LIPOIDS IN THE REACTIONAL TUBERCULOID LEPROSY GRANULOMA
THEIR DIAGNOSTIC VALUE
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The lepra cell, which Virchow first described and which bears his name, is the anatomic characteristic of the granuloma of lepromatous leprosy. Unna demonstrated that the vacuoles of the foamy cells of Virchow are due to fat in the cytoplasm, and not to edema as was thought by the author who saw them first. Mitsuda (4), in a paper published in 1936, claims to have stained that substance with sudan III in 1902 and, in more recent microchemical studies, to have proved that chemically it is a lipoid of unknown but possibly very complex formula. His views regarding the source of this substance will be considered later. Rath de Souza and Lecheren Alayon (6) have considered the matter of lipoids in the different lesions of leprosy, in the light of the new classification of the disease—conceived and, at that time (1942), accepted only by South American leprologists but lately approved, with slight modifications, by the Fifth International Leprosy Congress at Havana, in 1948—and their views will also be considered.

In the present paper is reported a study of the same problem, emphasizing the differential diagnosis between lepromatous and reactional tuberculoid leprosy, which is still a problem.

MATERIAL AND METHODS
Eighty-six biopsies of skin lesions have been made, the specimens derived from as many patients. By type, 32 of the cases were lepromatous, 22 tuberculoid, and 32 undifferentiated.1

Frozen sections were made of each specimen and stained with sudan IV (1). Also, in order to make histological diagnoses of the type of the disease, sections of each were stained with hematoxylin and eosin and by the Ziehl-Neelsen method.

To avoid prejudice, the search for the presence of lipoids was made without reference to the clinical and immunological data or the histologic

1 Designated "indeterminate" by the Havana Congress.—Editor.
diagnosis of type. Only after the presence or absence of lipoids was established, in one or more slides for each case, were the results correlated with those factors.

RESULTS

A. Lepromatous type.—Of the 32 specimens from lepromatous cases, no less than 30, or 94 per cent, were found to have lipoids in the granulomatous tissue; only 2 were negative in that respect.

These lipoids were predominantly within the cytoplasm of the lepra cells. Staining with sudan IV gave them a yellow-orange color, and usually they looked like small vacuoles 2-4 μ in diameter. In only a very few instances were round or oval masses 20-30 μ of diameter found; these specimens were old lepromas with Virchow’s cells in which the large vacuoles pushed the nuclei to one side. This aspect is different from the foamy or finely vacuolate cytoplasm of the lepra cells at the beginning of their development.

It is to be emphasized that not all of the monocytes of the lepromatous granuloma “take” sudan IV. Many of these cells remain uncolored by it, especially when they are located centrally in the granuloma. In general, it is safe to say that the affinity of the monocytes for sudan IV is directly related to their bacillary load.

Many of the cases with fat in the dermis also had this substance in the epidermis, mixed with shedding horny material.

<table>
<thead>
<tr>
<th>Classification of cases</th>
<th>Number of cases</th>
<th>With lipoids</th>
<th>Without lipoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepromatous</td>
<td>32</td>
<td>30 (93.7%)</td>
<td>2 (6.2%)</td>
</tr>
<tr>
<td>Tuberculoid</td>
<td>22</td>
<td>7 (31.8%)</td>
<td>15 (68.1%)</td>
</tr>
<tr>
<td>Quiescent</td>
<td>15</td>
<td>0 (0%)</td>
<td>15 (100.0%)</td>
</tr>
<tr>
<td>Reactional</td>
<td>7</td>
<td>7 (100.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>32</td>
<td>17 (53.1%)</td>
<td>15 (46.8%)</td>
</tr>
</tbody>
</table>

B. Tuberculoid type.—In only 7 of the 22 specimens from tuberculoid cases, or 32 per cent, were lipoids to be found in the granulomas; the other 15 were negative.

In positive cases, the lipoids occurred in the form of a very fine orange-colored dust, located in the cytoplasm of epitheloid
cells. In no case were there large masses such as were seen in the lepromatous granuloma. All of the positive cases were of the reactional tuberculoid form, while the lipoid-free tuberculoid specimens came from quiescent cases.

This condition was appreciated only after a comparison of the findings in sections treated with sudan IV and in those stained with hematoxylin and eosin. The observation indicates that the transitory foamy state of the epithelioid cells during the reactional phases of tuberculoid leprosy is not produced by edema, as has been believed (1), but by cytoplasmic lipoids resulting from the increased numbers of the Hansen bacillus which appear during the phases of reactional activity of tuberculoid leprosy.

C. Undifferentiated leprosy.—Of the 32 specimens from cases of this class which were studied, 17 or 53 per cent, had lipoids while 15 did not.

The reason for this difference in these cases we do not know. It is possible that some of the positive cases are old lepromatous ones in a healing state (1 post-L). It is possible, also, that some of them were prelepromatous cases; and if this should be so it would mean that the presence of fats is an early sign of a future differentiation towards that type of the disease. Unfortunately we could not make a clinical-pathological correlation—the only way to clear up the problem—because a great majority of the patients live in quite distant parts of the country, not staying in colonies because patients with that form of the disease are not segregated.

DISCUSSION

From our observations it appears that the cells of the granulomatous lesions of almost all lepromatous and reactional tuberculoid leprosy cases contain fatty material, whereas the granuloma of quiescent tuberculoid leprosy is wholly lacking in lipoids. The lesions of undifferentiated cases, in accord with the known lack of polarization of that group, may or may not show intracellular fats. We cannot say whether or not this fact may prove to be a valuable sign with regard to the future orientation of these cases toward the lepromatous or the tuberculoid type of the disease.

Our results are not in accord with those of de Souza and Alayon (6). They found 84 per cent of their lepromatous cases to be positive for lipoids, 33 per cent of their undifferentiated cases and only 17 per cent of their reactional tuberculoid cases. Most of their lipoid-positive cases of the undifferentiated form
were old lepromatous ones (I post-L). We were not able to find this relationship in our cases.

The outstanding difference between their results and ours is that they found lipoids in only 3 of 18 cases of reactional tuberculoid leprosy studied, whereas we found them in every one of our 7 cases. De Souza and Alayon conclude that the vacuolated appearance of the epithelioid cells of the reactional tuberculoid granuloma, ascribed by others to edema, is due to a technical artefact. On the contrary, we support the view that the foamy appearance is due, in great part if not entirely, to the fatty content of those cells in this form of leprosy.

From our findings it must be concluded that the search for lipoids in histological sections is not a valuable element in the differential diagnosis between lepromatous and reactional tuberculoid leprosy, since both forms of the disease almost always show them. What might be an indication with some value is the size or volume of the fat particles or globules, since in lepromatous cases they are usually of medium size or large, whereas in reactional tuberculoid leprosy they are very fine and look like dust. However, these differences are not constant enough to be of definitive value for differential diagnosis, because in some early cases of lepromatous development one may see the same picture as in the tuberculoid cases. It is possible that in the future, with a better knowledge of microchemical cell techniques, one can establish whether or not there are chemical differences in the lipoids of the two types of leprosy.

The source of the lipoids studied—whether they derive from the cell, or from the bacilli in it, or from the outside—is not known. Some hold that they are a by-product of the metabolism of the leprosy bacillus, or that they result from its involution (4). Others assume that the bacilli in the Virchow cells induce a fatty degeneration of them, this condition being at first favorable to the proliferation of the bacilli but later—when more advanced, resulting in decreased vitality of the cell and even its death—becoming unfavorable to the life of the mycobacterium, which then tends to disappear. This would be the picture of the regressive lepromatous lesions with much fat in the cells, karyolysis, and few bacilli, sometimes in a granular form and sometimes quite absent (4). Still others think that the lipoids come from the host; that the bacilli, in the cells of the reticulo-endothelial system which they have infiltrated, determine "a stimulation of granulopexic function" and specially "an enlivening of the lipopexic function" of those cells, with a consequent
storage of fats and lipoids taken from tissue and internal medium
(Artom, quoted by de Souza and Alayon).

Despite all this there are certain features which lead us to think that the source of the lipoids is the leprosy bacillus itself. Actually, the likeness in the staining between the bacilli and lipoids, when one uses the Zielh-Neelsen technique, is complete; and it is possible to see every intermediate stage between isolated bacilli and big round masses, the so-called "globi," which staining by sudan IV shows to be composed of lipoids. These globi originate by the grouping of bacilli, possibly dead, from the bodies of which there is liberated the wax which was an important constituent of them. Mitsuda (4) first inclined to this hypothesis, but then he partially discarded it because he did not find the same material in the reticuloendothelial cells of livers and spleens of lepromatous cases despite the heavy loads of bacilli which they bore. However, other authors (5), and we ourselves, have found large amounts of lipoids in those organs in lepromatous cases. This possible origin of the lipoid, therefore, seems to be the most likely one.

But in any case, there is one point on which everybody seems to agree. That point is that without M. leprae, in such quantity and quality as can be demonstrated by the stains commonly used for acid-fast germs, there are no lipoids in the tissues.

It would appear that there is a close relationship between the Virchow lepra cell and the epithelioid cell, and that their morphological differences are not definitive or irreversible (2). Both arise from the same cell, the monocyte. They differ as regards the ability to destroy M. leprae, that microorganism being phagocytized by both of them but destroyed only by the epithelioid cell (2). This capacity for lysis of the bacilli is a function of the resistance which in every case determines the evolution toward either the lepromatous or the tuberculoid type of the disease.

The monocyte of reactional tuberculoid leprosy is more like the Virchow lepra cell than like the epithelioid cell of the tuberculoid follicle. In fact, those two cells have several features in common: foamy cytoplasm, Hansen bacilli in the cytoplasm in important quantity, and lipoids. This histological likeness parallels the clinical similarity that exists between lepromatous leprosy and reactional tuberculoid leprosy, and explains the reported cases of transformation from the latter to the former.
SUMMARY

In the lepromatous, tuberculoid and undifferentiated granulomas of leprous etiology, lipoids occur in different proportions of cases.

Practically every lepromatous granuloma shows lipoids. On the contrary, the tuberculoid granuloma never has them except in reactional phases. The undifferentiated granuloma has lipoids in one-half of the cases. Whether their presence has any significance with regard to the evolution of the case we do not know.

In lepromatous leprosy the lipoids usually occur in medium-sized or large drops, while in the reactional tuberculoid condition they appear like a fine dust. This difference, although not constant, is indicative as regards the diagnosis between lepromatous leprosy and reactional tuberculoid leprosy.

The mechanism of deposit, or formation, of lipoids in the cells which form the different leprosy granulomas is not known, but it is evident that the lipid load is only found in those monocytes which do not have the ability to destroy the leprosy bacilli phagocytized by them. This lack of ability may be permanent, as in lepromatous leprosy, or transitory, as in reactional tuberculoid leprosy.

REFERENCES

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6. DE SOUZA, P. R. and ALAYON, F. L. Sobre a presença de lipídios nas lesões cutâneas de lepra. Subestado do diagnóstico diferencial entre as diferentes tipos de lesão. Rev. brasileira Leprol. 10 (1943) 373-401.