INTERNATIONAL JOURNAL OF LEPROSY

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

PUBLISHED WITH THE AID OF THE
LEONARD WOOD MEMORIAL

Publication Office: School of Medicine, Tulane University,
1430 Tulane Avenue, New Orleans 12, Louisiana
Entered at the Post Office at New Orleans as second-class matter.

VOLUME 25, NUMBER 3 JULY-SEPTEMBER, 1957

EDITORIALS

Editorials are written by members of the Editorial Board, and opinions expressed are those of the writers.

THE ISOPATHIC PHENOMENON OF SAGHER AND ITS POSSIBLE POTENTIALITIES

The serious student of leprosy is faced, these days, with difficulties in determining the essential nature of some of the kinds of cases that are ordinarily classed as lepromatous but which are not typical as regards their appearance, or the course of the disease, or their prognosis. These problem cases include, first of all, borderlines that are going far to the left, the lepromatous element tending to overwhelm the original tuberculoid character. Also the supposedly lepromatous cases which suddenly develop reactional lesions of tuberculoid aspect (the "reversion" reaction), and even at times cases of the indeterminate group.

It would be useful for the study of such cases of unusual or uncertain nature if we had a practical skin test which would reveal with reasonable certainty whether or not the basic condition is lepromatous. It would therefore seem in order that the nature and potentialities of the "isopathic phenomenon" which Sagher and associates have been studying should be noted and investigated.

The first observation[1] was of the structure of persistent skin lesions which had developed in two resolved lepromatous cases at the sites of positive tuberculin reactions. On biopsy these lesions proved to be granulomas indistinguishable from lepromas, being composed largely of foamy cells; but no bacilli were demonstrable. The observation was extended[2] to 14

[1] SAGHER, F., KOCSARD, E. and LIBAN, E. Specific tissue alterations in leprous skin. I. Transformation of the tuberculin reaction in leprous patients into lepromatous lesions. Internat. J. Leprosy **20** (1952) 341-346.

[2] 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.

other tuberculin-injected cases, most of whose specimens on section showed more or less leproma-like changes—changes not to be found in tuberculin-reaction lesions of normal controls. Later they obtained similar results after injections of peptone, milk, and leishmanin, and also in the sites of sand-fly bites, normal controls again being negative.[3]

At this time, for a further control, they examined 41 specimens from areas of normal-appearing skin of 34 lepromatous cases involved in the experiments, finding small foamy-cell nests in 10 and larger infiltrations in 4, whereas the other two-thirds (27) were quite negative.[3,4] The difference between the findings in the sites of the excitants, and in the control specimens from normal-appearing skin areas, was regarded as highly significant.

Proceeding then to trials with living microorganisms, they used BCG and—for something that would be antigenically quite different—*Leishmania tropica* flagellates.[5-8] Of 25 specimens from the 16 BCG cases, 22 showed some degree of the "leproma-like" change, usually marked, regardless of whether the patients had been tuberculin negative or positive and the reactions therefore normal or of the Koch type; the nonleprous controls showed the usual picture of tubercle-bacillus infection. Of the 23 leishmania-injected cases, 20 gave specimens with the "specific" (leproma-like) structure, controls again being negative for that. Combining these reports, over one-half of the scrapings made were negative for bacilli, and so were sections of three-fourths of the specimens. Here the authors graded the histological changes as "foamy-cell nests" (1+), "prelepromatous" (2+), and "leproma-like" (3+). Of the total of 69 specimens, 35 (50%) were 3+, and 12 others were of lesser grade; 21 were negative, or virtually so, for the specific change.

The findings of Sagher and associates have been confirmed, on a smaller scale first by Richter[9] and then by Waaler.[10] An especially interest-

---

[3] SAGHER, F., LIBAN, E. and KOCSARD, E. Specific tissue alteration in leprous skin. III. Specific reaction due to various agents. J. Invest. Derm. **20** (1953) 343-352.

[4] SAGHER, F. The isopathic phenomenon in lepromatous leprosy. Internat. J. Leprosy **25** (1957).

[5] 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.

[6] SAGHER, F. Isopathic phenomenon as an expression of specific tissue alteration in leprosy skin. Mem. VI Congr. Internat. Leprol., 1953; Madrid, 1954, pp. 488-490.

[7] 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.

[8] 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) 441-450.

[9] RICHTER, R. Das isopathische Phänomen in klinisch normaler Haut bei Leprakranken. Arch. klin. u. exper. Dermat. **202** (1956) 307-316; (*abstract* in this issue).

[10] WAALER, E. The isopathic reaction in leprosy. Internat. J. Leprosy **25** (1957) 207-212.

ing feature of Richter's report is that he used, for the first time, an inorganic excitant, india ink; and one of Waaler's reports is that he attempted to transfer the isomorphic reactivity passively to himself.

Richter tested only three cases, but with each he used three excitants (tuberculin, milk, and—as an innovation—india ink), and he made enough injections of each for biopsy specimens to be taken after 10 and 20 days and 1, 2 and 3 months. On the whole the india ink seemed the most effective activant, but there were marked irregularities from specimen to specimen and from case to case.

Waaler's attempt to transfer the isomorphic reactivity (to tuberculin) passively to himself was unsuccessful. The single active lepromatous case is shown to have developed a marked reaction lesion. One of the two long-inactive "maculoanesthetic" case also gave a definite reaction, which raises the question whether or not, many years ago, there may have been a lepromatous stage that was not recognized.

From these observations it appears that in lepromatous leprosy (tuberculoid cases have not yet been studied) there is a profound specific alteration of the tissue reactivity of the host which causes various substances to elicit changes characteristic of the disease process, irrespective of the stage of the disease and not due to selective localization of bacilli at the sites. This alteration may persist long after a case is bacteriologically negative; how early in the infection it develops is not known. There is no relation to the patients' reactivity to tuberculin or lepromin, and the nature of the injected material seems to be of little consequence. This type of tissue reaction of the skin to various inocula in lepromatous leprosy Sagher *et al.* call the "isopathic phenomenon."

At first they applied that term only to the reactions induced by the living organisms employed. However, Sagher (personal communication) has agreed that it would be odd to apply it to the reaction induced by living BCG or leishmania but not to the same kind of reaction induced by the same microorganisms killed by heat (if heat-killed BCG would have the same effect), and that it should be applied generally.

This *isopathic* phenomenon is a granulomatous condition, of specific histologic structure. This is in contrast with Koebner's *isomorphic* phenomenon in psoriasis and certain other conditions (see references in Waaler), which is a clinical manifestation not characterized by a specific granulomatous tissue reaction. Sarcoidosis is the only other disease in which the isopathic kind of reaction is known to occur.

About sarcoidosis, Lemming[11] was apparently the first to observe the effect, after injection of BCG (an interesting case). Warfvinge confirmed the findings after injections of a patient's own virulent[12] or heat-killed[13] tubercle bacilli. (Kveim, in his diagnostic test, had already produced such reactions by injection of a suspension of

---

[11] LEMMING, R. Development of Boeck's sarcoid at the place on the skin where a BCG vaccination had been made in a case of Schaumann's disease. Acta Med. Scandinavica **110** (1942) 151-160.

[12] WARFVINGE, L. E. Boeck's sarcoid, experimentally produced by virulent human tubercle bacilli in a case of Schaumann's disease. Acta Med. Scandinavica **114** (1943) 259-270.

[13] WARFVINGE, L. E. Uber eine von abgetöteten Tuberkelbazillen hervorgerufene Hautreaktion bei Lymphogranulomatosis benigna. (Vorläufige Mitteilung.) Acta Tuberc. Scandinavica **19** (1945) 126-141.

heated sarcoid-lesion tissue.) Lepromin may also elicit this response; in South America the writer was once shown a section of a beautiful sarcoid lesion induced in the skin of a sarcoid patient by the Hayashi-Mitsuda antigen. A discordant note, however, comes from Forgacs and associates,[14] who failed to find sarcoid histology in specimens from 9 cases injected with BCG and biopsied 6 weeks afterward.

Regarding terminology, the words "prelepromatous" and "lepromatous" are clearly inappropriate if not misleading for the reaction lesions are not lepromas. They are due to an altered tissue reactivity to various stimulants and not directly to the leprous infection, wherefore "paralepromatous" would seem to be appropriate, [15] although "leproma-like" is more informal, or even "lepromatoid."

A basic question is whether or not the reaction is actually specific for lepromatous cases. One of Richter's 3 cases was diagnosed as indeterminate (of 3 years duration), and 2 of Waaler's 4 cases were callled maculoanesthetic. If in the one which gave the isomorphic result the condition never was lepromatous, then the phenomenon is not confined to that form of the disease.

Another important question is what assurance there can be, in any given case, that the leproma-like condition found in the biopsy specimen was not a clinically inapparent but truly lepromatous lesion present before the excitant was injected. In discussing the matter Sagher[4] points out that their control specimens of normal-looking skin of patients being tested[3] showed that lepromatous changes may be found, not infrequently, but there is a significant quantitative factor involved in the production of visible lesions by the injections, especially of living inocula. He concedes that some proportion of the microscopic lesions found after testing with nonliving material may possibly have been pre-existent lepromatous changes, but the injection of living organisms (BCG or Leishmania) caused macroscopic lesions with changes so marked that they could not possibly have been there beforehand.

Be all that as it may, the observations so far reported suggest that this isopathic phenomenon is not merely a curiosity to be noted and filed, but a biological phenomenon worthy of investigation regarding the basic factors involved, and also for possible practical applications.

There are, however, certain questions of technique which must be answered before the test could be used widely. One is, what is the most useful excitant? For effectiveness should it necessarily excite a local inflammatory process? What is the proper time interval, with any particular excitant used, between injection and biopsy?

---

[14] FORGACS, P., MCDONALD, C. K. and SKELTON, M. O. The B.C.G. lesion in sarcoidosis. Lancet **1** (1957) 188-190.

[15] As the terms "parasyphilitic" and "paratuberculous" are used to signify conditions indirectly due to those infections. In connection with certain bacteria the prefix "para" is also used as meaning resembling, e.g., paratuberculosis and paratyphoid bacilli.

Apparently the excitant need not be particulate, provided it causes an inflammatory reaction, for it seems that Sagher and associates now depend upon tuberculin, and Waaler used it; but in Richter's cases (all tuberculin negative, be it noted) it gave at most a 2+ result. Of the infectious agents, leishmania could not be employed in many places, and BCG (living or dead) would complicate the picture with its acid-fast bodies. There is interest in Richter's use of india ink, since it is a bland particulate agent which seemed particularly effective in his cases.

The cytology of this lepromatoid lesion has yet to be studied in detail. Comparison photomicrographs that have been published, of specimens from tested patients and controls, show the differences described and that is all. Large numbers of serial specimens are needed, as in Richter's approach, to study the changes developing at different intervals of time, and the time required for young cells attracted to the site to undergo the typical vacuolation. Such studies, however, should be of material prepared with a fixative less liable than is formalin to give confusing shrinkage effects.

No discussion has been seen of why and how the histiocytes of the lesions become vacuolated, whether it is due to imbibition of water, as after the adminstration of plasma expanders like PVP[16] or dextran,[17] or to the accumulation of some other substance. It is obviously not dependent on any metabolic or degenerative product of the excitant, since it can be induced by india ink. Sagher *et al.* have spoken of the cells as sudanophilic, because of finding Sudan-positive material in some of the cells of a few specimens subjected to frozen sectioning. If lipids really collect in the cells of the isopathic lesions as they do in those of lepromas, that would be particularly interesting—and puzzling. Carbowax embedding may be indicated, so that serial sections of a given level of a given specimen could be stained for fat and in other ways. It has not been said if the paralepromatous foamy cells are to any degree acid-resistant after staining with carbol-fuchsin, as the foamy cells of leprosy normally are.

Regarding possible practical applications, Sagher *et al.* have suggested that the procedure may prove useful as a test to identify early lepromatous cases, or even to detect latent infections among contacts. This possibility of course depends upon how early in the infection the peculiar tissue reactivity develops. As for a test of improvement, or cure, of patients under treatment, that would depend on how long the peculiar tissue reactivity persists. The reports so far suggest that it may be very persistent, possibly even permanent. As we have suggested, however, it might well prove useful—provided it is type specific—in the identification of problem cases. It would be interesting, too, to see what would happen in lepromatous cases found reactive to lepromin.

Whatever practical value this isopathic phenomenon may be found to

---

[16] FROMMER, J. The pathogenesis of reticulo-endothelial foam cells. Effect of polyvinylpyrrolidone on the liver of the mouse. American J. Path. **32** (1956) 433-453. [Abstract in this issue.]

[17] WOLMAN, M. and WOLMAN, B. Effect of polysaccharides on the formation of granulation tissue. A.M.A. Arch. Path. **62** (1956) 74-84. [Abstract in this issue.]

have, if any, in the way of a serviceable skin test, it is of much academic interest. The indication that in lepromatous leprosy there is a fundamental alteration of the tissue reactivity, imitative of the lepromatous change, should be explored as a problem for basic research in cytologic histology. It is in the hope of arousing interest in the matter that this note is offered.

—H. W. WADE

ADDENDUM: Dr. R. Kooij, one of a few persons to whom copies of the draft of this editorial was sent to arouse interest in the matter, made a very sensible suggestion: "I would suggest that workers who undertake to investigate the isopathic phenomenon should cooperate as far as possible, using the same excitants, the same time intervals after injection, and the same histologic methods and criteria."