STUDIES ON TUBERCULOID VISCERAL LEPROSY
TUBERCULOID GRANULOMA IN THE LIVER, REVEALED BY PUNCTURE BIOPSY

SEITARO OKADA
National Leprosarium Tama-Zenshoen [1]
Tokyo, Japan

While there is no doubt that, in lepromatous leprosy, there exist specific lesions in the visceral organs, notably the spleen and the liver, it has not yet been determined whether or to what extent tuberculoid changes involve the viscera in tuberculoid leprosy. There are various factors which make this determination difficult. One of these is that not many active tuberculoid ("macular" in Japanese terminology) cases come to autopsy. Another is that if one finds a histologically tuberculoid lesion in a visceral organ, it may or may not be of leprous nature. It is particularly difficult to decide the true nature of such a lesion when tuberculosis co-exists with leprosy. Certain other diseases, such as syphilis and sarcoidosis, must also be differentiated.

Danielssen and Boeck (5), in their monograph, described macroscopic tuberculosis-like lesions which they thought were of leprous nature. Arning (1), in 11 of 17 postmortems done in Hawaii, found miliary tuberculosis-like lesions which he, contrary to the opinions of Hansen, Neisser and Leloir, believed to be leprous rather than tuberculous (2), and Schäffer (11) agreed with him. But clinically these cases were not of the tuberculoid type, but lepromatous, and it is very probable that the lesions they found were in fact not of leprous, but of tuberculous, nature. Rikli (10) also described as leprous a tuberculosis-like lesion found in the intralobular region of the liver, but this finding is not substantiated because his descriptions were confined only to the liver and spleen, while the lungs and other organs and the skin lesions were left untouched.

Since the word "tuberculoid" has acquired the special sense given it by Jadassohn (6), Klingmüller (7) has referred to the macular case of Wade and Pineda (13) in which these authors found tuberculoid changes in the nerves, lymph nodes and testicles as well as in the skin lesions. It is noteworthy that the inoculation of the materials obtained from this case into guinea-pigs was negative. In 1939, Mitsuda (9) found, in a case which terminated fatally in an early stage of lepromatous leprosy, tuberculoid changes in the skin, the inguinal and axillary lymph nodes, the right epididymis, and the left median nerve. He confirmed that there was no tuberculous lesions in any organ. This patient before death had shown

[1] Director, Dr. Y. Hayashi.

a negative response to the Mitsuda test, but lepra cells were not yet completely formed in the skin lesions, while epithelioid cells regarded as precursors of the lepra cells were seen in the right testicle. Later, Yoshie (14) reported finding, by biopsy, tuberculoid changes in the mucous membrane of the nasal turbinates of a macular case. The culture, as well as the inoculation of the material into guinea-pigs, was negative in this case. In 1950, Campos and Molina (3) found, also by biopsy (laparotomy), tuberculoid lesions in the livers of 5 macular cases and one "incharacteristic" case. On the other hand Kobayashi (8), Cochrane (4) and others (including Büngeler) have denied the existence of tuberculoid visceral leprosy.

The present paper reports the histological changes found in liver fragments obtained from five cases of "macular" (tuberculoid) leprosy by means of liver puncture. These five cases all responded positively to the Mitsuda test. In all of them the tuberculin reaction was negative, and the x-ray examination revealed normal lung pictures. Cultures of the sputa and feces for tubercle bacilli were negative. Clinical findings of present or past tuberculosis were not found. The Murata reaction also was negative, and there were no clinical findings of syphilis. The liver fragments, 2 mm. in diameter and 20 mm. in length, obtained by Tsurumaru's (12) puncture apparatus were imbedded in paraffin and serial sections were made. Out of every six sections two were taken systematically and stained with hematoxylin-eosin and Ziehl-hematoxylin. Data on age, sex and type of skin lesions of these cases are as follows:

Case 1. Male, 29 years old, annular lesions
Case 2. Male, 75 years old, major tuberculoid lesions
Case 3. Male, 70 years old, annular lesions
Case 4. Male, 19 years old, annular lesions
Case 5. Male, 42 years old, major tuberculoid lesions.

Because the most significant tuberculoid lesions were found in Case 5, I will describe that specimen first, and then deal briefly with those from the other cases.

CASE 5.—A relatively well-defined granuloma of oval shape was found in a liver lobule. In this lesion, 10 or more epithelioid cells and 2 Langhans' giant cells were surrounded by dense infiltration of lymphocytes mingled with a small number of plasmocytes, monocytes and fibroblasts. No acid-fast bacilli were found in this lesion (Fig. 5). Besides this granuloma, which was seen with difficulty with the naked eye, there were other lesions showing various stages of the granuloma formation from the initial change to a typical tuberculoid granuloma, as follows:

1. The initial lesion, composed of a stellate cell engulfing an acid-fast bacillus and surrounded by a small number of lymphocytes and monocytes (Fig. 1).

2. The infiltration of lymphocytes and a few monocytes along the blood capillaries in the liver lobules (Fig. 2).

3. More extensive infiltration along the blood capillaries. A few epithelioid cells are seen in the infiltration.

4. A lesion the outer portion of which was composed of a lymphocytic and monocytic infiltration extending along the blood capillaries. The central portion showed the

beginning of a granuloma which was composed of lymphocytes, monocytes and several compactly arranged epithelioid cells. A few liver cells were seen in this granuloma, and some of them showed a tendency to regressive degeneration (Fig. 3).

5. Compact mass of epithelioid cells surrounded by a zone of infiltration of other cell types. Giant-cell formation from epithelioid cells is present (Fig. 4).

6. Lesion showing infiltrations of lymphocytes, monocytes and occasionally of epithelioid cells in the interstitial tissue (Fig. 6).

In this Case 5, I inoculated the liver fragments on the Ogawa's modification medium of the Oka-Katakura medium, and the result was negative.

The histological findings of the other four cases are dealt with primarily by referring to the features of Case 5 described above.

CASE 1.—Of the features of Case 5, this specimen showed all but the one described as No. 1. In a granuloma of medium size found in a Glisson's sheath, a few acid-fast granules were found in the protoplasm of an epithelioid cell. Besides, in the interstitium a fairly large infiltration composed of lymphocytes and monocytes was found.

CASE 2.—This specimen showed features Nos. 2, 3 and 6 of Case 5. It was a very small fragment, and its examination disclosed nothing characteristic.

CASE 3.—Here all six of the features of Case 5 were seen. One lesion was regarded as an intermediate type between Nos. 3 and 4, and another showed a cellular infiltration similar to No. 4. In a lesion of the No. 5 type, epithelioid cells were in process of forming a giant cell.

CASE 4.—Here, again, all of the features of Case 5 were seen except No. 1. I found a rod-shaped acid-fast bacillus in an epithelioid cell which was in a nodular intralobular lesion composed of epithelioid cells, lymphocytes and monocytes. In the interstitium there was a group of epithelioid cells, which was surrounded by a small number of lymphocytes and fibroblasts.

The leprous nature of these lesions is favored over other possible conditions because of the following considerations:

Tuberculosis: As already said, the tuberculin reaction was negative in all cases, no tuberculous change in the lungs was found roentgenologically, cultures of sputa and feces were negative, and there were no clinical findings of present or past tuberculosis. Generally speaking, tuberculosis does not involve the liver primarily, and lesions do not occur there without some changes in other organs such as the lungs, intestines, etc. The acid-fast bacillus found in the stellate cell in Case 5 is not considered a tubercle bacillus for the culture made with the liver fragments was negative.

Sarcoidosis: The liver may sometimes be involved by this disease. However, the diagnosis of leprosy in our cases was conclusive.

Syphilis: The Murata reaction was negative in all cases, and there were no clinical signs of present or past syphilis. Although a gumma sometimes shows histologically tuberculoid changes, the lesions found in our specimens, showing abundant epithelioid cells, cannot be regarded as syphilitic.

Parasitic diseases: They are excluded by the stool examinations.

In Case 5 the tuberculoid lesion was typical. The lesions found in the other cases were less typical, but some of them presented more or less

characteristic pictures, such as the compact mass of epithelioid cells. Also, acid-fast bacilli were found in some of them. It is therefore concluded that these incompletely-formed tuberculoid lesions were also leprous.

On the basis of these findings the process of formation of the tuberculoid granuloma in the liver lobule can be explained. The photomicrographs of the plate illustrate various stages of development, as indicated in their legends. The letters used in the following (Figs. A to F) refer to Plate 4.

1. At first, leprosy bacilli are taken up by stellate cells. A few lymphocytes and monocytes gather around the stellate cells (Fig. A).

2. The wandering lymphocytes increase gradually, and are followed by an influx of monocytes, secondarily. This cellular infiltrate extends irregularly along the blood capillaries (Fig. B). Monocytes multiply in the central part of the lesion and transform into epithelioid cells. Infiltration of the central part then becomes more and more dense, so that the spaces between the liver-cell columns are more or less dilated. Thereafter the process can follow two courses.

3. When the process subsides relatively early, the monocytes will transform into epithelioid cells. In such cases the lesion will be localized as a small lesion composed mainly of epithelioid cells (Fig. C).

4. When the process does not subside, the lesion will extend further along the capillaries, and the monocytes will multiply in the central part and grow into epithelioid cells. The liver cells are then compressed, more or less dissociated, and undergo degeneration. Surviving liver cells persist in the center of the lesion (Fig. D).

5. When two layers of granuloma, namely the inner layer composed of epithelioid cells and the outer layer composed of lymphocytes, monocytes, etc., can be distinctly distinguished from each other and the lesion shows a nodular form, the lesion is classified as typical tuberculoid (Fig. E).

6. Finally, when epithelioid cells transform into Langhans' giant cells, the tuberculoid granuloma is completed (Fig. F).

In the interstitium, even though no typical tuberculoid lesion was found, some Glisson's sheaths were involved by small groups of epithelioid cells, lymphocytes and monocytes (photomicrograph, Fig. 6). Thus, the tuberculoid change can also involve the interstitium and in that event the process will be the same as that in the lobules.

The lesion composed of lymphocytes, monocytes and a few epithelioid cells such as Figs. A, B and D in Plate 4 may be regarded (not only) as pretuberculoid (but also as prelepromatous) while the lesion such as Fig. C in the same diagram is more properly considered tuberculoid, as well as Figs. E and F.

SUMMARY

By means of puncture biopsy a typical tuberculoid lesion was found in the liver of one "macular" (tuberculoid) case, and some incompletely-formed tuberculoid lesions were found in this case and in three other cases of the same type.

RESÚMEN

El autor discute la importancia de establecer la presencia de lesiones viscerales en casos de lepra tuberculoide y comenta el hecho de la escasez del material de autopsia en casos de lepra tipo tuberculoide. Por tanto advoca el uso de la biopsia hepática por medio de la aguja. De cinco casos así examinados, se observaron lesiones típicas tuberculoides en el parénquima hepático en 1, y lesiones sugestivas en otros tres.

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DESCRIPTION OF PLATE

PLATE (3)

FIG. 1. Beginning stages of granuloma formation. In the central part of the photograph some lymphocytes are seen gathering around a stellate cell, in the protoplasm of which an acid-fast rod can be seen under the oil immersion objective. Case 5.

FIG. 2. Lymphocytes and monocytes infiltrating along the blood capillaries. Case 5.

FIG. 3. Cell infiltration along the blood capillaries, more extensive than in Fig. 2. In its central part some epithelioid cells are seen. Case 4.

FIG. 4. A compact mass of epithelioid cells surrounded by lymphocytes. Case 3.

FIG. 5. A typical tuberculoid lesion in a liver lobule. Two Langhans' giant cells are seen. Case 5.

FIG. 6. Granuloma in the interstitium. Case 1.

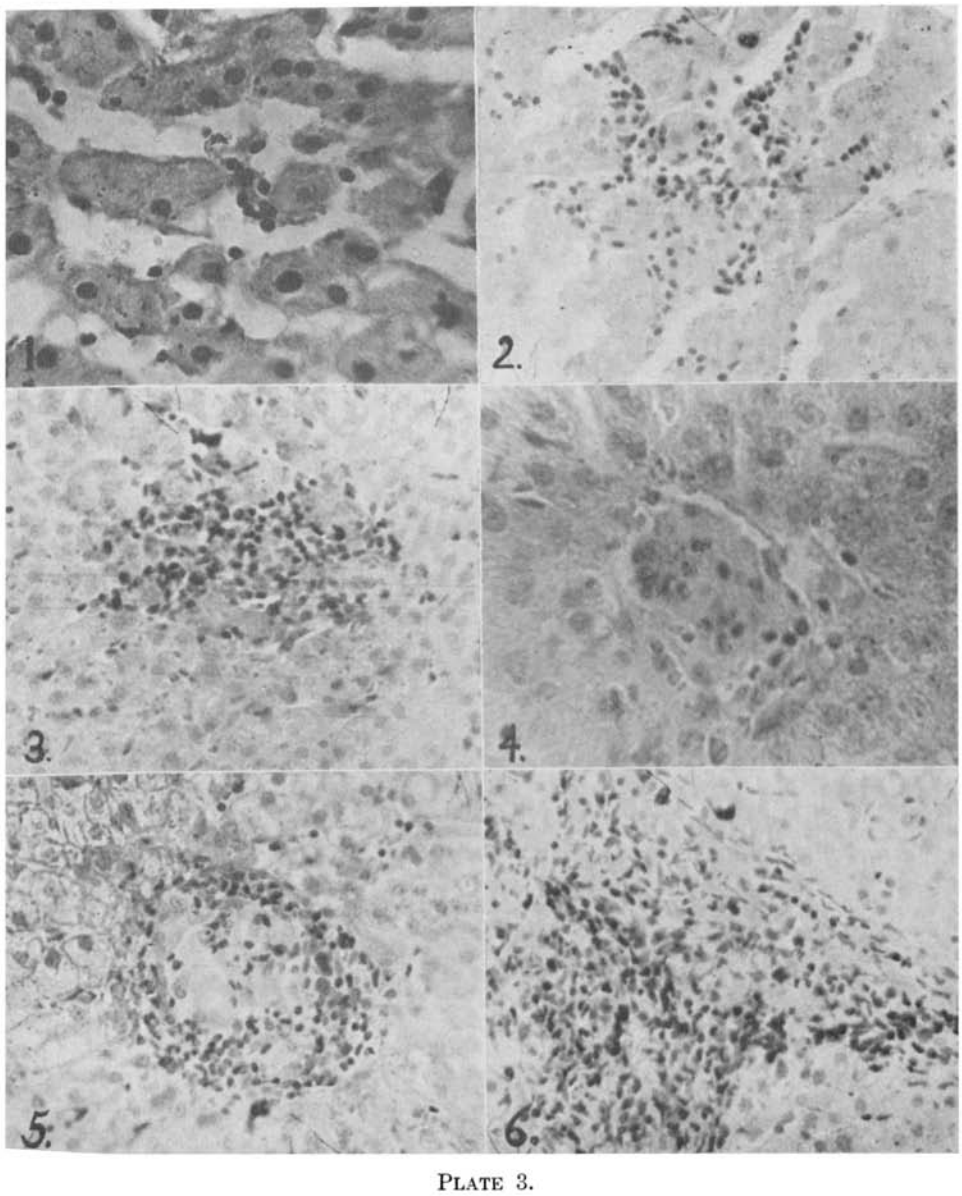

PLATE 3.

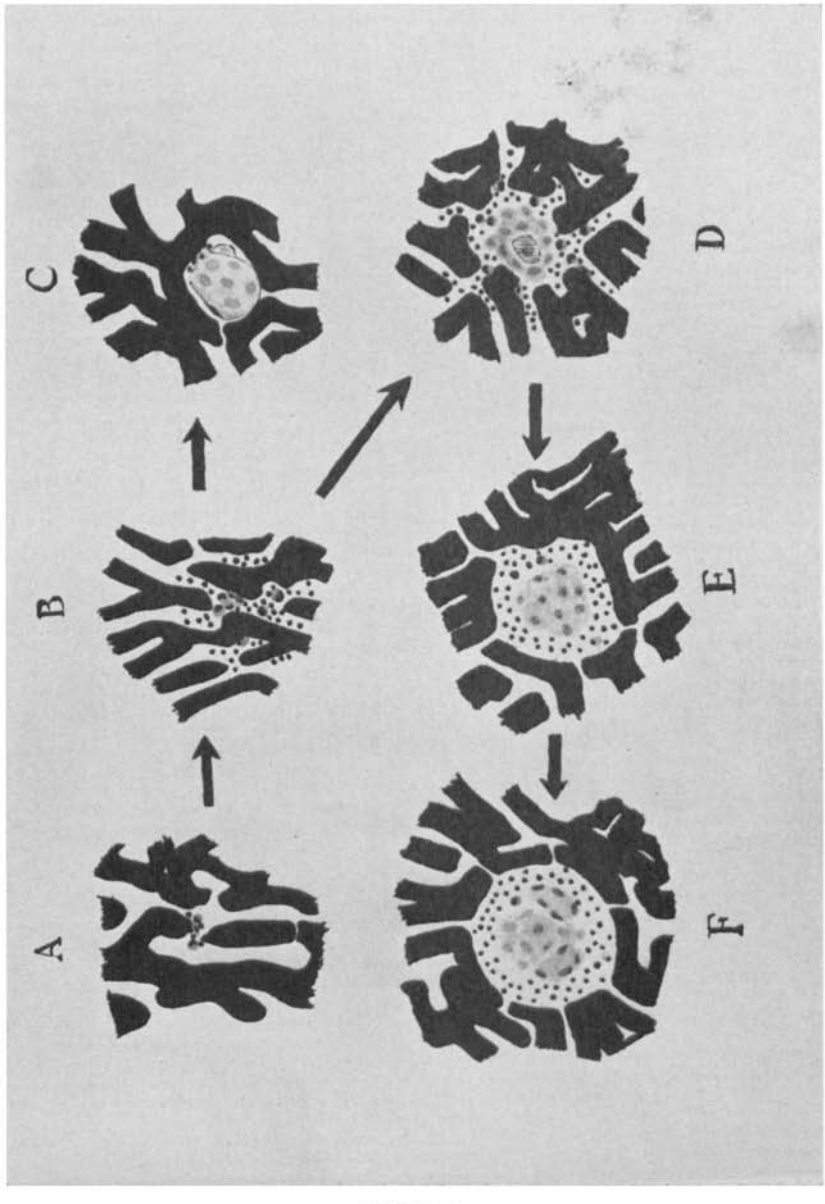

PLATE 4.

FIGURES A TO F. A diagramatic representation of the formation of the tuberculoid granuloma in the lever (see text).