

THE CUTANEOUS INFILTRATES OF LEPROSY

A Transmission Electron Microscopy Study*

BY GILLA KAPLAN, WESLEY C. VAN VOORHIS,
EUZENIR NUNES SARNO, NADIA NOGUEIRA, AND ZANVIL A. COHN

From the Department of Tumor Biology, Norwegian Cancer Society, Institute of Medical Biology, University of Tromsø, Norway; the Laboratory of Cellular Physiology and Immunology, The Rockefeller University, New York 10021; and the Departamento de Patologia e Laboratorios, Faculdade de Ciencias Medicas, Universidade do Estado do Rio de Janeiro, Brazil

Leprosy is a chronic bacillary disease with a spectrum of cutaneous responses ranging from the lepromatous to the tuberculoid (1). At the lepromatous pole the disease is progressive with extensive bacillary multiplication within macrophages and anergy to *Mycobacterium leprae* antigens expressed both by skin testing and in vitro lymphocyte proliferation. At the other pole is the circumscribed tuberculoid form in which intact bacilli are scarce and assays for cellular immunity are strongly positive (2, 3).

We have recently described the cellular infiltrates found in polar and intermediate disease states as ascertained by immunofluorescent monoclonal antibodies (4). The lepromatous infiltrates contained few lymphocytes and the majority were of the Leu2a/OKT8 T cell subset. As the tuberculoid pole was approached, T cells became more numerous and were predominantly Leu3a/OKT4 T cells. Based upon these observations regarding the infiltrates, we hypothesized that Leu2a/OKT8 cells suppressed local effector function to *M. leprae*, while Leu3a/OKT4 cells activated macrophages to control the infection.

We have now performed an electron microscopic study of predominantly the same sample of unselected patients representing the full spectrum of leprosy. Our morphological observations are consistent with the idea that both macrophages and T cells become activated as one approaches the tuberculoid pole. These results complement our previous fluorescence studies and provide structural information on the effector cells and the bacilli within the vacuolar system of macrophages.

Materials and Methods

Patient Population. Skin biopsies from 16 patients from Brazil and 2 patients from the U. S. with various forms of leprosy were examined. The Brazilian patients were studied in collaboration with the Department of Dermatology and General Pathology, Hospital de Clinicas, Universidade do Estado do Rio de Janeiro. The U. S. patients were studied at The Rockefeller University Hospital. Clinical diagnosis was established by Dr. Jarbas A. Porto in Brazil and Dr. W. R. Levis in the U. S. (5).

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After informed consent was obtained, either open, ellipsoid biopsies of 2×0.5 cm (Brazil) or cylindrical punch biopsies of 4 mm diam (U. S.) were taken deep enough to include the lower dermal layers (usually ~ 1 cm in depth). Biopsies were divided into portions for histologic diagnosis, immunofluorescent assays, and electron microscopy. Histologic diagnosis was established according to the Ridley-Jopling classification scheme (6) by Professor E. N. Sarno (Brazil) and Dr. C. K. Job at the U. S. P. H. S. National Hansen's Disease Center, Carville, LA (U. S.). Routine stains were hematoxylin eosin and Ziehl-Neelsen.

Immunofluorescence Assays. A sensitive biotin-avidin system was used to identify and enumerate the inflammatory cells in frozen sections by use of mouse anti-human monoclonal antibodies as described by Van Voorhis et al. (4). In short, acetone-fixed 8- μ m frozen sections were exposed for 1 h to monoclonal antibodies against surface antigens of leukocytes, lymphocytes and their subsets, and mononuclear phagocytes, as listed by Van Voorhis et al. (4). Unbound antibody was washed away and the sections were exposed to affinity-purified biotinylated anti-mouse IgG (Vector Laboratories, Inc., Burlingame, CA) for 30 min, rinsed again, and exposed to fluorescein-labeled avidin D (Vector Laboratories, Inc.) for 30 min. Sections were examined by epifluorescence. The antileukocyte common antigen T29/33 (7) was used to estimate the total number of infiltrating leukocytes in the sections and the numbers of mononuclear phagocytes and lymphocytes and their subsets recognized by the specific antibodies.

Electron Microscopy. A part of each biopsy was processed for transmission electron microscopy studies. Biopsies were washed in saline at 4°C, cut into 1- to 2-mm pieces, and fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer with 0.1 M sucrose, pH 7.4, for 16 h at 4°C. The tissue was cut to 1 mm or smaller and postfixed in 2% OsO₄ for 6 h at 4°C. The tissue was then stained en bloc for 2 h with 0.25% uranyl acetate, dehydrated in increments with ethanol, and embedded in epon blocks. Semi-thin sections were stained with methylene blue-azur-basic fuchsin and examined for areas containing infiltrating cells. Five blocks or more were selected for ultra-thin sectioning for each patient. Sections were stained with uranyl acetate and lead citrate, and examined with a Hitachi-HU-12 transmission electron microscope. The average density of the infiltrating cells (percent of area occupied by inflammatory cells) was estimated. At least 200 cells from each patient were examined initially. In infiltrates containing a high density of cells, the sections were photographed on Kodak electron image film. The cells in the micrographs were then identified and counted. In infiltrates containing a low cell density, the cells were identified and counted directly. All blocks were then retrimmed and the process described above repeated 2-4 times. In selected patients, $\sim 1,000$ cells were examined. Cells were identified by morphological criteria (8-11).

Results

General Considerations. Table I summarizes the clinical and pathological diagnosis, therapy, bacterial load, and ultrastructural findings from 18 unselected patients, who represent the full spectrum of disease. The biopsies studied were large, well preserved, and examined at multiple sites.

As one progressed along the spectrum of disease from lepromatous, through intermediate, to tuberculoid, the infiltrating mononuclear phagocytes in the skin contained fewer bacteria. The numbers of lymphocytes increased from very few to over half the inflammatory cells of the lesions. The macrophage morphology changed from foam cells to epitheloid and giant cells. Less plasma cells were found and more mast cells appeared. Long-term chemotherapy in lepromatous patients was associated with decreasing numbers of intact bacteria, while in tuberculoid patients it was associated with a decrease in numbers of lymphocytes. A detailed description of the ultrastructure of the cells in the lesions follows.

Lepromatous Leprosy (LL) (Patients 1-5). Diffuse, loosely organized, inflamma-

TABLE I
Diagnosis, Treatment, and Cell Types in Cutaneous Infiltrates from 18 Patients with Leprosy

	Patient No.																	
	1	2	3	4	5	6	7	8	9									
Diagnosis	L (ENL) LL	L (re) (ENL) LL	L (ENL) LL	L LL/L	L (ENL) BL/LL	B BL	B BL/BB	B BB	B BB									
Clinical* Histologic†	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative									
Mitsuda	Negative	Negative	Negative	Negative	ND‡	Negative	ND	Negative	Negative									
Treatment prior to opsy‡	None	DDS + Rif 4 yr irreg.	None	None	DDS + Rif 3 d	DDS + Rif 1 wk	None	None	None									
M. Leprae	6+	2+	4+	4+	6+	4+	6+	2+	—									
Inflammatory cell density (percent)	50-80	50-80	50-90‡	40-60	50-80	50-80	50-80	50-70	15-25									
Cell type percentage																		
Mononuclear phago- cytes**	80% FC	80% FC + Mφ	80% FC + Mφ	70% FC + Mφ	80% FC + Mφ	70% Mφ	60% Mφ	40% Mφ	50% Mφ + EC									
Lymphocytes	5	5	Few	20-30	5	10	10-20	40-50	10									
Plasma cells	5	Few	Few	Few	10-15	7-10	5-7	Few	10									
Mast cells	Few (2-4)	Few	Few	None	Few (2-4)	5-10	5	10	10									
	10	11	12	13	14	15	16	17	18									
Diagnosis	B (re) BB	B (re) BB	B BB/BT	T BT/TT	T BT/TT	T BT/TT	T BT/TT	T BT/TT	T (re) TT									
Clinical* Histologic†	Negative	Negative	Negative	Positive	Positive	Positive	Positive	Positive	Positive									
Mitsuda	Negative	Negative	Negative	Positive	Positive	Positive	Positive	Positive	Positive									
Treatment prior to biopsy‡	DDS + Rif 3 yr	DDS + Rif 2 yr	None	None	None	None	None	None	None									
M. Leprae	—	—	—	—	—	—	—	—	—									
Inflammatory cell density (percent)	50-60	30-50	50-60	60-70	20-25	40-60	40-60	70-80	40-80									
Cell type percentage																		
Mononuclear phago- cytes**	70% Mφ + EC	20-60% Mφ + FC	50% Mφ + EC + GC	40-60% EC + GC	40-50% EC + GC	40-50% EC + GC	40-50% EC + GC	50-60% EC + GC	80% EC									
Lymphocytes	Few	40-60	40	40-50	50-60	40-50	50	30-40	Few									
Plasma cells	Few	Few	None	None	Few	None	None	None	None									
Mast cells	10-15%	5-10	5-10	5	5	5-10	Few	10	5-10									

* L, lepromatous leprosy; B, borderline; T, tuberculoid; re, relapse; ENL, clinical signs of erythema nodosum leproae reaction.
 † Ridley-Jopling scale: LL, lepromatous; BL, borderline lepromatous; BB, mid-borderline; BT, borderline tuberculoid; TT, tuberculoid; I, indeterminate.
 ‡ Not done.
 § No. 3-5% PMNL.
 ** FC, foam cells; Mφ, macrophages; EC, epithelioid cells; GC, giant cells.
 The corresponding patient numbers reported by Van Voorhis et al. (5) are as follows, in parentheses: 1 (1); 2 (2); 3 (3); 4 (ND); 5 (9); 6 (10); 7 (11); 8 (ND); 9 (14); 10 (20); 11 (12); 12 (ND); 13 (17); 14 (ND); 15 (ND); 16 (ND); 17 (18); 18 (13).

tory infiltrates around skin structures or in a perivascular localization typified the lepromatous lesions. A striking absence of lymphoid infiltration was noted. The overall appearance of a typical lesion can be found in Fig. 1. The parasitized macrophages were embedded in a collagenous dermal matrix—occasionally in parallel arrays. Although not shown, Schwann cells were heavily infected with many organisms contained in large vacuoles. These were the only other cell type beside macrophages that were clearly infected. Demyelination of nerves was often evident and was consistent with the motor and sensory defects. Small blood vessels had markedly thickened walls with a few cells attached to the luminal surface.

Biopsies taken at almost any part of the dermis in exuberant cases revealed large foamy macrophages with an elongated nucleus, prominent nucleoli, and thin rims of heterochromatin (Fig. 2). Seemingly intact and partially degraded osmiophilic bacteria were found within large cytoplasmic vacuoles. No particular organization of organelles about the *M. leprae* vacuoles was noted. The majority of vacuoles were large and contained multiple organisms. The vacuoles in many cases had scalloped edges, providing evidence of vacuole-vacuole fusion (arrowheads in Fig. 1D) and contained in addition an electron-lucent matrix and osmiophilic debris. This matrix separated and surrounded individual organisms that were almost never clumped. Many of the bacilli in untreated lepromatous cases had well-defined outlines and the appearance of intact rods. Little internal structure was noted because of the intense osmiophilia. The macrophages contained many small vacuoles with a similar matrix but without organisms. Clear evidence of bacillary division was not noted, although the large numbers of bacteria in the vacuoles is consistent with this possibility. On occasion, a complex multilobulated vacuole containing bacilli and debris was separated from the cytoplasm by an electron-lucent zone (Fig. 2B, arrowhead) that had the same density and appearance as the interbacterial matrix. Other organelles of the macrophage cytoplasm, secondary lysosomes, mitochondria, and Golgi were not prominent in parasitized cells. These had the appearance of established, quiescent populations.

Mid-borderline and Borderline Lepromatous (BL-BB) (Patients 6–8). There were many differences between the lepromatous and the borderline lesions. The dermis contained large numbers of inflammatory cells with increasing percentages of lymphocytes of the T cell lineage (4) and an occasional mononuclear phagocyte of the epitheloid type. Plasma cells were closely apposed to infected macrophages. The majority of the mononuclear phagocytes in the lesions were infected (Fig. 3A and B). Rather than multiple organisms in distended vacuoles, the bacillary load was lighter. Organisms were most often found as singlets or doublets in a vacuole and appeared intact. Again the bacilli were surrounded by an electron-lucent halo that had a capsule-like appearance (Fig. 3A). Occasionally, macrophages exhibited long surface villi and cellular interdigitations. With a smaller proportion of the cytoplasmic volume taken up by organisms, larger numbers of electron-dense lysosomes and mitochondria were evident (Fig. 3B–D), suggesting that the macrophages were more recently recruited endocytes than those of lepromatous lesions.

Mid-borderline (BB) (Patients 9–12). This group of patients, classified into the

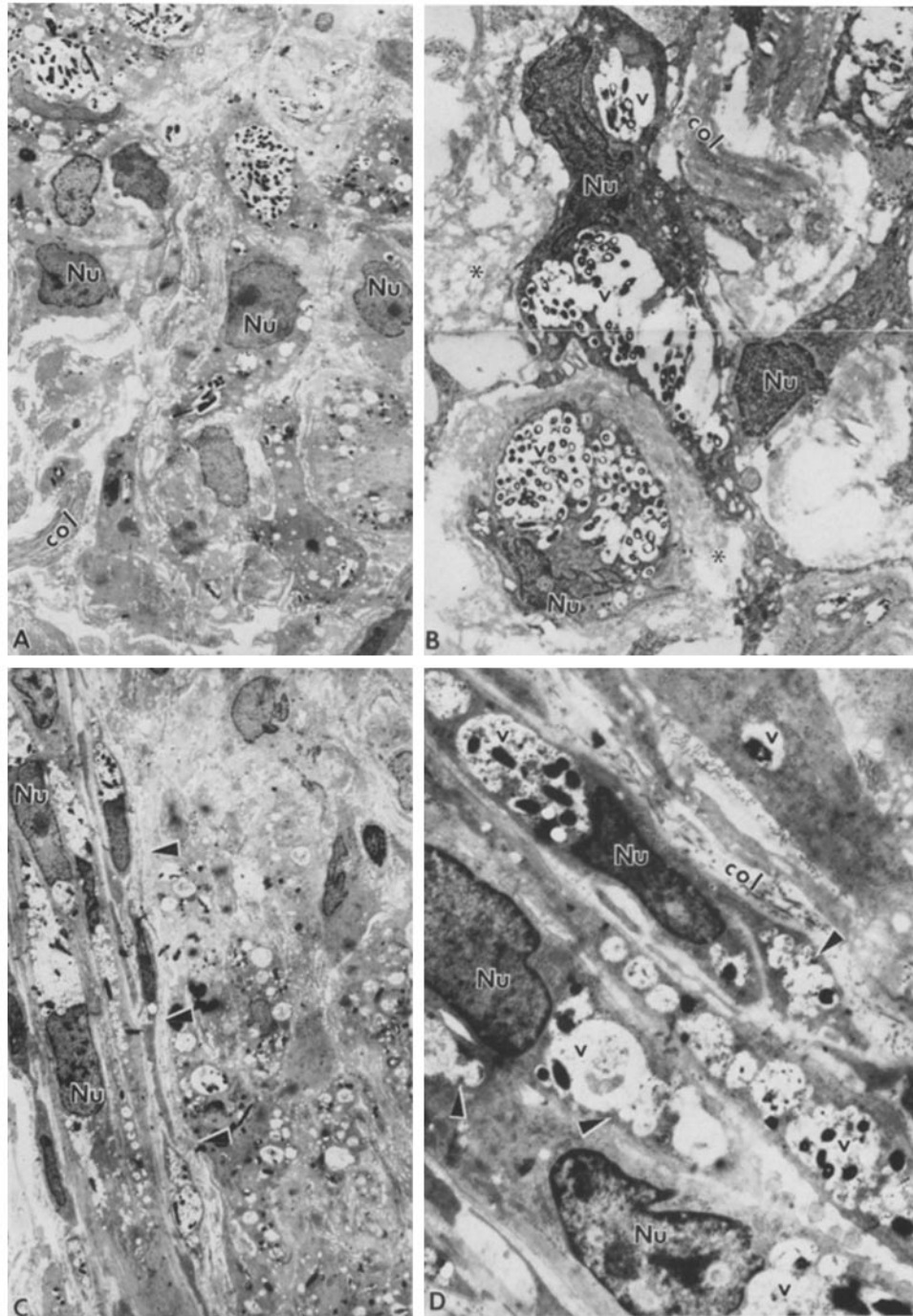


FIGURE 1. Transmission electron micrographs of cutaneous infiltrates from patients with lepromatous leprosy. (A) The inflammatory cells consist mostly of large foamy macrophages with seemingly intact osmiophilic bacteria contained in vacuoles of varying sizes. The cells are irregular in shape, have large nuclei (Nu), and are loosely embedded in a collagenous matrix (col); $\times 2,200$ (patient 1). (B) Three irregular, foamy macrophages (Nu), containing vacuoles (v) with large numbers of partially degraded bacteria, are seen. The extracellular matrix consists of collagen (col) and amorphous material (*); $\times 4,400$ (patient 5). (C) In some areas the macrophages are elongated in parallel arrays (arrowheads) while other cells are rounded and loosely packed; $\times 2,200$ (patient 1). (D) The macrophages are packed into parallel arrays. The vacuoles (v) contain intact osmiophilic bacteria and large amounts of electron-lucent matrix. Evidence of vacuole-vacuole fusion is seen (arrowheads). Small amounts of collagen fibers (col) are found between the cells; $\times 7,200$ (patient 1).

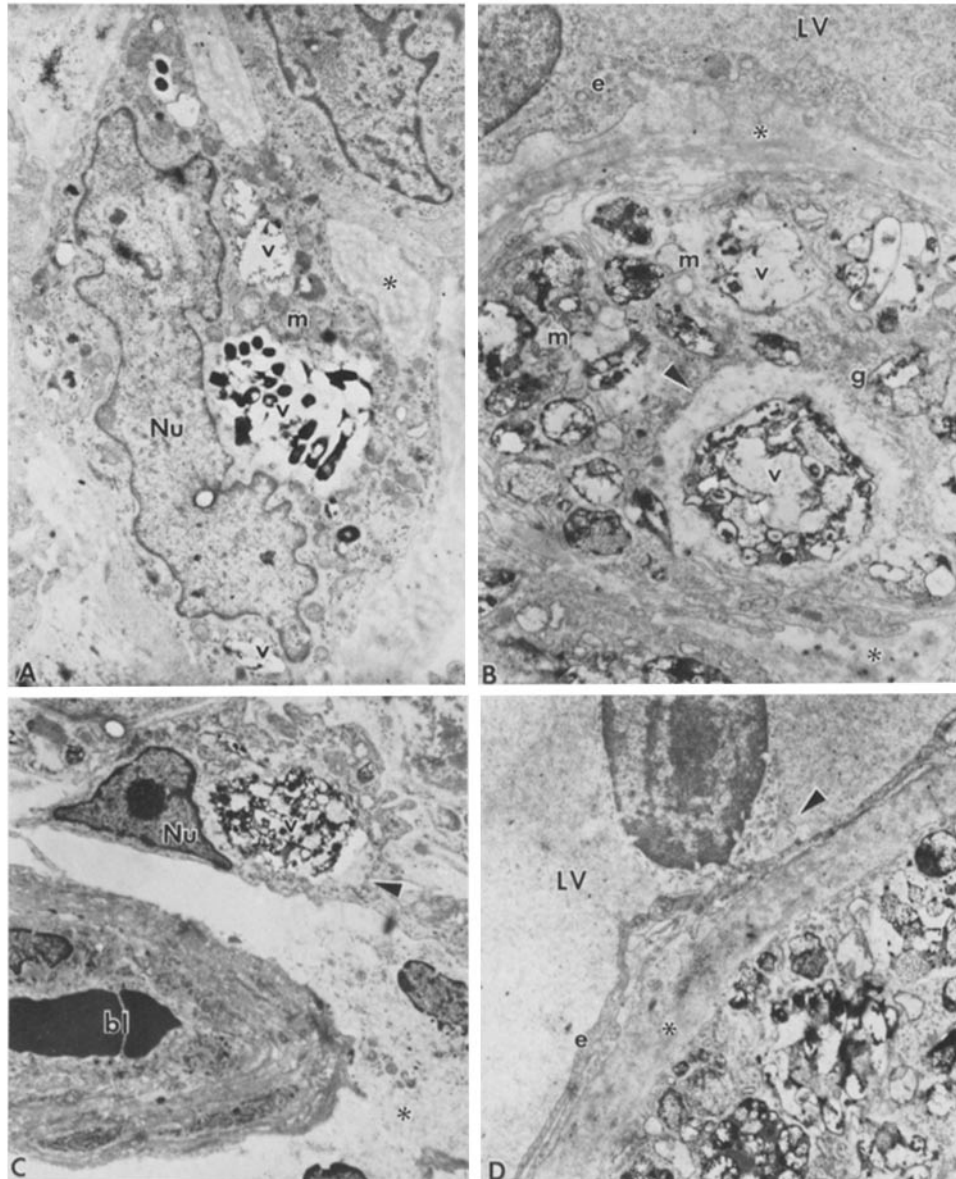


FIGURE 2. Micrographs of foam cells in cutaneous infiltrates from patients with LL/BL leprosy. (A) The macrophage embedded in an amorphous extracellular matrix (*) has an elongated irregular nucleus (Nu). Small mitochondria (m) can be seen in the cytoplasm. Vacuoles (v) of various sizes containing osmiophilic bacteria and bacterial debris are prominent; $\times 7,200$ (patient 1). (B) A foamy macrophage is observed directly below the endothelium (e) of a small lymph vessel (LV). The cell contains many membrane bound vacuoles (v) with bacterial debris. Some vacuoles are separated from the cytoplasm by electron-lucent zones (arrowheads). The golgi area (g) and swollen mitochondria (m) are evident; $\times 7,200$ (patient 2). (C) The macrophage nucleus (Nu) contains a thin rim of heterochromatin and a prominent nucleolus. The cytoplasm contains a large vacuole with bacterial debris (arrowhead). A small blood vessel (bl) has a thickened and infiltrated wall; $\times 4,500$ (patient 5). (D) A leukocyte attached to the luminal surface of a lymph vessel (LV) is observed (arrowhead). The endothelium (e) appears intact, and is separated from the foam cells by a layer of amorphous material (*); $\times 7,200$ (patient 2).

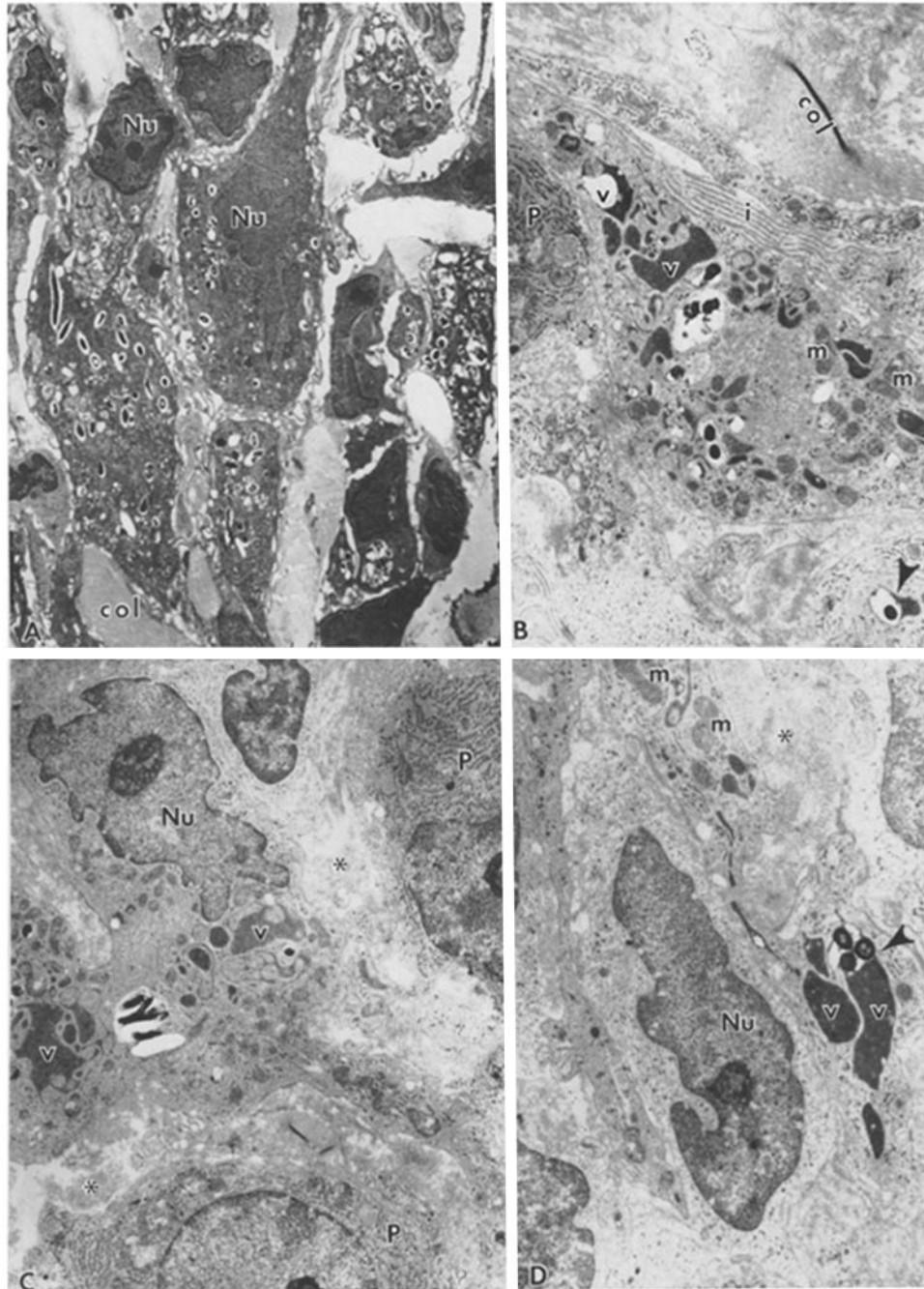


FIGURE 3. Micrographs of cutaneous infiltrates from patients with BL/BB leprosy. Nu, nucleus; col, collagen; (*) amorphous extracellular substrate. (A) Low magnification of macrophages containing vacuoles with single bacteria. The cells exhibit many surface villi; $\times 3,600$ (patient 7). (B-D) The macrophages contain prominent irregular electron-dense lysosomes (v), mitochondria (m), and membrane interdigitations (i). Possible phagosome-lysosome fusion is observed (arrowheads). Plasma cells (P) are prominent (patient 6); (B) $\times 7,200$, (C) $\times 5,800$, (D) $\times 8,400$.

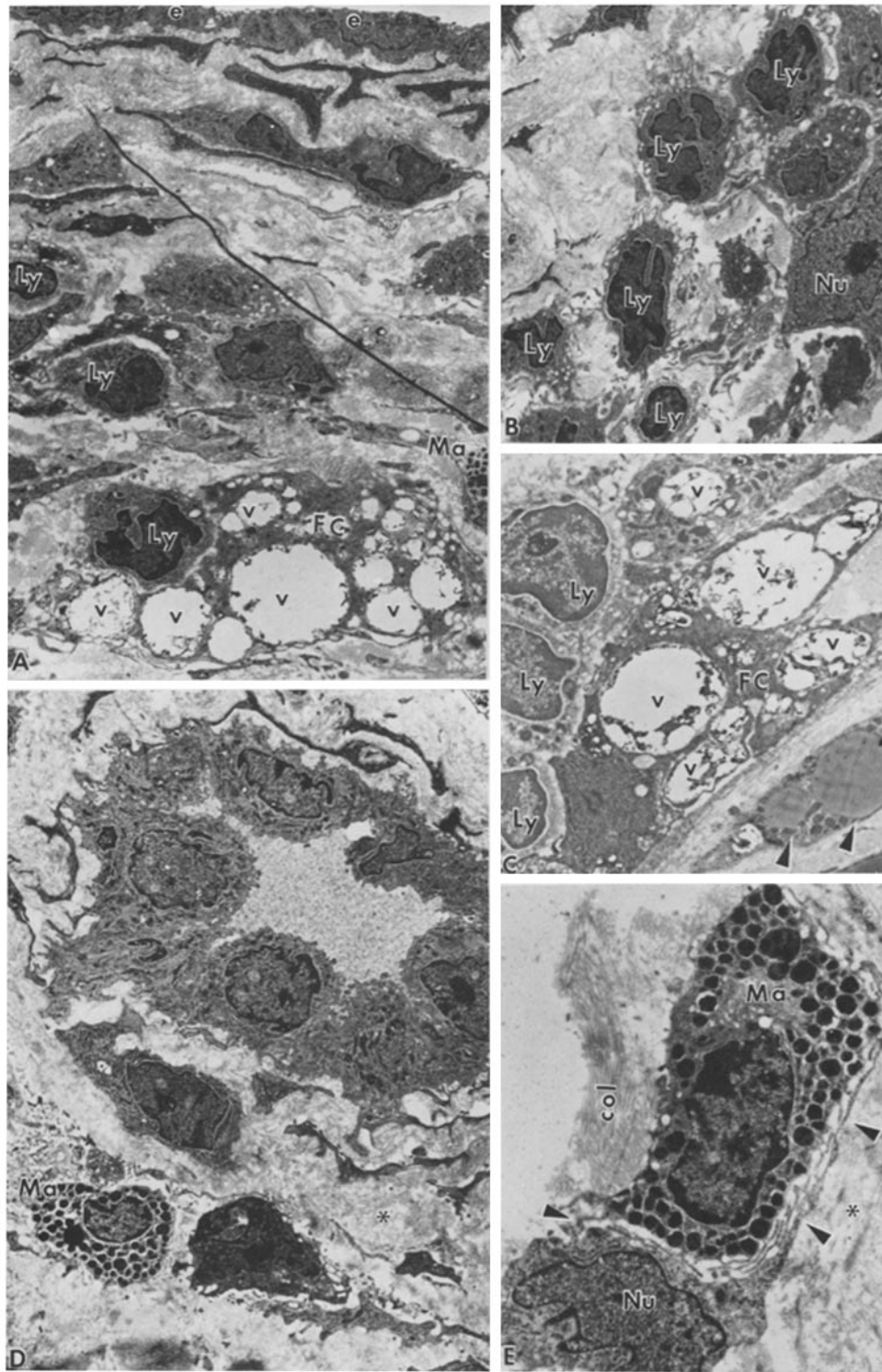


FIGURE 4. Micrographs of cutaneous infiltrates from patients with BB leprosy. (A-C) Perivascular infiltrates (e, endothelium) containing macrophages, foam cells (FC), lymphocytes (Ly), and mast cells (Ma) are observed. The foam cells contain large vacuoles with no bacteria and little debris (v). Some fat cells are observed (C, arrowheads); (A and B) $\times 3,600$ (patient 12); (C) $\times 4,400$ (patient 9). (D-E) The infiltrates are perivascular. Mast cells (Ma) are relatively common. They are found together with macrophages (Nu), often in very close proximity to them (arrowheads). Between the cells, collagen (col) and an amorphous substance (*) are observed (patient 12); (D) $\times 3,600$, (E) $\times 7,200$.

BB category, includes three individuals (patients 9–11) who received chemotherapy for varying periods of time. They represent an intermediate form of histology with somewhat fewer lymphoid cells than BT/TT infiltrates and an unusual mixture of mononuclear phagocytes. Lymphocytes were often in close apposition to the foamy macrophages, and mast cells (Fig. 4, *D* and *E*) were common, making up 5–15% of the cells in these lesions. About half of the mononuclear phagocytes had typical epithelioid cell morphology, with vacuoles, granules, endoplasmic reticulum, and many prominent mitochondria (Fig. 4 *A* and *B*). The remainder contained large electron-lucent vacuoles that were devoid of organisms and had little osmiophilic debris. These had the appearance of foam cells but in fact lacked organisms.

Borderline Tuberculoid and Tuberculoid Leprosy (BT-TT) (Patients 13–18). Approaching the tuberculoid pole, the lesions became increasingly cellular and took on the appearance of a granulomatous response. Epithelioid and multinucleated giant cells predominated. The mononuclear phagocytes were surrounded by mantles of lymphocytes. Our previous immunofluorescent studies indicated that these were predominantly of the Leu 3a/OKT4-positive subset. A significant proportion of the cells in the lesions had swollen mitochondria, and granular cytoplasm, and appeared either injured or nonviable (Figs. 5 and 6). Some areas were apparently necrotic but extensive necrosis of large areas of the dermis was not observed.

The intact epithelioid cells were elongated with abundant cytoplasm and nuclei with thin rims of heterochromatin and prominent nucleoli. Many small round mitochondria were found in these cells. The phagocytes gave the appearance of being very biosynthetically active. Organisms or bacillary debris were not seen either within mononuclear phagocytes or in extracellular sites.

A striking feature of these lesions were the unique lymphocytes found adjacent to the mononuclear phagocytes. Fig. 5 *A, B, C,* and *D* illustrates their appearance at low magnification. These cells typically had markedly irregular and often lobed nuclei with dense bands of heterochromatin that was quite distinct from mononuclear phagocytes. Their cytoplasm was electron dense and the plasma membrane extruded into villous processes of differing length and breadth. Fig. 6 shows these cells at higher magnification and emphasizes their polarity and the unique arborization of their surface membrane. On occasion (Fig. 6 *C* and *D*), it appeared that particles and organelles were in the process of being engulfed, but these probably represent only their extracellular presence in the lymphocyte villous network.

Discussion

The study reported in this article represents a comprehensive ultrastructural analysis of the lesions of leprosy. It combines, in a single study and with accompanying light and immunofluorescent microscopy (4), the spectrum of disease as seen in 18 unselected patients. The striking cellular changes evident in the progression from lepromatous to tuberculoid response allows speculation on pathogenesis and the roles and activity of effector cell populations. Macrophages of the lepromatous lesions contained large multibacillary vacuoles in their cytoplasm and few other cytoplasmic organelles, i.e., mitochondria, endoplasmic

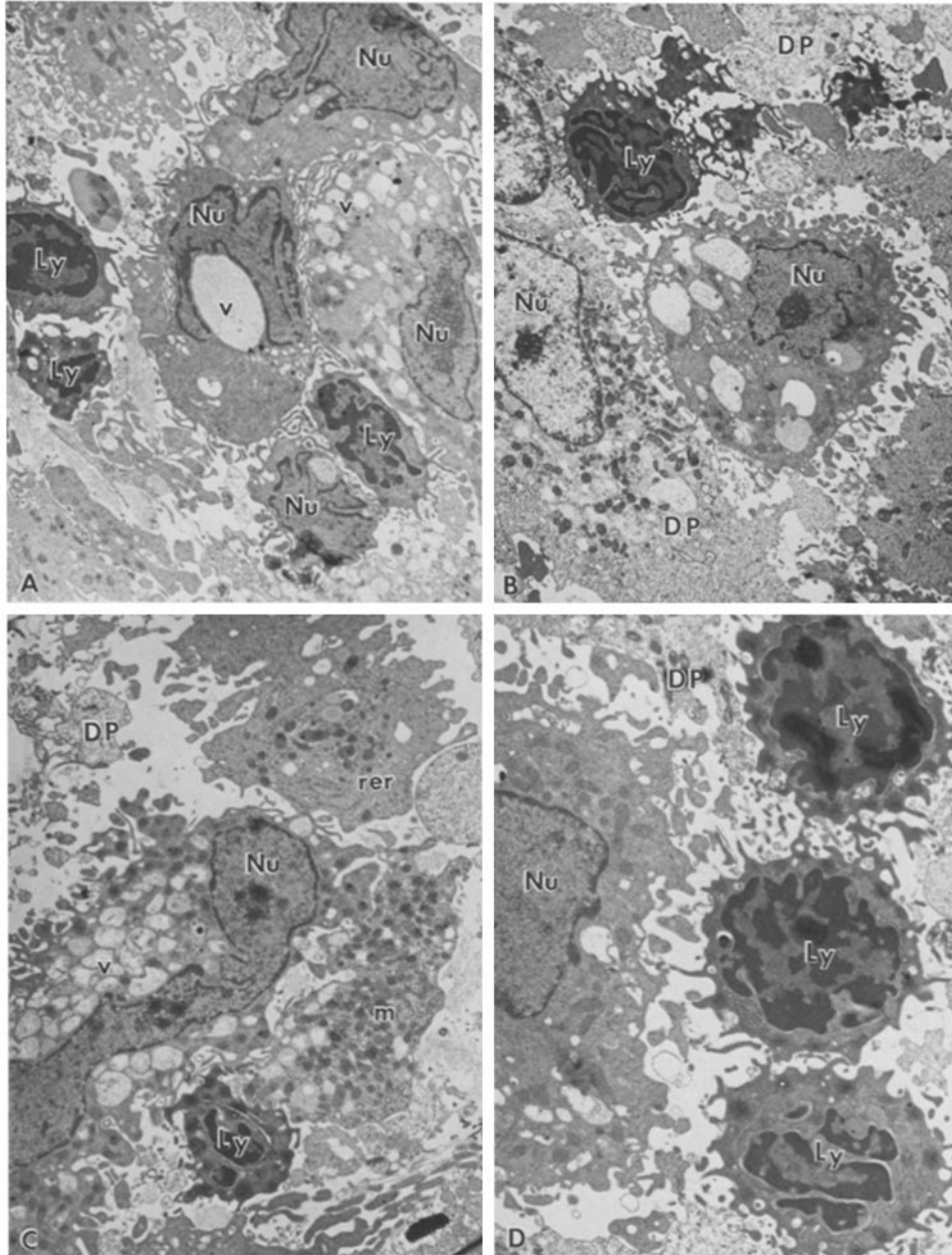


FIGURE 5. Micrographs of cutaneous infiltrates from patients with BT/TT leprosy. The infiltrates contain epithelioid cells with large irregular nuclei (Nu) and many vacuoles of various sizes (v), small dense mitochondria (m), and endoplasmic reticulum (rer). Many lymphocytes (Ly) are found around the mononuclear phagocytes. Many damaged or dead phagocytes are observed (DP). (A) $\times 4,300$ (patient 13), (B) $\times 3,600$ (patient 17), (C) $\times 4,800$ (patient 17), (D) $\times 7,200$ (patient 13).

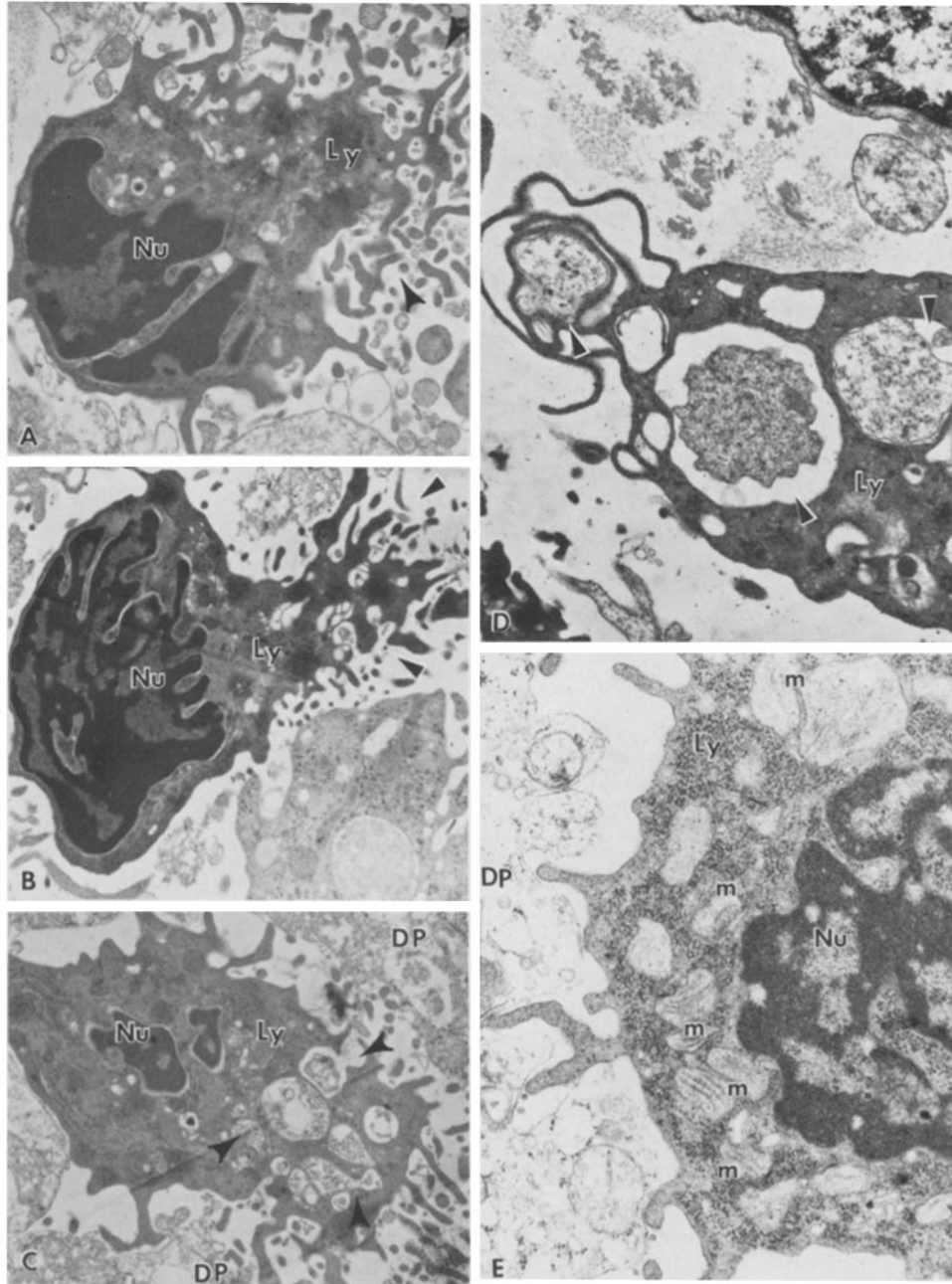


FIGURE 6. High magnification micrographs of lymphocytes from cutaneous infiltrates from patients with BT/TT leprosy. The lymphocytes (Ly) are very irregular in shape with lobed nuclei (Nu) and dense chromatin. The cytoplasm is electron dense and the cells are often polar. The plasma membrane is extruded into villous processes with folding of extracellular material (adjacent cells?) into the villi (arrows). Some of the lymphocytes contain many mitochondria (m). Many of the adjacent cells appear damaged and highly vacuolated (DP). (A) $\times 15,000$ (patient 17), (B) $\times 10,000$ (patient 13), (C) $\times 12,000$ (patient 17), (D) $\times 13,500$ (patient 13), (E) $\times 22,000$ (patient 13).

reticulum, and secondary lysosomes. One suspects that parasitized macrophages represent a large, long-lived, and relatively quiescent cutaneous pool that gradually accumulates from the intravascular monocyte. This occurred in association with huge amounts of antigen, local antibody formation (12), and the presence of plasma cells. As borderline disease was approached, the first evidence of macrophage activation was found. Specifically, fewer organisms were found, in smaller vacuoles; more cell organelles were evident, and epithelioid cells made their appearance. At the tuberculoid pole the predominant mononuclear phagocytes were epithelioid cells. These cells had virtually no bacilli and were rich in cytoplasm, mitochondria, and endoplasmic reticulum, suggesting a higher level of synthetic activity.

Essentially all visible bacilli are present within cytoplasmic membrane-bound vacuoles. It is this milieu in which bacterial growth and death take place. Yet we know little about the nature of the vacuole, its contents, or its dynamics. Most likely it is endocytic in origin, but whether fusion with primary or secondary lysosomes has taken place and whether it is acidified is unclear (13). Other factors may also complicate interaction within the vacuolar apparatus of the infected host. For example, the electron-lucent intraluminal material of the vacuole, perhaps of microbial origin, may play significant roles. Microbicidal products that inhibit the activity of lysosomal hydrolases or block fusion of phagosomes with lysosomes have both been reported (14–15). Studies are in progress concerning many of these questions using cytochemical techniques. These are important since even after one renders the organism nonviable, the host is faced with a huge mass of microbial products, many of a lipid nature, e.g., glycolipids, that must be hydrolyzed and dispersed. The resulting “storage disease” may lead to persistent cutaneous lesions and morbidity.

Lepromatous leprosy is associated with the lack of a cell-mediated response and the presence of small numbers of T cells predominantly of the Leu 2a/OKT8 suppressor phenotype (2–4, 16). The relative lack of T lymphocytes in these lesions may be associated with either the generation of inhibitory molecules or a lack of chemotactic factors, or both. As borderline disease was approached, more lymphoid cells were found in the lesions, particularly of the Leu 3a/OKT4 helper subset. The tuberculoid lesions require particular emphasis. In addition to the quantitative increase in lymphocyte numbers, the structure of the T cell appeared unusual. Their plasma membrane was thrown into multiple evaginations and many were in close proximity to mononuclear phagocytes. A majority of the T lymphocytes in these lesions were of the Leu 3a/OKT4-positive subset (4).

The appearance of damaged and dead epithelioid cells, also observed by Ridley (11), is of interest. The foci of necrosis were interspersed with large numbers of viable epithelioid cells and lymphocytes. This would suggest a “high turnover” lesion with the continuous death and disintegration of older cells and the influx of new cells from the circulation. The number and integrity of intracellular bacilli in macrophages appeared inversely related to the intensity and quality of the macrophage and T cell response. This indicates that factors are involved in the generation of the tuberculoid lesions that have the potential to activate macrophages for antimicrobial activity against *M. leprae*. To carry this analysis

further, more quantitative methods are necessary to assess bacterial viability. In the absence of such data, one may speculate that the organism is, in fact, susceptible to the known microbicidal products of the activated macrophage. In response to T cell-generated lymphokines, macrophages are induced to form toxic oxygen intermediates which in turn can destroy a variety of obligate intracellular parasites (17). In particular, hydrogen peroxide, hydroxyl radicals, and singlet oxygen are potential candidates (18).

The liberation of toxic oxygen intermediates in the confines of a highly cellular lesion may explain the apparent cell death and necrosis seen in these lesions. This is consistent with a role for lymphokine-producing helper T cells in the activation of mononuclear phagocytes. Another scenario is also possible. In this version, one may activate cytotoxic T cells of the OKT8 subset which would in turn recognize determinants on the parasitized mononuclear phagocytes, resulting in cell injury.

Summary

The dermal lesions of 18 patients with leprosy have been examined by transmission electron microscopy. The patients exhibited a spectrum of disease from polar lepromatous to polar tuberculoid with intermediate stages in various states of therapy and relapse. The nature and quantities of inflammatory cells and bacteria have been determined by electron microscopy to supplement previous light and fluorescence microscopy studies.

Lepromatous leprosy was characterized by many parasitized foam cells containing large, multibacillary vacuoles with intact, osmiophilic *Mycobacterium leprae*. Bacteria were embedded in an electron-lucent matrix. No extracellular bacteria were evident. Only small numbers of scattered lymphocytes were found. As one approached the borderline state, smaller numbers of bacilli were present as singlets and doublets in small vacuoles of macrophages. The more reactive forms showed increasing bacillary fragmentation, larger numbers of lymphoid cells, and an occasional epithelioid cell.

At the tuberculoid end of the spectrum, clear evidence of an exuberant lymphocyte response was evident. Large numbers of T cells with extremely long and complex filipodia were closely associated with epithelioid and multinucleated giant cells. Many of the mononuclear phagocytes appeared nonviable, and areas of necrosis were evident. Bacillary remnants were scarce and the cytoplasm of the epithelioid cells contained occasional dense bodies and many stacks of endoplasmic reticulum and mitochondria. These results suggest that Leu 3a/OKT4 helper cells may be capable of driving the effector function of mononuclear phagocytes. This would lead to a significant microbicidal effect on *M. leprae*, perhaps through the production of toxic oxygen intermediates.

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