SPECIFIC TISSUE ALTERATION IN LEPROUS SKIN V. PRELIMINARY NOTE ON SPECIFIC REACTIONS FOLLOWING THE INOCULATION OF LIVING MICROORGANISMS ("ISOPATHIC PHENOMENON") [1]

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In earlier experiments (1-4) it was observed that a characteristic focal histological lesion developed in the skin of leprous patients following the intradermal injection of specific or nonspecific proteins. Tuberculin, leishmanin, milk and peptone elicited a prelepromatous or lepromatous structure characteristic of lepromatous leprosy. The injection of these materials into the skin of normal individuals elicited a nonspecific inflammation, totally different from the lesion which developed in leprous individuals. Lepromatous and prelepromatous structures were also noted to have developed in lepromatous leprosy patients at the site of insect bites. From these observations it was concluded that lepromatous leprosy induces a specific altered reactivity of the skin which responds to various injuries with a histological lesion characteristic of the host's altered tissues.

A study of the reaction of leprous skin to living organisms was next considered desirable. Two series of experiments were performed, one with injections of living BCG bacilli and the second with living *Leishmania tropica* flagellates.

EXPERIMENT WITH BCG

BCG inoculation was selected for the following reasons: First, it has been reported that BCG inoculation might protect against infection with leprosy in healthy contacts. Second, it was desirable to investigate whether BCG vaccination was capable of converting a negative lepromin test to positive in leprous patients, since it is generally accepted that a positive lepromin test is a favorable prognostic sign. Finally, BCG produces in

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healthy individuals at the site of inoculation a specific and distinct lesion which is histologically different from that seen in lepromatous leprosy. It was thus possible to distinguish histologically between the altered reactivity of the leprous patient and the lesion of BCG. The histopathologic and bacteriologic findings will be reported here.

Doses of ten million living BCG bacilli each were injected intradermally in 21 patients suffering from lepromatous leprosy, 13 with and 8 without active skin lesions. All patients were receiving chemotherapy, and in 4 of them *M. leprae* could no longer be detected in smears from the mucous membrane of the nose and from the skin of the earlobe.

All of the leprous patients reacted clinically to BCG inoculation in the same way as do normal individuals without leprosy. Those who were tuberculin negative before vaccination developed a lesion at the vaccination site clinically similar to that seen in normal healthy individuals without tuberculosis. Those who were tuberculin positive before vaccination exhibited an accelerated clinical reaction that corresponded to a Koch phenomenon.

Twenty-five biopsies of the BCG inoculation sites were made from 16 of the 21 leprous patients, at times ranging between 4 days to 10 months after vaccination.

For control purposes 13 biopsies of BCG inoculation sites were made from 9 healthy individuals, 2 to 12 months after inoculation.

Results.—The intradermal injection of BCG into lepromatous patients elicited a histological reaction characteristic of leprosy. The lesions thus produced were the same in both tuberculin negative and tuberculin positive patients.

In 17 of the 25 biopsies of the leprous patients a leproma-like reaction was found (Fig. 1). In 4 of these leproma-like reactions, taken 5 to 6 months after vaccination, circumscribed focal granulomas were observed within an extensive aggregate of foam cells.

Bacteriological studies of these 17 biopsy specimens revealed the following: 5 cases with positive smears from the biopsy floor; 2 cases with acid-fast bacilli present in varying numbers in histological sections; 1 case in which acid-fast granules were seen in the histological material.

In 5 of the remaining 8 biopsy specimens prelepromatous reactions and foam-cell nests were observed. The other 3 specimens revealed no lesion characteristic of leprosy. One of these showed nonspecific granulation tissue 2½ months after inoculation. In this case a biopsy repeated 3½ months later revealed

a lepromatous reaction in the scarred dermis. The remaining 2 specimens were taken from inoculation scars and contained dense collagen and scattered lymphocytes.

In the 9 healthy individuals used as controls, the histological lesion elicited by BCG inoculation was completely different from that obtained in leprous patients. Seven biopsy specimens removed 2 to 5½ months after vaccination revealed a histological reaction characteristic of tuberculosis (Fig. 2). In 3 lesions, nonspecific inflammation and fibrosis were found, and in 3 specimens of vaccination scars collagen fibers and scattered lymphocytes were noted.

EXPERIMENT WITH LEISHMANIA

The question arose whether the phenomenon described occurred because of the close relationship of *M. leprae* and *M. tuberculosis*. To answer this question, further inoculation experiments with cutaneous leishmaniasis were performed. The inoculations of *Leishmania tropica* benefited the patients by immunizing them against this disease.

Twenty-two leprous patients were inoculated intradermally with one million culture flagellates, and in all of them typical nodose clinical lesions appeared after an incubation period of about two weeks. All lesions healed spontaneously within 8 to 14 months. Forty-six biopsies were made from the sites of these inoculations during the period between the earliest appearance of clinical lesions and their disappearance.

Results.—Lepromatous or prelepromatous structures were observed in 31 biopsies. In 9 of these specimens, focal granulomas composed of epithelioid and foam cells were present. In 8 further specimens abundant Leishmania parasites were observed, part of the granuloma was composed of histiocytes with many vacuoles as seen in lepromatous leprosy (Figs. 3 and 4). In an additional 4 specimens a granuloma was seen which corresponded to the lesion of early cutaneous leishmaniasis. A nonspecific inflammation was seen in 3 specimens.

The histological development of a granuloma characteristic of the host's altered tissue, in response to injected specific living organisms, has been designated as an "isopathic phenomenon."

Further studies are being carried out to demonstrate whether this phenomenon may be of use in detecting leprosy in contacts, and in determining the effectiveness of chemotherapy.

ABSTRACTO

Continuando su estudio del "fenómeno isopático" en la piel de pacientes con lepra lepromatosa cuando se le inyecta varias substancias, los autores informan los resultados de experimentos con BCG y *Leishmania tropica*. Con BCG en 21 pacientes, 8 de ellos sin lesiones activas y todos recibiendo quimioterapia, las lesiones producides demostraron conglomerados de histiocitos o lesiones prelepromatosas en casi todos los casos, mientras que en los testigos las lesiones fueron características de tuberculosis. Con *L. tropica* en 22 pacientes, estructuras lepromatosas o prelepromatosas fueron halladas en 31 de 46 biopsias, y cambios sugestivos en otras 8. El desarrollo de granulomas histológicos característicos de los tejidos anormales del enfermo, en lugar de los cambios producidos en testigos normales, se ha designado "el fenómeno isopático".

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DESCRIPTION OF PLATE

PLATE (11)

FIG. 1. Leproma-like reaction, six months after BCG inoculation in a tuberculin-negative patient with lepromatous leprosy. Compare the foam-cell aggregates with the tuberculous lesion in Fig. 2. Hematoxylin and eosin, ×460.

FIG. 2. Tuberculous granulation tissue, four months after BCG vaccination in a tuberculin-negative, nonleprous child. Hematoxylin and eosin, ×400.

FIG. 3. Leproma-like reaction, seven months after inoculation of living *Leishmania tropica* in a patient with lepromatous leprosy. Aggregates of foam cells containing Leishman-Donovan bodies. Hematoxylin and eosin, ×550.

FIG. 4. A nodose lesion of cutaneous leishmaniasis (Oriental sore) in a nonleprous individual, showing numerous Leishman-Donovan bodies in macrophages. Hematoxylin and eosin, ×550.

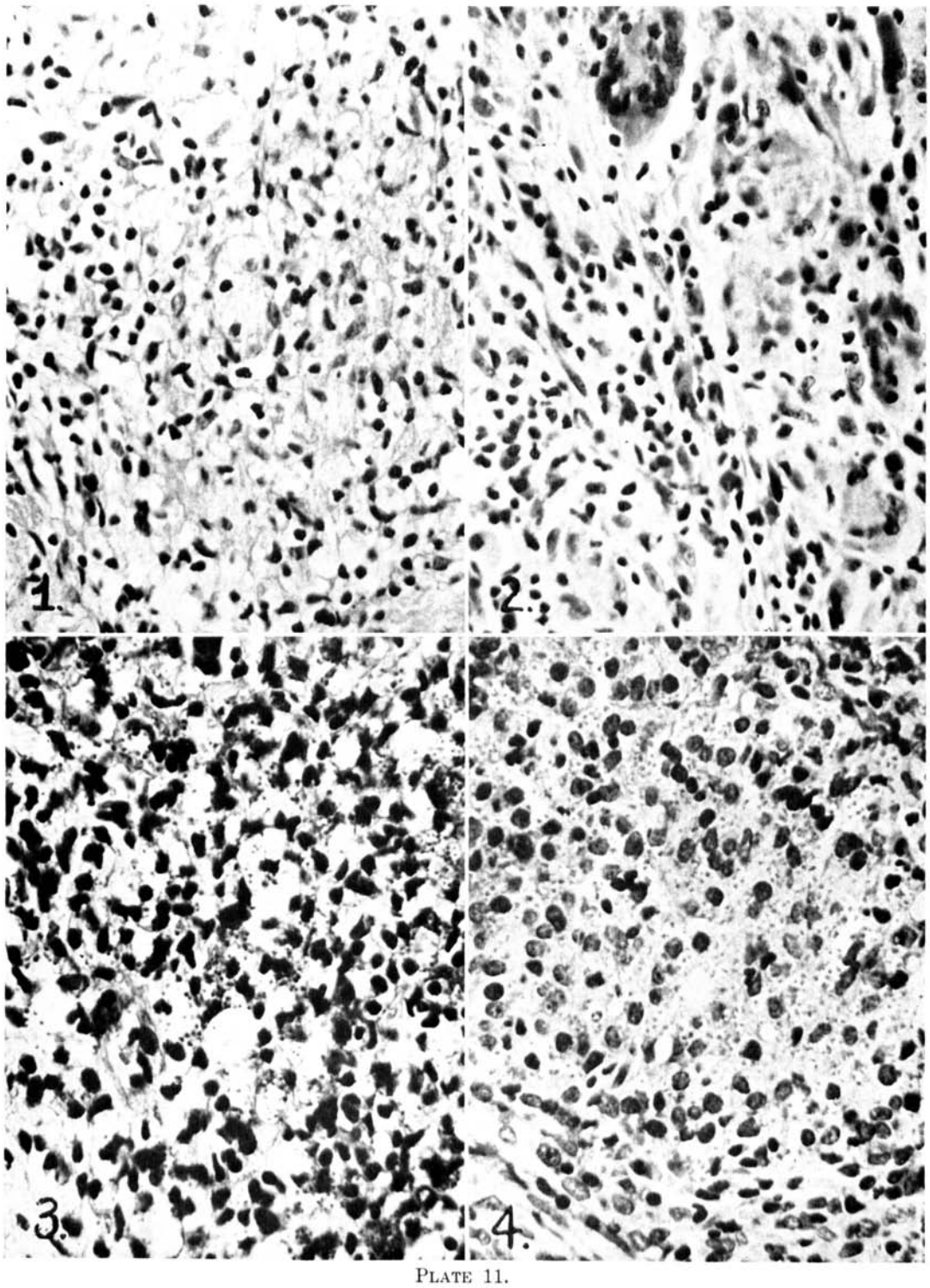

PLATE 11.