Late last year, while leafing over an issue of the *British Medical Journal*, we chanced upon a brief review with the above heading.[1] The word "lysosomes" meaning nothing to us, we awoke to the fact that there had developed a new field of cell study of which we were not aware. The review, being obviously of advanced work, did not convey an idea of the "lysosome concept" itself, except that it pertained to a special class of intracellular bodies containing enzymes, but it was evidently not a particularly new concept since de Duve and associates were credited with having discovered these bodies in 1955. It also appeared that the subject must be of some importance, since the Ciba Foundation was led to convene a symposium on it, and one of some size since the report contains some 450 pages—and costs £3!

The word "lysosome" was not found in the medical dictionaries available, but after all none of them is of recent vintage. It was some consolation, however, to find that the name had not yet been accorded a place in the subject index of *Index Medicus*.[2]

A search of the author indices of that publication revealed that de Duve's name had appeared repeatedly for some years (often as a joint author), notably in a numbered series of no less than 15 articles

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[1]CAMERON, R. Lysosomes. Review of a Ciba Foundation Symposium. British Med. J. 1 (1964) 1102-1103.

[2]The subject lysosomes appeared later in *Index Medicus*, in the January 1965 issue.

in the *Biochemical Journal* on tissue fractionation studies, reporting biochemical work with the rat liver which led to the discovery of the lysosomes. About 1960, it appeared, de Duve began publishing on the subject of lysosomes, first in European periodicals and finally in the *Scientific American*,[3] an advanced popular science magazine.

None of the several available articles encountered in that search and since gives any comprehensive notion of de Duve's ideas of what the lysosomes are, since they deal with special phases of the matter. Usually the only significant reference to an article on the lysosomes by de Duve is to his relatively early contribution to a book that is not widely accessible.[4] The *Scientific American* article, when procured, was found to be basic and to cover the subject from the beginning, and a review of it has been prepared for this issue of THE JOURNAL. For anyone as completely ignorant of the subject as we were, it might be well to read that item first. The note on the Ciba symposium in the *British Medical Journal* which started our search is also published as a review, by permission.

Of the several series of articles found in the *Journal of Experimental Medicine*, the most helpful is a series, mainly by Cohn and Hirsch (or vice versa), from the Rockefeller Institute, on the granules of the leucocytes. In none of the titles does the word "lysosome" appear, but it does appear in the text of some of them. In some, the pictures—especially the electron micrographs—are valuable.

Passing up three articles by Cohn and Morse that appeared in 1959 and 1960, the first of three by the Cohn-Hirsch team [**112** (1960) 983-1004] tells of the isolation of the specific cytoplasmic granules of the polymorphonuclears, and of the chemical and enzymatic analyses applied. It was concluded that the granules "seem to be analogous to those of liver lysosomes described by de Duve." There are two electron micrographs of ultra-thin sections, one of a centrifuged granule pellet, and for comparison one of a rabbit polymorphonuclear. (This article has been abstracted.) The other two articles [**112** (1960) 1005-1014 and 1015-1022] deal with the degranulation of the leucocytes following phagocytosis of microorganisms, without mention of lysosomes. A study by Hirsch [**116** (1962) 827-833] is particularly interesting. By cinematography he showed the fusion of the membranes of granules of chicken polymorphonuclear leucocytes and those surrounding ingested bodies [i.e., the "phagosomes"]. Again the granules were said to resemble closely the lysosomes of de Duve. (Abstracted.)

Eosinophiles were dealt with, in the same way, by Archer and Hirsch [**118** (1963) 277-281]. (Abstracted.) Those of the horse were used, for their granules are few and relatively huge. These cells, too, are regarded as lysosome-like.

The macrophages were studied by Cohn and Wiener [**118** (1963) 991-1008 and 1009-1019]. (Abstracted.) These cells were from rabbits, those obtained from the alveoli of the lungs after BCG stimulation being the most useful. At the end it is said that some ingested particles, like those of carbon, are retained indefinitely [in the "digestive body" created by the fusion of the granule with the phagosome]. In this connection, passing mention is made of the lesions of tuberculosis and leprosy.

Finally, a further study of the degranulation of leucocytes after phagocytosis

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[3]DE DUVE, C. The lysosome. Scientific American **208** (1964) No. 3 (May), 64-72.

[4]DE DUVE, C. Lysosomes: a new group of cytoplasmic particles, *in* Subcellular Particles (T. Hayashi, ed.), New York, Ronald Press Co., 1959, p. 128.

of zymosan, by Zucker, Franklin and Hirsch [**120** (1964) 569-575], demonstrates the fusion of the granule [lysosome] and the phagosome, in which process the continuity of the combined cell wall is maintained. This report is notable for the excellence of the electron micrograms with which it is illustrated. One of them, for example, made at a magnification of 153,000, shows the identity of the double-layered membranes that surround the phagosome (derived from the cell wall), the lysosome (derivation not known), and the cell wall itself.

The several other articles avowedly on lysosomes that have appeared in the *Journal of Experimental Medicine* are on particular studies of no special interest here. Mention may, however, be made of three articles by an English group [**117** (1963) 879-887; **121** (1963) 463-474 and 477-486] which deal with the effects of cytopathic and noncytopathic viruses on the lysosomes of chick embryo cells in cultures.

Mycobacteria.—The interest of leprologists in the matter of the lysosomes is naturally concerned with their effects on mycobacteria, specifically the leprosy bacilus.

The only thing found about that bacillus is a brief mention in the second edition of Cochrane's book. Although the word lysosomes does not appear in the index, mention of these objects is found in the contribution by Brieger and Allen.[5] They tell of (and show in two electron micrographs) dense bodies sometimes found in the cytoplasm of lepra cells [apparently the opaque bodies of Nishiura and Imaeda[6,7]] which they regard as of the class of lysosomes of de Duve. They hold it to be "very probable that the precursors of the lepra cell inclusions

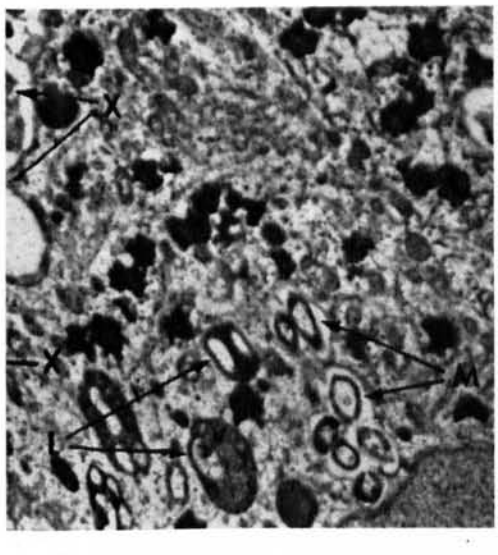

FIG. 1.—Ultrathin section of a histiocyte in an H37Rv mouse 31 days after infection (11,200 ×). Showing **(M)** several bacilli in a single sac (phagosome), and some bacilli embedded in lysosomes **(L)**. (Also at **X**, certain objects called "X" bodies, but see Fig. 2.)

[5]BRIEGER, E. M. and ALLEN, J. M. The submicroscopical structure of *M. leprae*, *in* Cochrane, R. G. and Davey, T. F. Leprosy in Theory and Practice, Bristol, John Wright & Sons Ltd. 2nd ed., 1964, pp. 39-40.

[6]NISHIURA, M. The electron microscopic basis of the pathology of leprosy. Internat. J. Leprosy **28** (1960) 357-379.

[7]IMAEDA, T. and CONVIT, J. Electron microscope study of *Mycobacterium leprae* and its environment in a vesicular leprosy lesion. J. Bact. **83** (1962) 43-52.

and possibly the inclusion itself are signs and symptoms of lysosome activity in these cells." This, they add, may throw new light on the host cell-parasite relationship in leprosy.

The only article encountered that is particularly concerned with acid-fast bacilli is by Merckx, Brown and Karlson,[8] of the Mayo Clinic. They injected large groups of white mice intravenously with *M. tuberculosis* (R37Rv) and with the Battey bacillus (B41), studying the

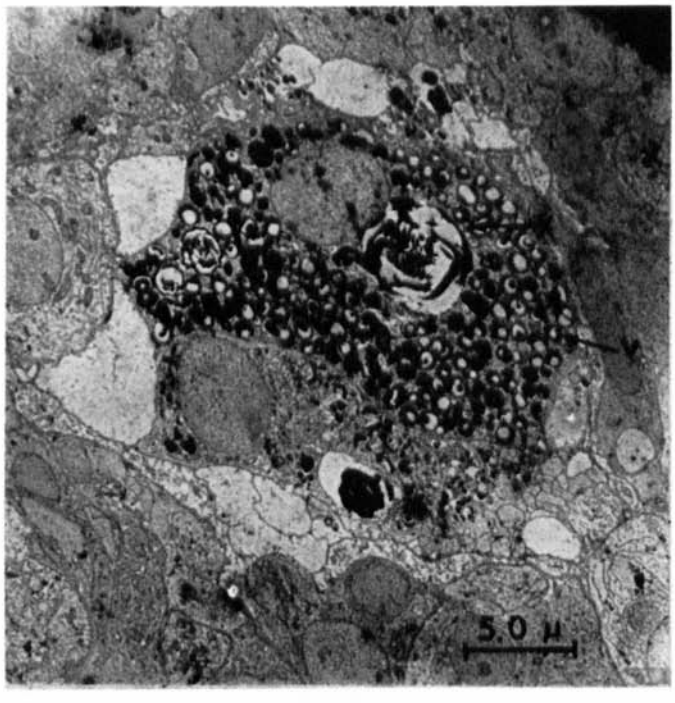

FIG. 2.—Showing "Y" bodies (marked **Y**) in the lung of a B41 mouse 150 days after infection (2,800×). Also several "**X**" bodies, the largest and most typical marked X.)

lesions produced at varying intervals by both light and electron microscopy. Some of the findings are of special interest from the present point of view.

An observation of incidental interest was recorded in the first of the reports of Cohn and Morse that we passed over [*J. Exper. Med.* **110** (1959) 419-443], which is concerned mainly with the effects of polymorphonuclear leucocytes on staphylococci. In one experiment they tested for comparison several other species of bacteria, including two acid-fasts (*M. smegmatis* and *M. fortuitum* Penso). These mycobacteria were readily phagocyted but not killed by the leucocytes; they were not "susceptible to intraleucocytic bactericidal mechanisms."

In the studies by Merckx, Brown and Karlson, the bacilli were found to be surrounded by electron-transparent zones outlined by membranes, as reported for *M. leprae* and other mycobacteria; these represented phagosomes (Fig. 1, M).[9] Some were embedded in "electron-

[8]MERCKX, J. F., BROWN, JR., A. L. and KARLSON, A. G. An electron-microscopic study of experimental infections with acid-fast bacilli. American Rev. Resp. Dis. **89** (1964) 485-496.

[9]The pictures used here were kindly supplied by one of the authors (Dr. Karlson).

opaque bodies," which have been described in leprosy lesions; these bodies they regarded as lysosomes (Fig. 1, L). One type of intracellular bodies, the "Y" bodies—small, electron-dense, and frequently vacuolated (Fig. 2, Y)—were often found extracellular in terminal stages of the infection. These and certain other bodies they thought might all be lysosomes in different stages of activity. (Another type, the "X" bodies [Fig. 2, X], were found only in the lungs, and are not of present interest.) Finally, they described and pictured a peculiar kind of intrabacillary spherule, which is discussed in the accompanying note.

It remains to be seen what a thorough study of leprosy bacilli in the lesions will reveal with respect to some of these bodies. Structures similar to the "opaque bodies" which Brieger and Allen, and Merckx and associates, regard as lysosomes, have been repeatedly demonstrated in leprosy, but no others of the lysosome forms have been reported. It seems possible that lepromatous lesions are not favorable material in which to search for advanced forms of such bodies, since the bacilli are so well tolerated in them and multiply. It may perhaps be that such forms should be sought in the normal torpid nonreactional tuberculoid lesions, for in them one sometimes finds, with the light microscope, an occasional acid-fast bacillus in the process of disintegration.

—H. W. Wade