The Submicroscopic Pathologic Anatomy of Leprosy

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Jadassohn ([5]) and Victor Klingmüller ([9]) described tuberculoid leprosy exactly in its clinical and histologic aspects about the beginning of the present century. Later, after correct interpretation of the lepromin test, it was the merit of Büngeler ([1]) to recognize the malady in terms of a defensive granuloma, in opposition to the concept of "thesaurismatic" leprosy. The modern classification of leprosy has followed these pathologic-anatomic principles. Remarkably, electron microscopy has, to a great extent, proved these special morphologic statements, as shown by papers published in Japan, Germany, the United States and Russia.

We have reported on the submicroscopy of leprosy in detail. Summarizing, we may note the following. The structure of the mycobacterium gives hints on its metabolism, growth, division, and virulence. Up to now the virus has been found only intracellularly in histiocytes and Schwann cells, and sometimes in fibroblasts, but not extracellularly. Phagolysosomes are formed, i.e., ferment-active lysosomes containing residual bodies of lipoid nature, especially in histiocytes. The lipoid substances can be demonstrated easily by their sudanophilic staining nature.

Up to now the tuberculoid defense granuloma has scarcely been distinguishable by electron microscopy from lupus vulgaris or sarcoidosis, i.e., diseases characterized by epithelioid and giant cells. While Orfanos ([11]), in the case of lupus vulgaris, identifies dense intracytoplasmic granules as bacteria or the remains of bacteria, similar structures occurring in tuberculoid leprosy cannot yet be looked upon for certain as bacterial in nature.

The dimorphous transient forms of leprosy show bipolar characters with a submicroscopic image similar to that seen under the light microscope, in which, according to expectancy, the primary manifestations (here tuberculoid and there lepromatous) are at first prevalent and mingle with other types of reaction according to the prevailing state of immunity.

It is not quite accurate to see in dimorphous leprosy simply an intermixture of the polar histopathologic structures without reactive cell processes. For this reason the dimorphous form of the disease cannot be sufficiently delimited from the various reactions of leprosy. This holds particularly for submicroscopic conditions, which, in the light of the manyfold structure of the tissue, can lead to enlightening findings only through careful comparison with the clinical picture.

Since, as noted above, there are basically uniform concepts of the submicroscopy of leprosy, and thus the clinically developed principle of classification has been proven, it might now seem proper to turn to certain special questions.

1. Nishiura *et al.* ([10]) reported specific changes in nerves and presented a scheme for survey. Yet he could look only at specific changes in nerves, and not at early processes, as Imaeda ([2]) did. With respect to the technical difficulty of analyzing smaller nerves by electron microscopy, it is still necessary to await further statements. In any event it is worth discussing if enveloped afferent nerve fibers might not have phagocytic activity for leprosy bacilli. It could then be considered whether or not bacteria in the neuroplasm can be transported centripetally.

Here we touch upon general anatomic questions concerning the occurrence of axons above the epidermal basal membrane. In Paget's disease we have been able to observe axons among the keratinocytes [Ishibashi *et al.* ([4])], but have not yet been able to find them in the skin of leprosy patients. Yet these findings are of some significance in a discussion of possible bacterial infecting routes, for at present there are better hints at the manner of

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transport (erosion?) through the epidermis.

2. Unfortunately as yet there has been no success in demonstrating bacteria in keratinocytes by electron microscopy, as Ishibashi ([3]), in contrast, has shown by light microscopy. Leprosy bacilli have not yet been observed in melanocytes, except in the eye, nor in the Langerhans cells of the skin.

On the other hand we were able to make this demonstration in nevus cells ([7, 8]). The findings are important for two reasons. In the first place they furnish additional proof of the close affinity of melanocytes—at least, perhaps—and nevus and Schwann cells, as Kawamura has explained in another connection. Secondly, there must be a conducting path through this syncytial system of cells, with penetration during bacterial infection. The admission of viruses into nevus cells is strange, for all optical light observations suggest a noteworthy inertness in these cell hamartomes, at least as they lie in the skin. It is in that site, apparently, where they show their kinship with Schwann cells. Nevus cells, in contrast, contain a striking content of mitochondria ([12]), a characteristic that has been difficult to interpret up to now.

3. Observation of a patient with lepromatous leprosy and neurofibromatosis of Recklinghausen has led to extension of our knowledge in this respect. The submicroscopy of neurofibromatosis must be taken for granted at this point; we shall report on it elsewhere. If it is assumed that neurofibromatosis arises more or less from two tissue sources, in accord with recent opinion, leprosy bacilli should be expected to be found in derivatives of degenerated Schwann cells, rather than in cells of fibroblastic mesenchymal origin. Up to now we have not yet been able to detect viruses in those cells of unmistakably fibroblastic character. On the other hand, singly situated, apparently well-formed bacilli, surrounded by a light halo, more or less at random, are commonly seen in similar cells, though surrounded by a consolidated zone of cells. They show the characteristics of fibroblasts rather than histiocytes, for they contain rough endoplasmic reticulum, degenerated mitochondria, and again lyso-

somes. Further analysis of these cells is essential.

In comparison with the now rather well known submicroscopic structure of the foamy cells of lepromatous leprosy, once thought to be histiocytes, but now looked upon as belonging to the macrophage group, the cellular changes around the bacilli differ from those described above in showing less reaction. The changes are reminiscent of findings we have described in a lepromatous patient in reaction. In that case distinctly rimmed, vacuolated elements were found in relation to bacteria in fibroblasts. Be that as it may, the findings support the concept of admission of bacilli through fibroblasts, as Yoshie ([15]) and Jadin ([6]) have already supposed in fibroblast cultures. The latter apparently can change their structure, and thus probably their function, for as a rule we know that histiocytes phagocytose and fibroblasts synthesize.

4. In some respects neurofibromatosis calls to mind the variety of lepromatous leprosy called "histoid" by Wade ([14]). The dense complexes of spindle-shaped cells are interpreted as histiocytes. This is perhaps not quite correct, for only individual cells contain bacilli, and occasionally even large vacuoles of fat with bacilli. The histoid leproma is of some significance in the understanding of sulfone therapy. Rodriguez et al. ([13]) have raised the question if results could be conditioned by variation of leprosy bacilli made resistant by therapy. To me this supposition seems still premature. Rather, it seems logical to believe that sulfones reach the viruses only with great difficulty whenever the latter have penetrated fibroblasts.

As it is, the problem of the therapy of leprosy cannot be seen simply from a purely bacterial point of view, with a one-sided preference for chemotherapeutic concepts. It is of course true that this problem in modern therapy has been known since 1942. The complex electron microscope structures teach us how well sealed off viruses are, lying, as they do, and increasing in the cells. On the basis of our knowledge of cytology three fundamental types of leprosy seem to exist: (1) with bacilli in histiocytic

foamy macrophage cells, (2) with bacilli in fibrocytic-fibroblastic cells, and (3) in the epithelioid cell form of defensive granuloma.

It would not be wise to expect success solely with chemotherapy, for example in the case of the first mentioned, histiocytic form of lepromatous leprosy. That would represent an isolated therapy in fighting the virus, but not reaching it. Substances attacking the lysosomal organelles would seem more effective. This is a complicated system. At present corresponding possibilities seem plausible. In the light of our experience with psoriasis, we are inclined to think of oral high dose administration of vitamin A, which can be carried out under so-called chemotherapeutic protection by sulfones. Researches on this problem are under way.

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