

## CORRESPONDENCE

*This department is provided for the publication of informal communications which are of interest because they are informative or stimulating, and for the discussion of controversial matters.*

### THE LEPRA CELL

Once upon a time, to begin as an old story should, we had an idea of working up a "symposium by correspondence" of views of the nature of the lepra cell. The idea was expressed in a letter to a certain correspondent, essentially as follows:

*Editor, to a correspondent (March 21, 1960).—As for a definition [of the lepra cell] . . . it seems to me at least theoretically logical that any bacillus-containing histiocyte which contributes to the structure or mass of a leproma should be considered a stage of a lepra cell—which definition would have nothing to do with cells fed the bacilli otherwise than by and in the lesion [as may be done in the test tube]. There must be in mind some distinguishing morphologic feature, but that cannot be the globus vacuolation. For one thing, there may be in active lepromas considerable areas of bacillus-loaded cells without globus formation; and then, too, there is what I call the histoid leproma which typically is entirely devoid of globus-bearing or foamy cells.*

I am led to wonder if it might not perhaps be worth while to obtain, from several laboratory men working in leprosy, their individual definitions of "lepra cell" for publication as a symposium. . .

Three other persons were consulted about the matter, and copies of this letter were sent to them. From one, no reply was received. Another expressed himself as favorable to the idea, and said that he would prepare a contribution to the subject when he should return from a trip on which he was shortly to embark, but that was the last heard from him about that matter. The third, Dr. George L. Fite, of Carville, La., took the inquiry seriously and submitted two communications, one relatively short and simple, the other of such nature that any other contribution that might be received afterward would probably be anticlimactic. For that reason, and not because "argument as to the nature of the 'lepra cell' has lost all appeal," we sought no further.

There is no valid "alibi," no good excuse, let alone a compelling reason, for the fact that these contributions have reposed in the pending correspondence file so long. It happened; but they are used now.

It is not to be understood that we endorse all of the ideas expressed. It would be most unusual, not to say unnatural, for two leprologists to see eye to eye about all features of so complicated a matter. Certain of the points of differences of opinion are commented on, without augmentation, at the end of the note.

*From Dr. George L. Fite, first communication (April 8, 1960).—It is my impression that, because of the extensive historic usage as such, the term "lepra cell" must usually refer to that described originally by Virchow as "physaliferous." It is this sense that has been applied to it throughout the 80 or more years of active use of the phrase. Some may today prefer a more descriptive term such as a "vacuolated cell." Still further, the phrase bacillus-containing cell is useful.*

It has come to be recognized that not all bacillus-containing cells in leprosy are vacuolated, or even of histiocytic origin. Bacilli are observed in epithelial cells, endothelial cells, connective tissue cells, spermiogenic cells, and others. None of these host cells undergo the characteristic vacuolization of the "lepra cell," which is of histiocytic origin.

In the extremely fresh and vegetative type of lesion, which is almost pure granulation tissue except that it is infected with lepra bacilli, it is usual to see every type of histiocytic and fibroblastic cell of the granuloma with numerous intracytoplasmic bacilli. Some of these show small globular masses of bacilli within ill-defined hollows in the cytoplasm, which are not clearly developed vacuoles. The greatest numbers of bacilli in such lesions are formed in packets and bundles. It is nearly impossible to label these cells except in terms of immature developments. How is it possible to know that they will, or will not, become vacuolated? Certainly in some lesions they will remain for a considerable time just as they are, organized into a fibrous sort of granuloma. It is impossible to define many of these cells as other than connective-tissue cells, some as simple histiocytes, others as macrophages, and still others as more or less vacuolated.

When older lesions are seen, or lesions reactivated after a long quiescence, the formation of bacilli in packet may be conspicuously absent, even though the bacilli are present in large numbers. Cells are usually vacuolated. It is clear that the growth patterns of *M. leprae* may vary greatly, and that the cellular response varies with it.

*Second communication (July 26, 1960).*—During the past century of pathology, especially under the influence of Virchow's "cellular pathology" which dominated early studies, there was a natural and constructive meaning given to the individual cells involved in any pathologic process. Wherever a process evoked a particular type of cell, a particular name might be given to that cell. The usefulness of doing this is apparent. It is still common practice. It is more useful to speak simply of an LE-cell than to try to give it a scientifically descriptive or functional name.

In infectious diseases it has become recognized that many of the cells involved are seen over and over again in various processes. The epithelioid cell is still recognized as such, but recognized as occurring in a host of chronic infections. It is also recognized that the macrophage-histiocyte-mononuclear wandering cell may develop in a variety of ways, according to the specific circumstances and environment in which it is involved, in typhoid fever, leishmaniasis, or histoplasmosis. It is not always given a specific name-type, except when it develops something of a specific appearance.

Unfortunately, perhaps, the term "lepra cell" has been widely used to suggest a characteristic cell of leprosy. There is no doubt that Virchow's vacuolated physaliferous foamy cell dominates the picture of the lepromatous type of leprosy in its chronic form. However, two other facts enter the picture. First, similar cells are encountered in many other chronic dermal lesions, not dominating the picture but nonetheless present. Second, the occurrence of the leprosy bacillus is by no means restricted to cells of what may be called the macrophage series.

The most elementary type of bacillus-containing cell is not physaliferous and not vacuolated. It is a very simple compact mononuclear cell, or histiocyte, which cannot be easily categorized. It is seen plentifully during the most active phase of bacillus-rich lepromatous leprosy, in the active, rapidly progressing granuloma. It is not a large cell, does not have a vesiculated nucleus, and has a variety of shapes, perhaps largely determined by pressures from neighboring cells or tissue elements. It is this cell which shows to the greatest advantage the formation of bacilli in packets. These bundles of bacilli may be multiple within the cell, with their longitudinal axes often directed toward a common area in the cytoplasm, perhaps the centrosome. Or, this cell may contain a microcolony of bacilli, not oriented in packets. This formation probably corresponds to Cowdry's "seed globus," not to be confused with globus-formation in vacuolated cells. Some large packets or bundles of bacilli may also constitute essentially "seed-globi," so that there may be several within a cell. But these are not the vacuoles described correctly

by Virchow as appearing to contain nothing but water. In hematoxylin and eosin sections these little globi show a protein matrix, which stains lightly with hematoxylin.

At the same time, within this same type of fresh lesion, there are other nonvacuolated cells which are elongated and often somewhat spindle-shaped. Their nuclei may also be spindle-shaped. Whether these cells are, or are not, fibroblasts has not been specifically studied, but they have all the appearances of fibroblasts. Within such lesions so many undefinable cells are seen that one is strongly tempted to assume a common histiocytic origin for both of these primitive bacillus-containing cells.

There occur, in leprosy, infrequent lesions in which this fibroblastic type of cell becomes the dominant cell of the final leproma. In such lesions these cells retain their general elongated shape, and the lesions are quite fibrous, containing much collagen. These cells do not become vacuolated. Whether or not they elaborate collagen is not known. Such lesions undoubtedly contain many mature connective tissue cells, sufficient to account for the collagen present. Vacuolated cells will also be found in varying measure, but the appearance of these "fibroblastic" lepromas, rare though they are, is quite striking. I have recently seen one of these occurring superficially upon an old chronic leproma, making one wonder if some tendency to keloid formation was involved in the process.

To continue with the connective tissue cell as a bacillus-containing cell, it is only necessary to study nerves in lepromatous leprosy, in which there is much connective-tissue proliferation of the outer sheath. Here the adult spindle-shaped connective tissue cells are commonly found to contain bacilli, usually at the poles of their nuclei, without vacuolization.

Apparently vacuolization is a feature of the macrophage. Endothelial and epithelial cells containing bacilli do not show this characteristic. It seems correct to emphasize that vacuolization of the macrophages is not present in the earliest phases of acquiring bacilli, and does not necessarily or inevitably result. That vacuolization does occur in time in most of the lepromatous cells is obvious to every student. But the examples in which it does not occur are sufficiently striking to have led me not to use terms such as "foamy cell" or "lepra cell," and to prefer the specific use of "vacuolated cell" when a vacuole is present.

Consequently, if I am asked for a definition of the lepra cell, I am lost for an answer. The evolution of bacillus-containing cells is still a fascinating problem, with questions much alive today as to the significance of infection of Schwann cells and other cells supporting terminal nerve fibers. It is certainly blindness to dismiss the matter with dogma and reference to past descriptions, or embroil the matter in personal opinions. There is a clear opportunity for study of the dynamic qualities of the cells in leprosy, and argument as to the nature of the "lepra cell" has lost all appeal.

*Comment.*—To come down from the erudite heights reached by the author of these notes to the every-day practical level, it is beyond doubt useful to recognize and identify the cell which composes the greater part of the leproma.

At the outset the author points out that, from long usage, the term "lepra cell" must apply to the physaliferous, or vacuolated, cell, which condition he shows occurs only in the histiocyte. At the same time, it is also said that the phrase "bacillus-containing cell" may be useful, whether the cells be vacuolated or not.

It is then shown what a variety of cells may contain bacilli. It nevertheless remains a fact that epithelial cells in which bacilli are included, when that happens, constitute by no means a significant element of the leproma; that although endothelial cells are frequently

infected they do not contribute materially to the bulk of the leproma; and that true epithelioid cells—at least in lesions of tuberculosis, or of tuberculoid leprosy, or even the tuberculoid foci that not infrequently are found in nodular lesions of the histoid variety of lepromatous leprosy—are hostile in the corresponding bacilli and destroy them. Epithelioid cells are not an element in the composition of the typical, uncomplicated leproma. Not every cell of epithelioid morphology is of that nature functionally.

As for the role of the connective-tissue element in the leproma, ordinarily it—along with reticulin—constitutes the supporting network of the well-established leproma, but it has no regular role in the harboring and nurturing of the bacilli. We fail to recognize the “fibrous sort of granuloma” mentioned.

The author touches, rather cautiously, on what are in fact certain features of the histoid leproma, the tissue of which is normally spindle-shaped, loaded with bacilli, and not globus-forming. Photomicrographs of that lesion were posted in the exhibit room at the Tokyo Congress (1958), which the author attended. That lesion in its earliest form contains no connective tissue elements demonstrable with Mallory’s aniline-blue stain, and the irregularly-distributed connective-tissue elements which develop with age are ordinarily not bacillus-containing.

It may be a question whether or not the author—or, for that matter, the commentator—succeeded in not “embroiling this matter in personal opinions.” Be that as it may, the matter is by no means a settled one, and would make a valid topic for a panel of a leprosy congress.—EDITOR.