

## Observations on Ultrastructure of Histoid Leproma<sup>1</sup>

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Since Wade (<sup>15</sup>) described the histoid variety of lepromatous leprosy, many authors (<sup>1-14</sup>) in different countries have reported this unusual form of leprosy lesion, including both its clinical and histopathological aspects. A number of studies on its pathogenesis and histogenesis have been made, but controversy still exists. In 1977, we analyzed ten cases of histoid leproma (HL) and found that their pathologic changes were in the nature of a spectrum. We suggested that HL was merely a special type of lesion rather than a variety of lepromatous leprosy (LL) (<sup>2</sup>). Few studies other than those of Job, *et al.* (<sup>4</sup>) and Ridley and Ridley (<sup>11</sup>) have been made on the ultrastructure of HL. We report here the electron microscopic findings in two further cases of HL.

### MATERIALS AND METHODS

Young histoid nodules were biopsied from two patients with BL leprosy with clinically characteristic and histopathologically confirmed histoid lepromas. One half of the biopsied specimen was fixed in 10% neutral formalin solution, processed, and embedded in paraffin; 7  $\mu$  thick sections were cut and stained with hematoxylin and eosin (H&E) and Harada's modification of the acid-fast stain. The other half of the biopsy was cut into approximately 1 mm cubes and fixed in 5% glutaraldehyde in phosphate buffer at pH 7.2 at 4°C. The specimens were then post-fixed in 1% osmic acid, processed in graded alcohol-acetone, and embedded

in Epon. Ultrasections were stained with uranyl acetate and lead citrate and examined in a Philips EM-400 electron microscope.

### RESULTS

#### Histopathology (Fig. 1)

The H&E stained sections of both biopsies showed the characteristic features of histoid lepromas. They were well demarcated with a pseudocapsule in the periphery. This was especially clear in the first case. They were mainly composed of long, thin, spindle-shaped macrophages arranged in many areas as interlacing bundles and whorls. The nuclei were oval, elongated, or convoluted. Occasionally mitotic figures were present. Some of the cells had various degrees of vacuolization or foamy formation. This was particularly marked in the second patient. Acid-fast stain revealed solid bacilli in abundance, present singly or in parallel collections within the cells. A few globi were also noticed. Some bacilli were found in the endothelial cells of blood vessels.

#### Electron microscopic findings

**Type of cells in HL.** The appearance of the HL cells varied from place to place. Usually, in the central area of the lesion the cells were polygonal or of the ordinary type. In the periphery, on the other hand, they were spindle-shaped or elongated, especially in the area adjacent to the pseudocapsule. The lesion consisted of a mixture of inflammatory cells. Their ultrastructural characteristics were as follows.

Bacilli-loaded cells consisted of a) ordinary macrophages, b) fusiform or elongated macrophages, and c) foamy macrophages. Ordinary macrophages (Fig. 2) had an irregular or polygonal contour, with oval, kidney-shaped or convoluted nuclei. Their

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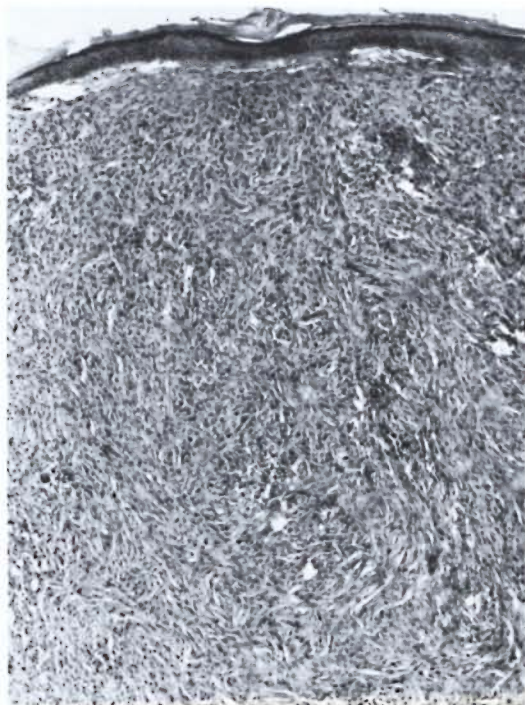


FIG. 1. Histopathological picture of HL showing subepidermal grenz zone and proliferative infiltrate of macrophages (H&E  $\times 100$ ).

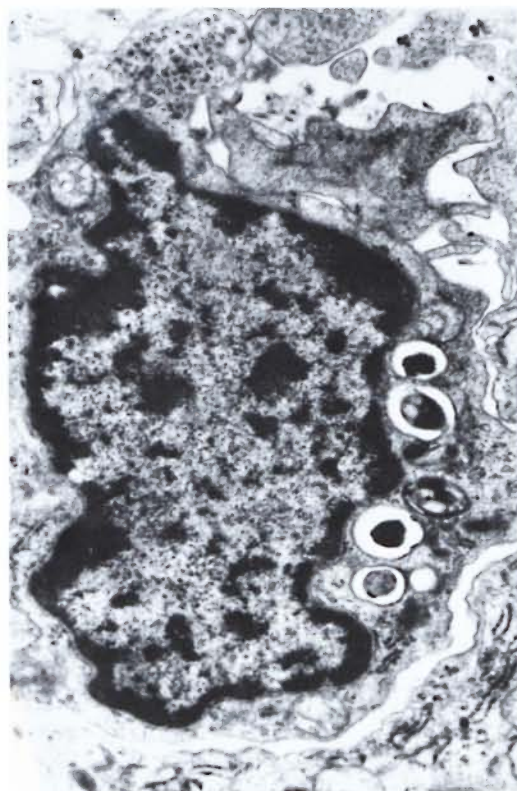


FIG. 2. Ordinary macrophage showing several scattered bacilli with an electron transparent zone (ETZ) around each of them ( $\times 11,000$ ).

heterochromatin aggregated into small clumps. The cytoplasm was abundant and contained many mitochondria and lysosomes of various sizes and different shapes. Often the cytoplasm was filled with bacilli. Some macrophages mimicked epithelioid cells in the shape of their nuclei, which were oval and mainly consisted of euchromatin. Heterochromatin was scarcely located at the nuclear membrane. The nucleoli were prominent.

Fusiform or elongated macrophages (Fig. 3) had oval or rod-shaped nuclei, and their cytoplasm and organelles were less than those of the ordinary macrophages. Many collagen filaments were seen between or around the cells. Bacilli were also present and always solitary.

Foamy macrophages were particularly remarkable in the second case, and were similar to the foamy cells in ordinary LL lesions except that in HL rod-shaped bacilli were present (Fig. 4).

In addition to these three types of macrophages containing bacilli, some transitional forms were also seen.

There were inflammatory cells in the lesions which did not contain bacilli. Plasmacytoid cells (Fig. 5) had eccentric nuclei, oval in shape, with heterochromatin aggregated along the nuclear membrane. They had abundant cytoplasm. Rough endoplasmic reticulum (RER) was abundant, and was arranged in a lamellar appearance around the nuclei, somewhat resembling plasma cells. No bacilli were found. In addition to these plasmacytoid cells, lymphocytes and, rarely, plasma cells and mast cells were found.

**Morphology of bacilli in HL.** The leprosy bacilli were numerous. Most of them were solid in appearance with uniform electron density. Usually the bacilli were scattered singly, but globi were also seen (Fig. 6). Sometimes several cross divisions of bacilli were noticed (Fig. 7). Some of the solid bacilli were also found in the lysosomes (Fig. 8). An electron transparent zone (ETZ) was always seen around single bacilli or globi.



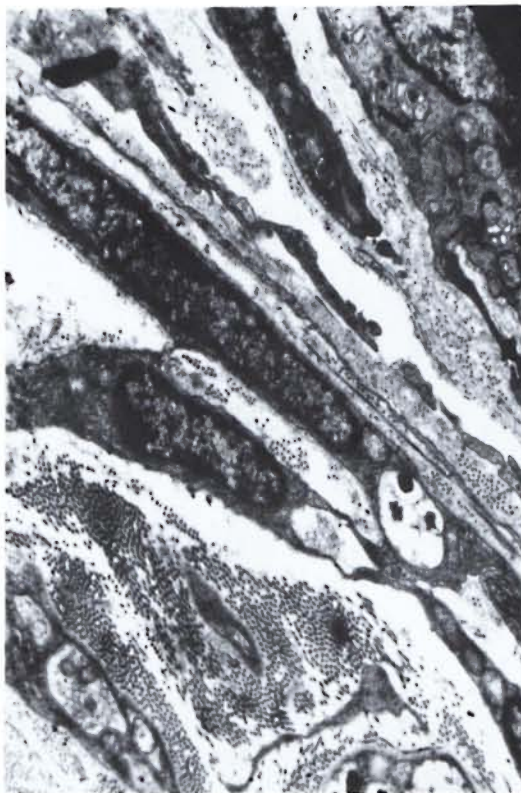


FIG. 3. Fusiform or elongated macrophages with bacilli in the cytoplasm and collagen filaments around them ( $\times 6450$ ).



FIG. 4. Foamy macrophage showing a rod-shaped bacillus in the cytoplasm ( $\times 8350$ ).

**Changes in organelles of cells of HL.** Both primary and secondary lysosomes were abundant, mainly in the vicinity of the bacilli. Their shapes were variable: round, oval or rod-like, and sometimes they were unusually large. Often, a few bacilli and residual mitochondria were located within them; most of the bacilli remained solid. Occasionally, a myelin-figure-like structure was found.

Mitochondria were abundant and varied in shape. Frequently they appeared swollen, disrupted, or showed a disappearance of the mitochondria crista. Some even showed vacuolization. Myelin-figure-like structures could also be found.

The amount of RER was variable. There might be very little in some macrophages indicating a stage of immature differentiation. In other macrophages, RER was very abundant, especially in the plasmocytoid cells, indicating their active proliferation.

Other organelles such as the Golgi apparatus showed no special changes.

#### DISCUSSION

It was formerly emphasized that the histological differential diagnosis of HL from LL was mainly based upon no evidence of foam cells and globi. On the other hand, in our experience (<sup>2</sup>) and in the presently reported cases, there may still be some foamy macrophages (foam cells) and globi in HL. This feature is now confirmed by our electron microscopic study.

In HL, the main cells are varied in shape, but all have the fundamental, characteristic features of macrophages. They may be divided into three types: a) the ordinary macrophage, b) the fusiform or elongated macrophage, and c) the foamy macrophage. These may represent different locations, activities, functions, and differentiations of the macrophage. Thus we agree with Job's idea that the histogenesis of HL might be



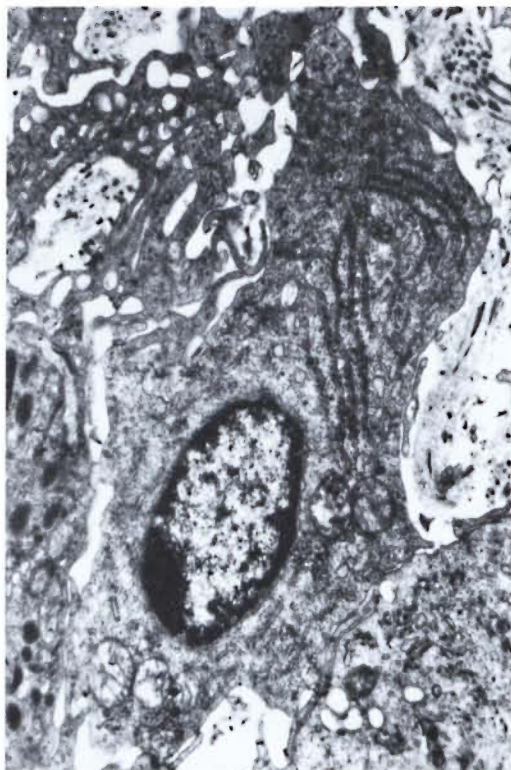


FIG. 5. Plasmacytoid cell showing abundant rough endoplasmic reticulum (RER) around the nucleus ( $\times 8350$ ).

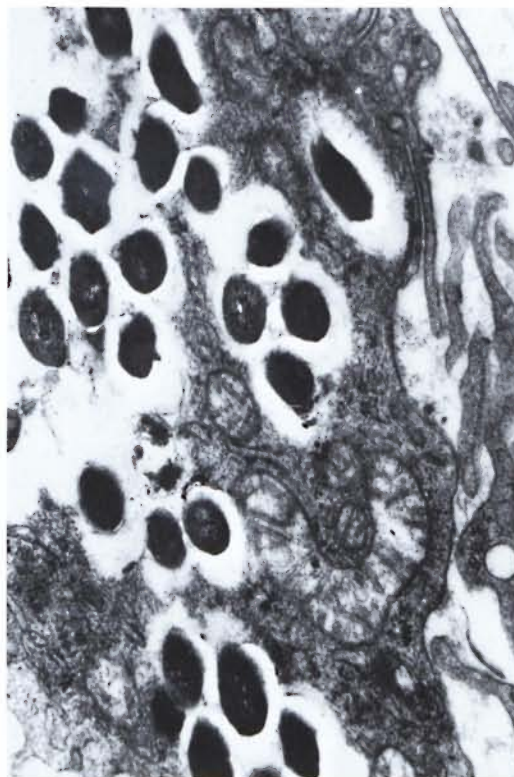


FIG. 6. Globi showing many bacilli in cytoplasm and an electron transparent zone (ETZ) around every bacillus ( $\times 50,000$ ).

explained by the localized active proliferation of the histocytes as in a tumor. This is supported by the features we observed in our two cases with electron microscopy.

The stimulus for the development of HL might be the rapid multiplication of *Mycobacterium leprae*. This opinion would be supported by the presence of cross divisions of the bacilli in the lesions. The appearance of bacilli in endothelial cells of blood vessels indicated the presence of bacteremia which might contribute to the dissemination of the HL lesions.

Desikan and Iyer <sup>(3)</sup> described cases of HL that showed drug resistance. In our previous study we noticed that drug resistance must be an important factor <sup>(3)</sup>. Focalized rapid multiplication of *M. leprae* resistant to sulfone may be one of the reasons for the development of HL. But Price and Fitzherbert's patients <sup>(9)</sup> responded well to antileprosy chemotherapy, and in Ramajam and Ramu's series <sup>(10)</sup> 78 out of 100



FIG. 7. The cross division of a bacillus ( $\times 50,000$ ).





FIG. 8. Solid bacillus in a lysosome ( $\times 23,000$ ).

cases improved with standard dapsone (DDS). Therefore, the pathogenesis of these cases is still to be explained.

Job, *et al.* (<sup>4</sup>) claimed the change in the behavior of the organism could be due to several factors working together or separately. There might be a loss of immunity in localized areas of the skin resulting in enhancement of bacillary multiplication. In our study, the proliferative macrophages in HL contained many lysosomes, suggesting that they had good phagocytic function. On the other hand, the fact that solid bacilli were still found in the lysosomes indicates their defective function in digestion and this might be a factor in the bacillary multiplication. Thus we agree with Job's opinion. However, the basic cause of HL is still unresolved and further investigation will be necessary.

### SUMMARY

An electron microscopic study of histoid leprosy was performed. Cells containing bacilli could be divided into three types, or-

dinary macrophages, fusiform or elongated macrophages, and foamy macrophages. The pathogenesis of these lesions is discussed.

### RESUMEN

Se hizo un estudio al microscopio electrónico de la lepra histioide. Las células que contenían bacilos se pudieron separar en tres grupos: macrófagos ordinarios, macrófagos fusiformes o alargados, y macrófagos espumosos. Se discute sobre la patogénesis de estas lesiones.

### RÉSUMÉ

On a mené une étude de la lèpre histioïde au microscope électronique. Les cellules contenant des bacilles peuvent être divisées en trois catégories: des macrophages ordinaires, des macrophages fusiformes ou allongés, et des macrophages spumeux. La pathogénèse de ces lésions est discutée.

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