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Untreated Lepromatous Leprosy: Histopathological Findings in Cutaneous Blood Vessels[1]

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Referring to the earlier work of Neisser in 1881 and Touton in 1886, Metchnikoff described the presence of leprosy bacilli in endothelial lining cells of blood vessels in his lectures on "The Comparative Pathology of Inflammation" in 1892, saying that in some cases they occurred in such large numbers as to obscure the nucleus ([24]). In his textbook of 1930, Klingmüller ([20]) described and illustrated leprosy bacilli in capillaries and veins, and in 1941 Fite ([10]) published a detailed account of the nature, frequency, and significance of vascular involvement in 77 patients suffering from various types of leprosy. In his famous *Atlas* of 1952, Mitsuda ([26]) illustrates marked vascular involvement with thickening of the media and intima, and proliferating bacilli within intimal cells in a small artery and vein of the tunica alba in the tail of the epididymis. On the other hand, other standard reference books, e.g., Cochrane and Davey ([5]) hardly refer to vascular involvement except perhaps in the context of the unusual Lucio-Latapí type of lepromatous leprosy, occurring mainly in Mexico. The histopathological findings in blood vessels of skin were described in 205 patients with leprosy by Popov in 1966 ([29]) and in 90 selected biopsies by Santos and Beja in 1969 ([37]). Other authors ([2, 8, 17]) have described vascular changes in tissues infected with leprosy, often in the context of nerve involvement, while Skinsnes, *et al.* ([40]) and Kaur, *et al.* ([19]) have given detailed accounts of the vascular defect in leprosy, mainly of the larger limb vessels, in relation to the dystrophic changes and mutilations which are so characteristic of this disease.

In recent years it has been a) re-emphasized that there is a continuous bacteremia in lepromatous leprosy ([9, 38])* and b) shown that biting arthropods are, under experimental conditions, capable of taking up and transferring leprosy bacilli from infected patients to the footpads of mice ([27]). These observations, together with the possibility that endothelial cells may be an important site for the multiplication of leprosy bacilli and their seeding into the blood stream and that the media of blood vessels may be a site in which bacilli persist despite adequate therapy, have largely prompted the present study. We report our findings in the skin vasculature of 100 patients with untreated lepromatous leprosy.

PATIENTS AND METHODS

The majority of the patients (81 percent) were taking part in a trial of rifampin (Rimactane®) together with dapsone, organized by Ciba-Geigy Ltd., Basle, Switzerland, preliminary results of which have already been communicated ([21]), and they were attending centers in India, Africa, and South America. The remainder (19 percent) were from the Medical Research Council Unit at the Sungei Buloh Leprosarium, Malaysia, and also entered drug trials as previously untreated patients. The biopsies from these 100 patients of this study represent the most recently received in this unit up to the time of this writing (August 1978). The lepromatous classification included polar lepromatous (LLp) and subpolar lepromatous (LLs) ([33, 34, 35]) and was established by clinical findings, multiple slit-skin smears, and the biopsy itself.

Skin biopsies were taken under local anesthesia by standard technics ([15]), fixed in either 10 percent formalin or a modification of formol-Zenker, embedded in paraffin

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* Editor's Note: One of the reviewers of the manuscript points out that "Índice Bibliográfico de Lepra," 1500–1943, Vol. I, organized by Luiza Keffer, and published by the Biblioteca do Departamento de Profilaxia da Lepra do Estado de São Paulo, Brazil, in 1944, contains approximately 70 references to articles dealing with bacillemia in leprosy published between 1889 and 1940.

TABLE 1. *Type of skin vessel, lesion observed, and numbers (percent) in skin biopsies from 100 patients with untreated lepromatous leprosy.*

Type of vessel and lesion	Number of cases (also percent)
1. Small vessel lesion	
a. Presence of bacilli in the endothelium	100
2. Large vessel lesions	
a. Presence of bacilli in the endothelium or vessel wall (media)	85
b. Hyalinization, fibrosis, and/or infiltration of the vessel wall by macrophages (in different degrees)	85
c. Granuloma in the vessel wall	9
d. Thrombosis	2
e. No abnormality found	15

wax, and cut in serial sections at 5 microns. These were stained with hematoxylin and eosin, the Fite-Faraco modification of Ziehl-Neelsen, or with a combined Masson trichrome and Fite-Faraco (TRIFF) ([42]).

RESULTS

Blood vessel lesions were divided into two groups according to the size of affected vessels: a) small vessel lesions included lesions of the papillary capillaries, arterioles, and venules of the subepidermal plexus and new vessel formations in lepromatous infiltrates and b) larger vessel lesions consisted of lesions of arteries and veins of the subdermal vascular plexus and subcutaneous tissue.

The incidence of lesions in these two groups of vessels and other cutaneous structures is shown in Table 1.

Small vessel lesions. The most common finding in the capillaries, arterioles, and venules was the presence of *Mycobacterium leprae* in the endothelial cells. Bacilli were present singly, in small groups, or in larger masses (globi) containing uncountable numbers of organisms. Although a few cases showed only single or small groups of bacilli, there were large numbers of bacilli in endothelial cells in the majority of lesions. Even though laden with bacilli, these cells usually presented no other abnormality (Fig. 1), but in a few instances endothelial proliferation and protrusion of the cell cytoplasm into the lumen were also seen (Fig. 2). In several biopsies, some parts of the section showed that the numbers of bacilli in endothelial cells were greater than those in macrophages in the adjacent lepromatous infiltrate (Fig. 3). *M. leprae* were also seen in the smooth muscle cells of media and in pericytes of arterioles and venules (Figs. 4 and 5). Adventitial cells were frequently seen to harbor bacilli, and both within and outside the main masses of granuloma, bacilli-laden macrophages were prominent around small vessels. Bacterial emboli in the papillary capillaries were rarely observed in the subepidermal clear zone.

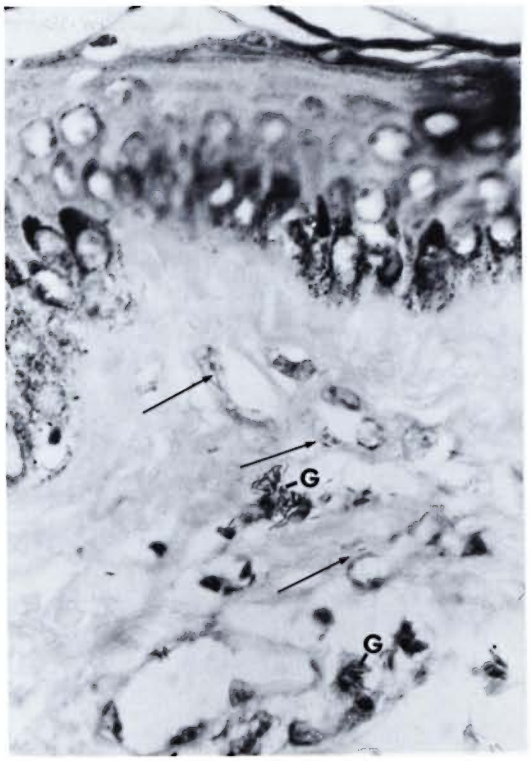

FIG. 1. Papillary capillaries and small vessels of subepidermal plexus. Bacilli are seen singly or in small groups in capillary endothelium (arrowed) and as globi (G) in perivascular histiocytes. Original magnification ×1000. Fite-Faraco stain.

Larger vessel lesions. As defined above, larger vessels showed the following changes: 1) the presence of *M. leprae* as solid-staining bacilli, small groups, or single globi in

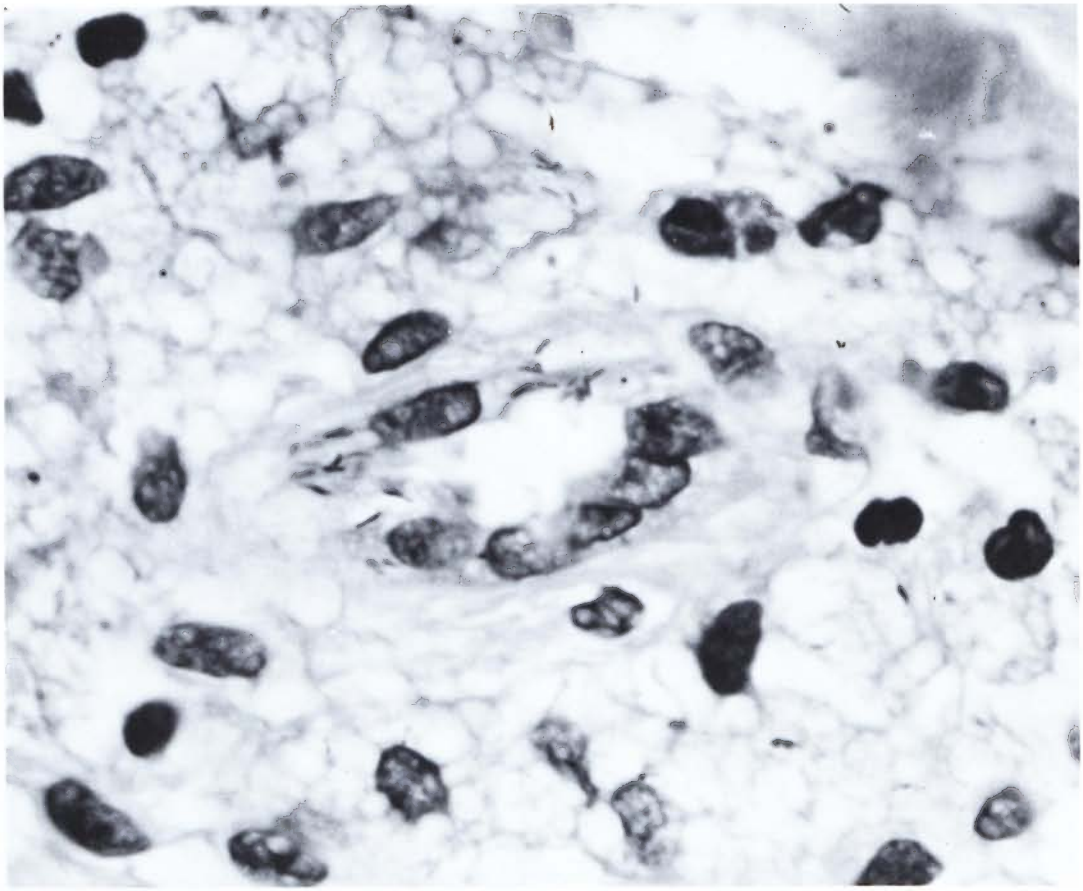

FIG. 2. Terminal arteriole within the granuloma, showing proliferation and protrusion of endothelial cells into the lumen, and the presence of single, solid-staining bacilli within them. Original magnification ×1000. Fite-Faraco stain.

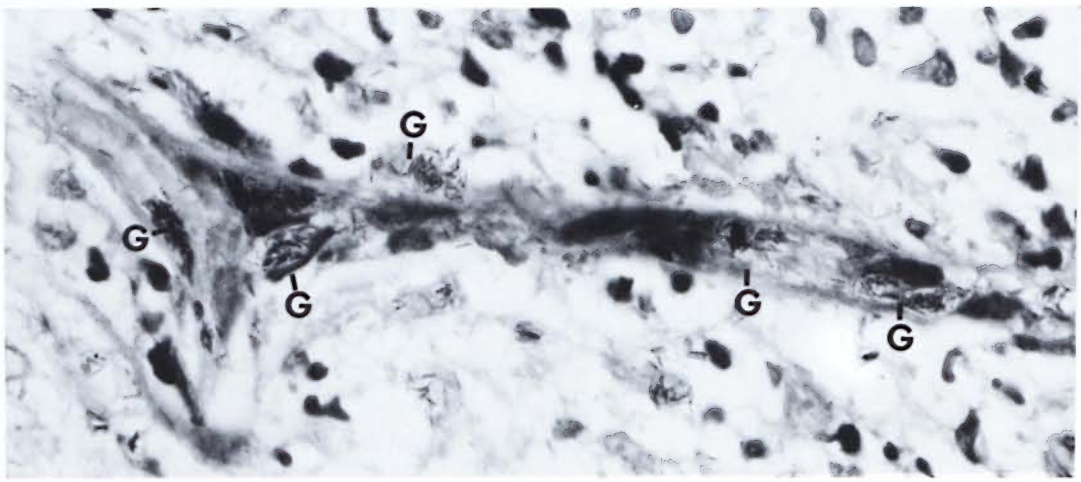

FIG. 3. Globi (G) in the endothelial cells of collapsed venules within the lepromatous granuloma. The density of bacilli in the vessel is greater than in macrophages of the surrounding granuloma. Original magnification ×1000. Fite-Faraco stain.

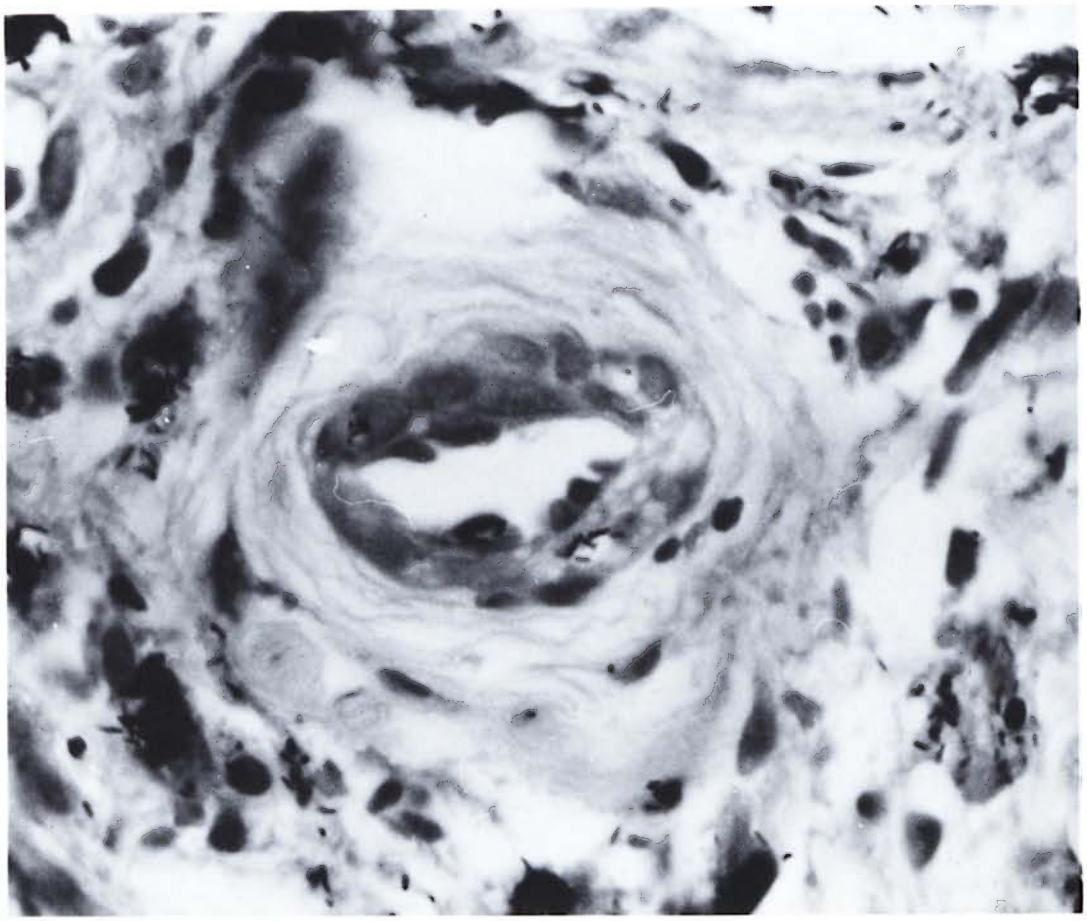

FIG. 4. Solid-staining bacilli are seen in the media of an arteriole in the lower dermis. Original magnification ×1000. Fite-Faraco stain.

a) the endothelium, b) smooth muscle (media), and c) pericytes; 2) asymmetrical fibrosis and homogenization of the vessel wall; 3) lepromatous infiltration in the vessel wall; 4) thrombosis and recanalization of the veins without any histological changes in adjacent tissues.

Endothelial phagocytosis of *M. leprae* was also the commonest feature of larger vessels, and here again the presence of bacilli was usually not accompanied by significant pathological changes in these host cells (Fig. 6). However, the majority of vessels, especially veins (Figs. 7 and 8), contained bacilli in other layers in addition to the endothelium. Hyalinization, fibrosis and infiltration of the vessel wall by macrophages were features in some arteries where the endothelium, loaded with bacilli, projected into the lumen (Figs. 9 and 10).

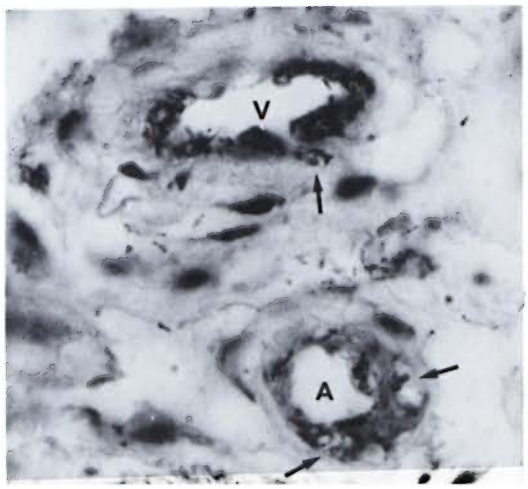

FIG. 5. Heavy endothelial bacillation in arteriole (A) and venule (V) in subepidermal plexus, obscuring most of the nuclei. Bacilli are also present in pericytes (arrowed). Original magnification ×1000. TRIFF stain.

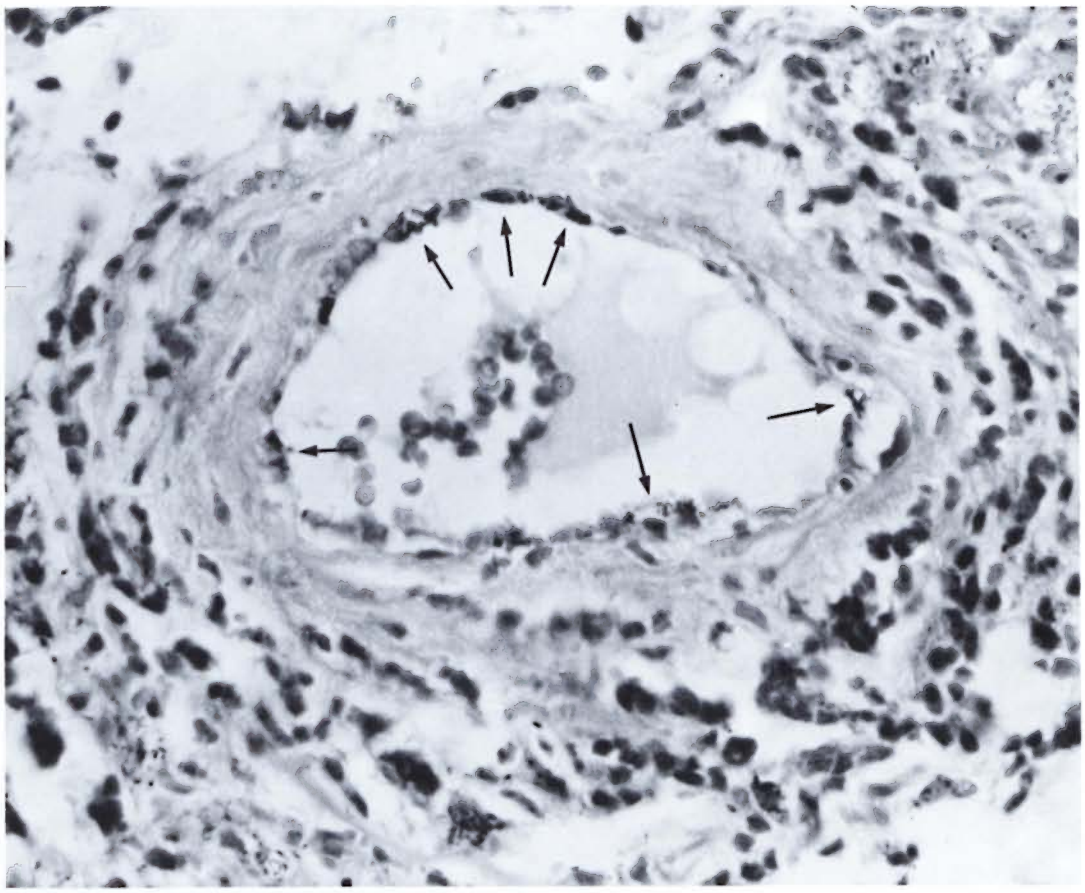

FIG. 6. Numerous bacilli (arrowed) in endothelial cells of a vein in the subdermal plexus, with minimal edema and histiocytic infiltration of the vessel wall. Original magnification ×400. TRIFF stain.

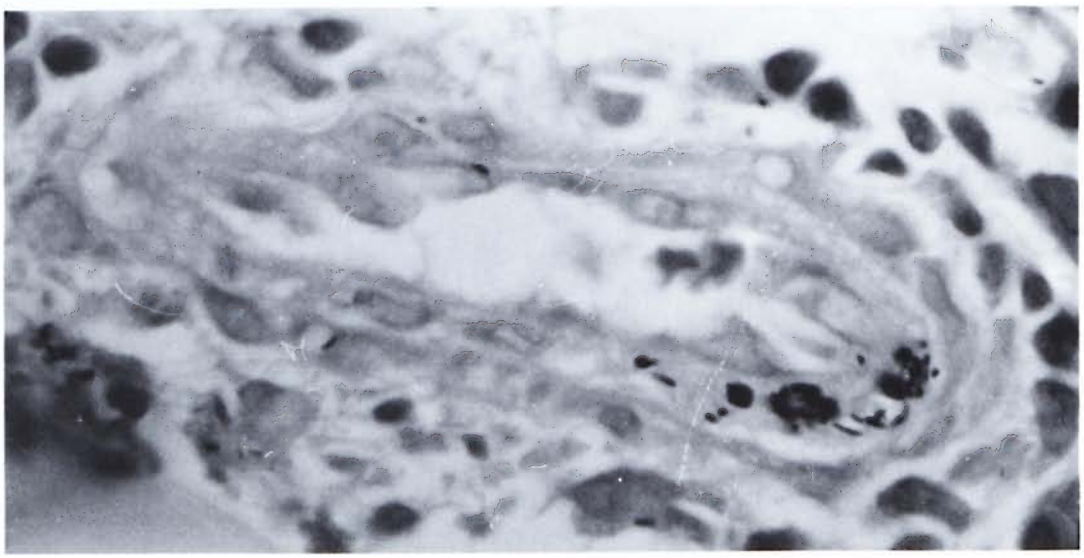

FIG. 7. Single bacilli and small globi are seen in media of a small venule in the mid-dermis. Original magnification ×1000. TRIFF stain.

FIG. 8. Globi in smooth muscle cells and pericytes of a larger vein in the subdermal plexus. Original magnification ×1000. Fite-Faraco stain.

Lepromatous infiltrates in the vessel wall were observed in 9 patients, and in some of these, lepra (Virchow) cells had accumulated in the intima and media, with narrowing of the lumen (Fig. 11). In one instance, intima and media were completely replaced by the infiltrate, the muscle layer being hardly visible around the granuloma (Fig. 12); the endothelial cells lining the narrow cleft-like lumen were packed with bacilli (Fig. 13).

Organized and recanalized thrombi were observed in biopsies from two patients, in one of which solid-staining bacilli were present in the shrunken, fibrotic intraluminal mass (Fig. 14). Fibrinoid necrosis, neutrophil polymorphonuclear cell infiltrate or leukocytoclasis were not observed in any of the 100 biopsies in this study.

Lesions of other structures of the skin. Nerves and arrector pili muscles contained *M. leprae* in all of the biopsies. Hair folli-

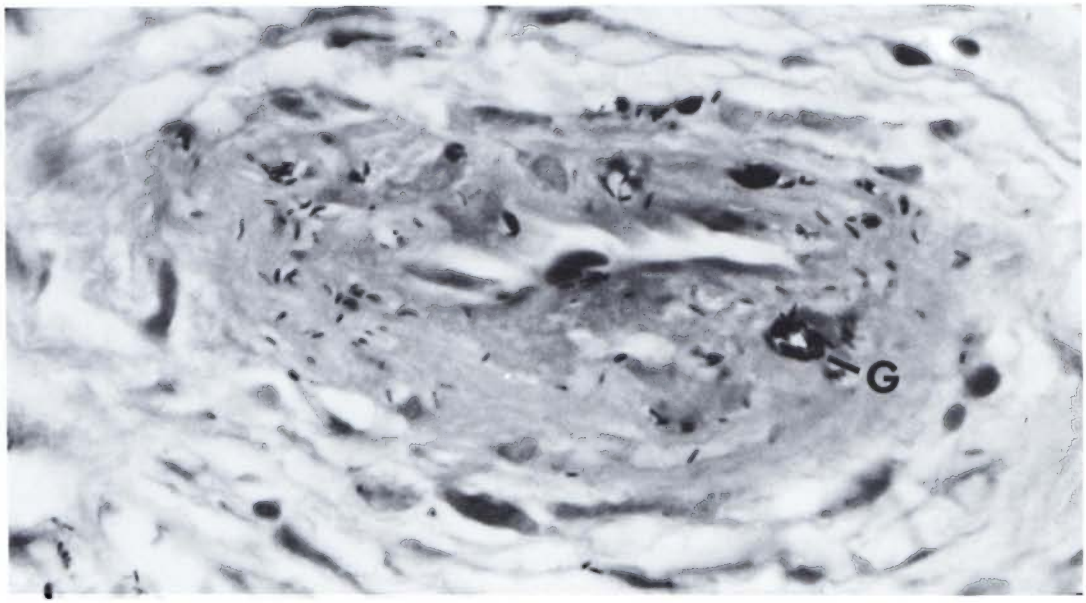

FIG. 9. Asymmetrical fibrosis in an arteriole wall, which harbors single bacilli and a globus (G) which is probably within the cytoplasm of an infiltrating macrophage. Original magnification ×1000. Fite-Faraco stain.

FIG. 10. Proliferation and protrusion into the lumen (L) of endothelial cells containing numerous *M. leprae*, in a small arteriole. The wall was partly fibrotic and infiltrated by macrophages. Original magnification ×1000. Fite-Faraco stain.

cles were present in 87 of the 100 biopsies and in 67 (77 percent) of them, bacilli were present in the outer root sheath cells. Bacilli were also found in the inner root sheath cells on one occasion and around the hair shaft in the infundibulum in biopsies from two patients.

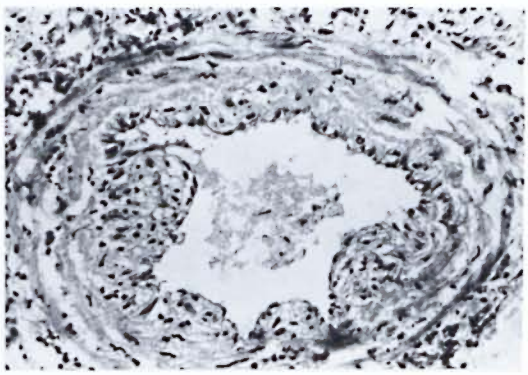

FIG. 11. Accumulation of Virchow (lepra) cells in the intima and media of a subcutaneous vein. Original magnification ×400. Fite-Faraco stain.

No sweat glands could be found in the biopsies of 9 patients, probably because of obliteration by diffuse leprous infiltrate, but bacilli were found in the secretory or ductal cells, or in the lumen, in 54 out of the remaining 91 biopsies (59 percent).

DISCUSSION

I. The incidence of vascular lesions. Although the presence of *M. leprae* in vascular endothelial cells has been recognized since the work of Neisser in 1881 ([24]), surprisingly few detailed studies have been undertaken on the incidence of vessel involvement in skin biopsies.

Fite ([10]) and Kaur, *et al.* ([19]) examined skin biopsies from different types of leprosy patients and found vascular lesions in 42 and 50 percent respectively, while Desikan and Iyer ([8]) found an incidence of 63 percent in lepromatous and borderline cases. Our present findings are very much in agreement with those of Fite who noted the common occupation of small vessels by

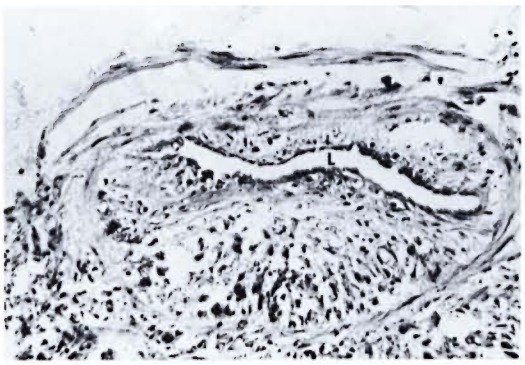

FIG. 12. Lepromatous infiltration in the wall of a large subcutaneous vessel. Cleft-like lumen (L) is still present. Original magnification ×400. TRIFF stain.

bacilli and their presence in the media and adventitia in addition to the endothelium, together with lepromatous infiltration of the vascular wall. Popov [29] and Santos and Beja [37] studied cutaneous vessel lesions in different types of leprosy patients, using the terms "sclerosis and homogenization in the vessel wall," "lepromatous endarteritis" and "lepromatous obliterative panarteritis." Other authors [1,2,4,9,14,17,23,28,32] have described the presence of *M. leprae* in the endothelium of blood vessels in skin, nerves, and nasal mucous membranes. The incidence of vascular lesions in previous studies which are comparable with our own is shown in Table 2.

II. The significance of the presence of *M. leprae* in vessels walls: (A) Endothelial lining cell; intima. The very considerable accumulation of bacilli within endothelial lining cells of blood vessels of skin, as confirmed in this study, is not seen in other mycobacterial diseases, even in the miliary form of tuberculosis. The finding of organisms in that location is unusual in other diseases apart from those due to the *Rickettsiae* and certain viral infections where the vascular endothelium may be an important site of replication and shedding [25]. We associate it with the known, continuous, and totally asymptomatic bacteremia of untreated lepromatous leprosy [9,38] while acknowledging the difficulty of knowing whether this process occurs at an early stage in the development of this type of leprosy or only in the later stages. Light and electron microscopic studies indicate that under normal conditions the vascular non-reticuloendothelial system is not phagocytic. On the other hand, some of the factors which may stimulate or activate endothelial cells to become phagocytic have been described by Cotran [6], Florey [11], and Luk and Simon [22]. With regard to experimental material such as colloidal carbon, "overloading" of

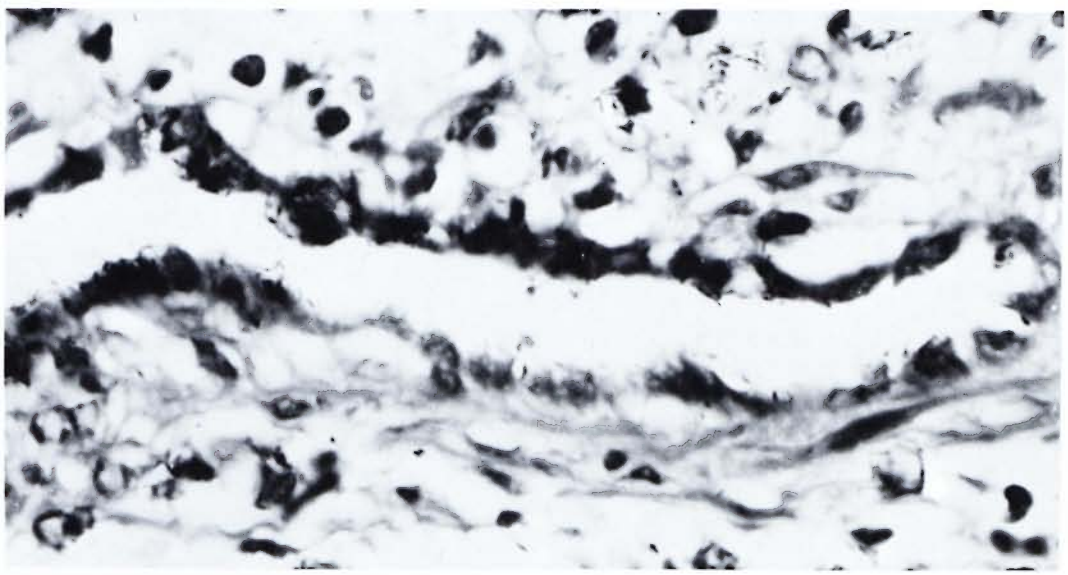

FIG. 13. Acid-fast bacilli were present in virtually every endothelial lining cell of this section, from the same vessel as shown in Fig. 12. Original magnification ×1000. TRIFF stain.

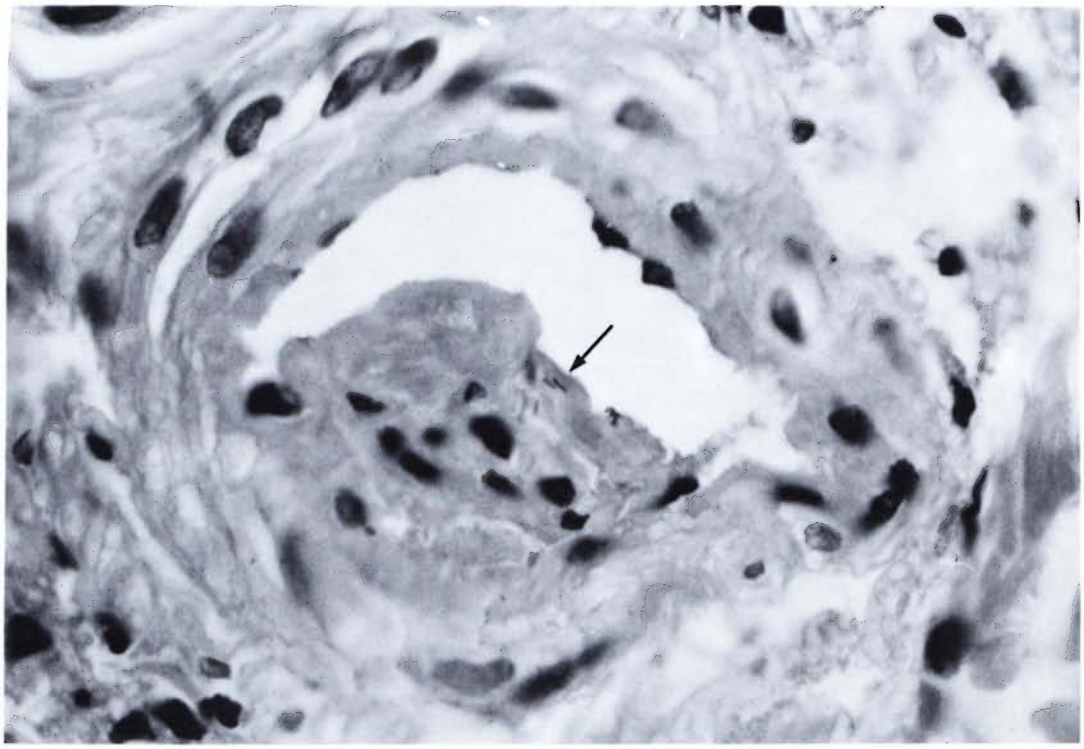

FIG. 14. Thrombosis and recanalization in a larger vessel of the subdermal plexus. Note solid bacilli (arrowed) in the thrombotic mass. Original magnification ×1000. Fite-Faraco stain.

the circulation has been shown to be important in achieving this. It may be that the continued presence of 10^5 *M. leprae* per ml of blood in a disease where the incubation period is commonly between two and five years, and may be longer, accounts for the finding of so many organisms in the endothelium of blood vessels in skin biopsies taken when the disease is established. Using a related organism, *Mycobacterium lepraemurium*, the cause of rat leprosy, Kato and Gozsy [18] stated that in the early stages, the endothelium was in fact activated by injury or infections and so was not subject to the entry of bacilli. In advanced infection, they concluded that endothelial activation broke down, contributing to the general dissemination of the infection. The potentially damaging effect of stasis on the endothelial cell has been fully discussed by Ryan [36].

The finding of numerous solidly-staining

TABLE 2. *The incidence of vascular lesions in previous publications compared with the present study.*

Date of publication	Author(s)	Type of leprosy	Number of patients	Percent of vessel involvement
1941	Fite [10]	Different types, from lepromatous to tuberculoid	77	42
1972	Desikan and Iyer [8]	Lepromatous and borderline	100	63
1976	Kaur, *et al.* [19]	Different types, from lepromatous to borderline	35	50
1978	The present study	Lepromatous (polar and sub-polar)	100	100

organisms is indicative of bacillary viability ([30]) and, taken with the presence of many globi, is strongly in favor of active proliferation of bacilli in the intimal layer. From endothelial cells, as pointed out by Desikan and Iyer ([8]), spread could easily occur to most parts of the body. Furthermore, it is possible that large numbers of bacilli could move from one body site to another in view of the known circulation of endothelial cells ([3, 16]). Recent experimental work on the possible role of biting arthropods ([27]) and of certain flies, including the biting stable fly, *Stomoxys* ([12]), in the transmission of leprosy raise the possibility that there may be more to the localization of *M. leprae* in superficially placed blood vessels than mere phagocytosis due to overloading of the blood with bacilli or the selection of cells which happen to lie in a body plane where the temperature and other tissue factors are conducive to survival. Just as the proliferation of leprosy bacilli in the nose of lepromatous patients is favorable for the spread of the organisms to the environment ([39]), so perhaps one should consider that their presence in large numbers in the endothelium of skin vessels is favorable for transmission by biting insects, such as appears to be the case for certain viruses and *Rickettsiae*.

B. Smooth muscle cells; media. Both in this study of 100 patients and in a wide range of other biopsies from lepromatous patients seen in this unit during the past eight years, including the examination of vessels accompanying the biopsy of superficially placed peripheral nerves, we have been impressed by the numbers and density of bacilli which may be seen in smooth muscle cells of the media (Figs. 4, 7, 8, and 9). Solidly-staining bacilli and globi are as common in this layer at the outset, i.e., before treatment, as they are in other smooth muscle tissues such as the arrector pili and dartos. The present study clearly does not deal with the histopathological findings after treatment, but in discussing the significance of bacilli in this layer as seen on the first biopsy, it is relevant to record that they are liable to a) linger in this site, as they do in the arrector pili, hair follicles, and dermal nerves, sometimes after many years of treatment, thus persisting in the bacteriological sense ([41]) or b) give rise to an immune-complex syndrome of which erythema nodosum leprosum (ENL) in the skin is a well-known component.

While reporting new clinical and bacteriological data, Davey and Rees ([7]) have summarized the published work on the overwhelming importance of the nasal discharge in the dissemination of leprosy bacilli into the environment. As regards the route of entry, however, despite the experimental work on inhalation quoted above, the commonest route of infection of human beings is, in fact, still unknown and difficult to investigate. Direct inoculation through the skin remains a distinct possibility. In describing histopathological findings in the early lesions of leprosy, Ridley ([31, 32]) has reviewed the evidence for this route of entry. The present study clearly deals with lepromatous patients at a relatively advanced stage and sheds no light on the skin as a possible portal of entry. It nevertheless underlines the enormous numbers of bacilli which have established themselves and are successfully multiplying in this body tissue, many of them in blood vessel walls, including the proliferated capillaries of the lepromatous infiltration. From the endothelium, bacilli may continuously contaminate the blood stream; in the media, they may persist despite many years of treatment. "Escape" of viable bacilli from the skin and hence into the environment may obviously occur from cuts, abrasions, scratches, or as a result of skin ulceration due to secondary infection and possibly also in the sweat. An additional exit route, and one to which the present study lends some support, concerns the vast numbers of bacilli which are present not only in skin macrophages but also in the walls of blood vessels, ideally situated for uptake by biting arthropods. Particularly if the mode of feeding involves extravasation of blood from a lacerated capillary to form a pool in the tissues, as it may be in the case of mosquitoes ([13]), heavy involvement of cutaneous vessels could be advantageous to the leprosy bacillus in pursuing this route of infection.

SUMMARY

Skin biopsies from 100 patients with untreated lepromatous leprosy from Malaysia, India, Africa, and South America were

examined with particular regard to pathological changes in intima, media, or adventitia of blood vessels and to the presence of leprosy bacilli in these layers.

Bacilli were found in capillaries, venules, or arterioles in all cases, and in many instances they were present in endothelial lining cells or smooth muscle in large masses (globi). In several cases, solid-staining bacilli in endothelial lining cells were especially prominent.

The findings are discussed in relation to a) the continuous bacteremia of lepromatous leprosy, b) the role of endothelial cells in phagocytosis, c) smooth muscle cells of the media as a site in which bacilli may persist, and d) the transmission of human leprosy by biting arthropods.

RESUMEN

Se examinaron biopsias de piel de 100 pacientes con lepra lepromatosa, originarios de Malasia, India, Africa y Sudamérica. El examen se hizo con particular atención a los cambios patológicos en la íntima, media y adventicia de los vasos sanguíneos, y a la presencia de bacilos de la lepra en estas capas.

Se encontraron bacilos en capilares, vénulas o arteriolas de todos los casos examinados. En muchos casos los bacilos se encontraron presentes en las células endoteliales o en el músculo liso en grandes masas o globi. En varios casos fue particularmente prominente la presencia de bacilos teñidos sólidamente en las células endoteliales.

Los hallazgos se discuten en relación a a) la bacteremia continua de la lepra lepromatosa, b) el papel de las células endoteliales en la fagocitosis, c) las células del músculo liso de la media, como un sitio en el cual pueden persistir los bacilos y d) la transmisión de la lepra humana a través de la mordedura de artrópodos.

RÉSUMÉ

On a examiné une série de biopsies recueillies chez 100 malades souffrant de lèpre lépromateuse non traitée, en Malaisie, en Inde, en Afrique, et en Amérique du Sud. Ces biopsies ont été examinées afin d'étudier les modifications pathologiques survenues au niveau de l'intima, de la media ou de l'adventice des vaisseaux sanguins, et également pour mettre en évidence la présence de bacilles de la lèpre dans ces tuniques.

Des bacilles ont été trouvés dans les capillaires, dans les vénules et dans les artérioles, dans tous les cas; chez beaucoup de malades, on trouvait également des amas de bacilles (globi) dans le revêtement cellulaire endothélial ou dans les muscles lisses. Dans plusieurs cas, la présence de bacilles colorables de façon massive, dans les cellules du revêtement endothélial, était particulièrement notable.

Ces observations sont discutées en rapport avec a) la bactérémie persistente dans la lèpre lépromateuse, b) le rôle des cellules endothéliales dans la phagocytose, c) la localisation persistente des bacilles dans les cellules musculaires lisses de la media, et d) la transmission de lèpre humaine par la morsure d'arthropodes.

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