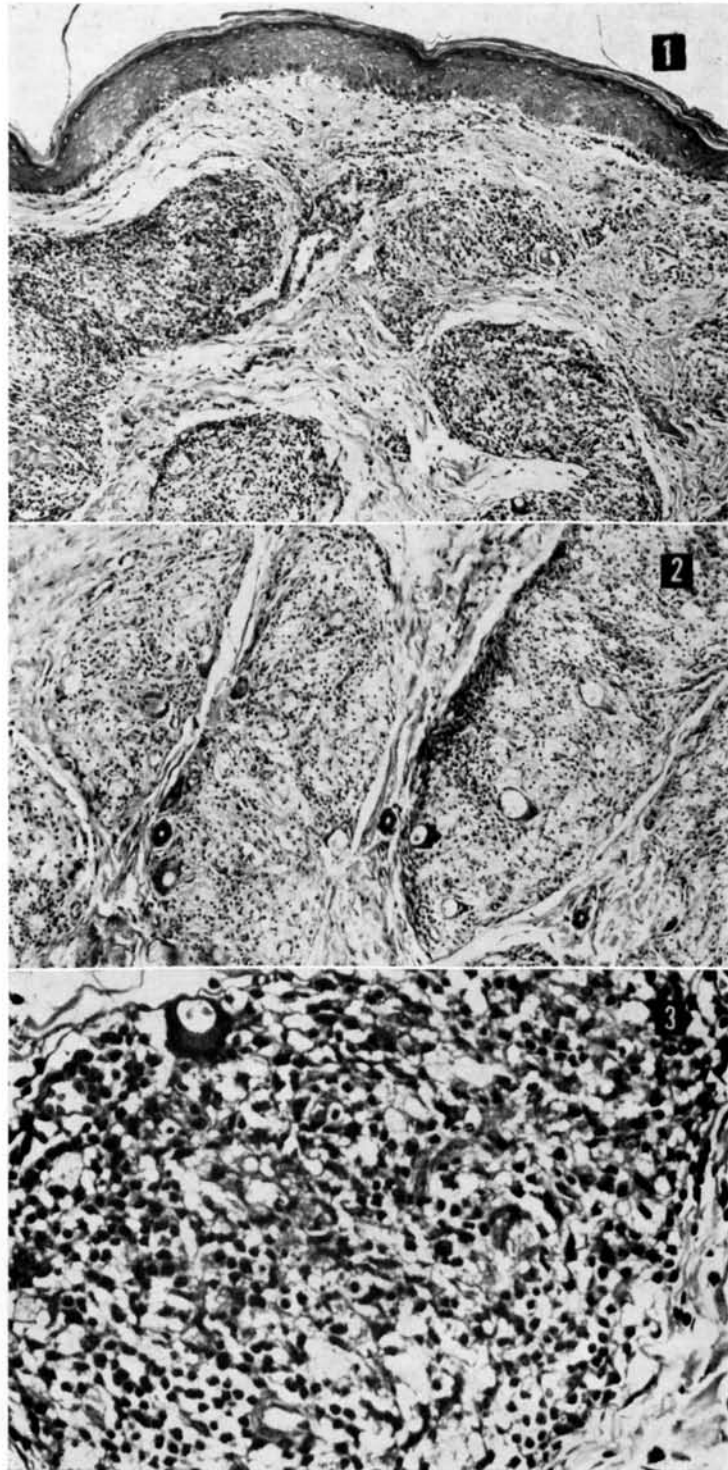


PLATE 11

PLATE No. 12

FIG. 4. Reaction to tuberculin in Case 2, 5th day. Small nodules with foamy cells scattered irregularly in the corium. Hematoxylin and eosin, 90X.

FIG. 5. Higher magnification of one field in Fig. 4, showing a foamy-cell collection in detail. Hematoxylin and eosin, 360X.

FIG. 6. Tuberculin reaction in a normal subject. There is a cellular reaction with lymphoid and plasma cells, but no foam cells and no nodules. Hematoxylin and eosin, 300X.



PLATE 12