The Identification of Leprosy Among Epithelioid Cell Granulomas of the Skin^{1,2}

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The World Health Organization in 1966 estimated (2) that the world prevalence of leprosy was 10,786,000 and in 1970 stated that, since the previous report, 500,000 new cases had been registered. In the mainland of the United States, Hawaii, Puerto Rico and the Virgin Islands there are approximately 2,600 known cases.

In the past two decades many citizens of the U.S.A. traveling or serving in areas where leprosy is endemic, have had possible exposure to leprosy. During the same periods many residents of endemic areas have come to the U.S.A. for education or other purposes.

During recent years civilian pathologists have submitted for consultation to the Armed Forces Institute of Pathology an increasing number of cases in which the diagnosis of leprosy had been made or considered a possibility, The cases present-ing the most difficulty, both to contributing pathologists and to the staff of the AFIP, have been those which histopathologically demonstrated an epithelioid cell granulomatous reaction. Most pathologists in the U.S.A. have had no opportunity to gain practical experience in the histopathologic diagnosis of leprosy. Emphasis on leprosy is probably lacking in many pathology training programs. The pathologist confronted by a biopsy from a patient in which leprosy is considered a possibility, usually has to consult a textbook for assistance. If the lesion is one of lepromatous leprosy and his laboratory succeeds in successfully

staining the leprosy bacilli, the diagnosis should not be a difficult problem. Should the lesion, however, present histopathologically an epithelioid cell granulomatous reaction, a specific diagnosis will be difficult to make. The problem would be that of differentiating tuberculoid leprosy from tuberculosis or other mycobacterial diseases of the skin, sarcoidosis, mycosis, syphilis, berylliosis, erythema annulare, etc.

In the course of attempting, by histopathologic methods, to specifically diagnose epithelioid cell granulomatous lesions of the skin, particularly when leprosy was considered a possible diagnosis, we have used special procedures and made certain observations which may be useful to pathologists confronted with similar problems.

Importance of histopathologic examination of the skin in the diagnosis of leprosy. The pathologist may wonder if there are not simpler means to diagnose or exclude leprosy than the histopathologic examination of a skin biopsy specimen including a meticulous search for acid-fast bacilli.

Leprosy cannot be excluded by a negative history of exposure to leprosy in the family or community. Badger (1) reported that of 294 patients admitted from the State of Louisiana to the National Leprosarium at Carville, only 63.6% had known exposure to leprosy. In addition, the tremendous increase of international traffic in recent years and military operations presently, and during the past decades, in areas with a high incidence of leprosy have considerably increased the number of people living in non-endemic areas who may have had possible contact with leprosy patients.

The human leprosy bacillus has not yet been acceptably cultivated in vitro. Inoculation of Mycobacterium leprae in animals has produced in ears and foot pads of rodents mild but characteristic infections with primary invasion of dermal nerves

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(³). Shepard (⁹) has been successful in using the foot pads of mice to demonstrate multiplication of the leprosy bacilli, but to obtain measurable growth 3,000 organisms must be inoculated. This method therefore cannot be used in diagnosing tuberculoid or other paucibacillary types of leprosy because a homogenate of the biopsy specimen usually would not yield enough bacilli for successful inoculation of a mouse. Even if there were enough bacilli for animal inoculation, six months or more would be required before the results were known.

At present there is no practical laboratory method for establishing or confirming a clinical diagnosis of leprosy other than the histopathologic examination of a biopsy or the demonstration of acid-fast bacilli in a smear made from a lesion in a patient with lesions clinically typical of leprosy. The latter examination is usually of no help in a case of an epithelioid granulomatous inflammatory response because of sparsity of acid-fast bacilli. For such cases histopathologic examination of a biopsy is the only valid laboratory method for confirming or excluding a clinical diagnosis of leprosy.

Because of the grave psychologic and social effects on the patient and his family that may follow a diagnosis of leprosy a physician often hesitates to make this diagnosis on the findings of clinical examination alone. The pathologist therefore should give as much support as possible to confirm or reject a diagnosis of leprosy.

The pathologist should always keep in mind the possibility of leprosy any time in his routine practice that he encounters an enigmatic inflammatory lesion of the skin, even if leprosy is not suspected by the clinician. In the files of the Armed Forces Institute of Pathology there is a significant number of cases in which pathologists have accurately diagnosed leprosy when that diagnosis had not been considered by the clinician. The correct identification of the disease by pathologists resulted in the administration of effective treatment before irreversible deformities occurred. Three illustrative cases have been reported (⁴).

Epithelioid cell granulomas in leprosy. In this paper there will be no attempt to discuss comprehensively the features of the several types of leprosy. However, to place

the epithelioid granulomatous lesion of leprosy in proper perspective, it should be stated that the first sign of leprosy is usually a macular lesion of the skin that may be hypesthetic or anesthetic. Microscopically, such lesions reveal a nonspecific dermatitis with involvement of small dermal nerves. This stage of the disease is called INDE-TERMINATE LEPROSY. Progression of the infection in most instances produces either one of two distinctly different types of disease: LEPROMATOUS LEPROSY or TUBERCULOID LEPROSY; or a form with features of both called BORDERLINE (DIMORPHOUS or INTERMEDIATE) LEPROSY.

In lepromatous leprosy numerous lesions develop in the skin, the superficial nerve trunks, and the mucous membranes of the upper respiratory tract. The eyes, lymph nodes, and testes are often affected and, in addition, microscopic lesions occur in the liver, spleen, and bone marrow. The lesions are composed almost entirely of histiocytes which contain numerous acid-fast bacilli. It is generally believed that in lepromatous leprosy there is lack of effective cellular immunity against the bacilli.

In tuberculoid leprosy, lesions occur principally in the skin and superficial nerve trunks. Although the number of skin lesions is usually small, they may attain very large sizes. The natural course of tuberculoid leprosy is characterized by exacerbations and remissions occurring at irregular intervals. Long periods of complete arrest of the disease are observed in many patients.

Active lesions usually reveal distinct epithelioid cell granulomas, but in regressive centers of skin lesions, the original epithelioid cell granulomas often disappear and the inflammatory reaction becomes nonspecific and finally subsides completely. The bacilli are usually very difficult to find in tuberculoid leprosy. It is generally believed that the growth of M. leprae in tuberculoid leprosy patients is limited because of cellular resistance. Considering the small number of bacilli demonstrable in tuberculoid lesions, the epithelioid cell granulomatous response is very severe. In contrast to lepromatous leprosy, in which nerves, although heavily infected, are well-preserved for a long time, the

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dermal nerves in tuberculoid lesions are soon destroyed after being invaded by very few bacilli. The severe inflammatory response in lesions of tuberculoid leprosy is considered to be a manifestation of delayed type hypersensitivity.

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In the borderline (dimorphous, intermediate) lesions in which the epithelioid cell granulomatous reaction is predominant, bacilli, as in the tuberculoid lesions, may be difficult to demonstrate.

Distinct characteristics of leprotic epithelioid cell granulomas of the skin. Leprosy bacilli have the unique propensity to invade and multiply in perineural and intraneural cells and spread within nerves. This so-called PRIMARY INVASION of nerves demonstrates a poorly understood host parasite relationship. M. leprae is the only acid-fast bacillus known to occur in human disease that primarily invades nerves. Evidence of primary invasion of nerves by acid-fast bacilli therefore warrants a definite diagnosis of leprosy.

In contrast with advanced lepromatous leprosy the number of skin lesions occurring in patients with tuberculoid leprosy is small. The epithelioid cell granulomatous inflammatory infiltrates are often distributed around and within nerves. Nerves apparently are the loci minores resistentiae in this resistant form of leprosy.

Technic of examination. The biopsy specimen should be taken from the periphery of the most active appearing lesion of the skin, as determined by the degree of elevation and erythema. It should include a narrow margin of normal appearing skin peripheral to the lesion. To provide opportunity to identify and examine nerves in depth, it should include the entire thickness of the dermis and a thin portion of subcutaneous adipose tissue. The specimen must be cut on the microtome in a plane perpendicular to the margin of the lesion so that the histologic sections will include a narrow margin of apparently normal skin.

Two hematoxylin and eosin, and ten acid-fast stained sections usually provide sufficient material for examination. The Fite-Faraco acid-fast method (5) is far superior to the standard Ziehl-Neelsen method for the demonstration of M. leprae in tissue sections. The keratin of hairs is

stained red in properly stained sections. Decolorization should be sufficient to adequately decolorize the small nerves and the The histopathologic technician stroma. should have unstained sections of known leprosy tissue to demonstrate the adequacy of staining.

In his daily practice that includes specimens of skin, the pathologist commonly pays little attention to the dermal nerves, because they usually reveal no changes contributory to the diagnosis of most dermatologic conditions. Since the dermal nerves are often severely damaged and therefore are difficult to recognize in tuberculoid leprosy, the pathologist may easily overlook the distinct characteristics of leprotic nerve involvement in an epithelioid cell inflammatory lesion of the skin. This, and the paucity of acid-fast bacilli, make it necessary that the pathologist follows a systematic pattern of examination to make or reject a diagnosis of leprosy in an epithelioid cell inflammatory lesion of the skin.

The hematoxylin and eosin stained sections are examined first. As will be discussed later, it will be helpful for the pathologist to draw an outline of the section on a piece of paper and to sketch inflammatory infiltrates and nerves in this outline. The number of nerves, or rather, the number of cuts across nerves, is counted. In this way the relationship between nerves and inflammatory infiltrates is determined.

In our practice the search for M. leprae in epithelioid cell granulomas of the skin is usually restricted to nerves, remnants of nerves, foci of necrosis, and subepidermal free zones. In case the dermal nerves are destroyed beyond recognition, the centers of large inflammatory infiltrates are searched. These centers are most likely the sites where nerves were situated previous to their destruction.

On observing an acid-fast bacillus in a skin lesion, the pathologist obviously must determine under an oil immersion lens that it is located in tissue and is not a "floater." If the sections were stained along with other sections containing acid-fast bacilli, a bacillus situated on the surface of the section could be a contaminant. Also, a bacillus located upon or under rather than within a nerve may be a displaced bacillus.

The limitation of the search for M. leprae to the above mentioned areas in tuberculoid leprosy makes the examination of ten acid-fast stained sections feasible for the practicing pathologist who desires to document or reasonably exclude a diagnosis of tuberculoid leprosy.

In order to chart the amount and distribution of the infiltrates in epithelioid cell granulomas of the skin and show the relation of the infiltrate to nerves and bacilli, we prepared illustrative profiles of the sections.

Preparation of profiles. In each case a low power photomicrograph of the entire section stained with hematoxylin and eosin was mounted on a piece of glass. The parts of the dermis and subcutaneous tissue which were not infiltrated were cut out with a razor blade and removed from the plate. The resulting silhouette of the inflammatory infiltrates, epidermis and nerves was photographed.

On the photograph of the profile the NERVES were marked with black or white dots and indicated by horizontal arrows. In cases with few bacilli, arrows were mounted vertically to point out the areas where acidfast bacilli were observed in one or more sections stained by the acid-fast method. Areas selected for high power photomicrographs were indicated by a capital letter and a symbol ¹.

DERMAL EPITHELIOID CELL GRANULOMA

Tuberculoid leprosy compared with sarcoidosis; importance of bacillary nerve involvement in leprosy.

Case 1. Figure 1 demonstrates the margin of a single lesion on the dorsum of the left forearm of a 13 year old Surinam girl of East Indian descent.

The elongated large infiltrates in the lower part of the figure are located at the site of the neural plexus of the lower dermis. The small infiltrates in the mid-dermis and in the superficial dermis follow the pattern of distribution of the comparatively small motor nerves that come from the plexus. There are only three nerves. Two nerves are severely damaged.

Three acid-fast bacilli are observed in one specially stained section. One bacillus is located in a damaged nerve. The other two bacilli are located in the midst of inflammatory infiltrates probably at the sites of totally destroyed nerves.

Severe damage of the dermal nerves, perineural focalization of the inflammatory infiltrate, and the occurrence of bacilli in a nerve and at the possible sites of destroyed nerves are outstanding features of the involvement of nerves in tuberculoid leprosy. In this paucibacillary epithelioid cell granulomatous inflammatory lesion of the skin, the observation of a single acid-fast bacillus in a nerve is acceptable proof of leprosy.

Case 2. Figure 2 demonstrates a sarcoid lesion on the skin of the right forearm of a 54 year old man.

The infiltrates of the lower dermis are circular and distinct rather than elongated or plexiform. Perineural distribution of the inflammatory infiltrate is not evident. There are 11 well-preserved nerves in one section. Acid-fast bacilli are not observed.

In such an epithelioid cell inflammatory lesion of the skin with infiltrates in all levels of the dermis, the absence of involvement of dermal nerves is evidence against leprosy. The patient had several classical signs of sarcoidosis.

It is of interest to note that in Figure 1 and in Figure 2 respectively, the evidence of involvement of dermal nerves and the lack of evidence of involvement of dermal nerves appear only in the lower part of the dermis. If the biopsies had been taken superficially so that the level of the neural plexus of the lower dermis had not been included, distinction of the two lesions would likely have been impossible.

Focally necrotizing epithelioid cell granulomas in tuberculoid leprosy with conspicuous involvement of dermal nerves.

Case 3. Figure 3 demonstrates a lesion on the left forearm of a 50 year old diabetic woman in Guam. She had a history of recurrent, erythematous, annular and arcuate infiltrations on the trunk, face and extremities.

The elongated infiltrates follow the pattern of distribution of the dermal nerves. The centers of two infiltrates are necrotic. The necrosis is indistinguishable from caseation as occurring in tuberculosis. There is only one nerve that can be iden-





FIG. 2. Sarcoidosis: no involvement of dermal nerves. Lesion on forearm of 54-yearold man. AFIP Acc. 314241.

Old man. AF IF ACC. 014241. (A) Profile of epidermis and infiltrate. The dots represent eleven well-preserved nerves which are indicated by horizontal arrows. Hematoxylin and eosin x $5\frac{1}{4}$ AFIP neg. 67-4659. (B) Well circumscribed distinct epithelioid cell granulomatous infiltrates at B' in A. The horizontal arrows indicate three well-preserved nerves in the margins of the infiltrates. Hematoxylin and eosin, x 42. AFIP neg. 67-1738. (C) Infiltrate at C' in A, x 265. The horizontal arrow points to an undamaged nerve. Hematoxylin and eosin, AFIP neg. 67-1739.

tified. It is severly damaged and contains one beaded, acid-fast bacillus.

Perineural focalization of the epithelioid inflammatory infiltrate, the severe nerve damage and the demonstration of an acidfast bacillus in a nerve are characteristic for tuberculoid leprosy. Although the clinical picture with multiple lesions on trunk, face and extremities might suggest dimorphous leprosy, the histopathologic features in this biopsy are those of tuberculoid leprosy. Case 4. More of a diagnostic problem was the biopsy of a plaque-like lesion on the cheek of a 20 year old Surinam man of East Indian descent demonstrated in Figure 4. The man had, in addition, erythematous plaques on his trunk and extremities.

The predominately epithelioid cellular inflammatory infiltrate is massive and replaces the entire dermis. Some epithelioid foci of the mid-dermis show central necrosis. Nerves are not observed in multiple

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FIG. 1. Tuberculoid leprosy with conspicuous involvement of dermal nerves. Margin of single lesion on forearm of 13-year-old Surinam girl. AFIP Acc. 1122490.

of single lesion on forearm of 13-year-old Surinam girl. AFIP Acc. 1122490. (A) Hematoxylin and eosin, x 7½. AFIP neg. 65-1637. (B) Profile of epidermis and infiltrate demonstrated in A. Horizontal arrows point toward three dots that represent all nerves observed in this section. Vertical arrows point toward the sites of three bacilli observed in one acid-fast stained section. The extent and distribution of the inflammatory infiltrates correspond with the pattern of dermal nerves. Hematoxylin and eosin, x $6\frac{1}{2}$. AFIP neg. 65-1637. (C) A higher power of the perineural infiltrate at C' In B. There are a few remaining nerve fibers which are indicated by the horzontal arrow. The inset shows one bacillus in same nerve in an acid-fast stained section. Hematoxylin and eosin, x 130. AFIP neg. 65-1641. Inset: Fite-Faraco acid-fast stain, (x 1.350) AFIP neg. 65-1640. (D) Infiltrate at D' in B, x 150. The remaining fibers of a severely damaged infiltrate at E' in B demonstrates a typical tuberculoid epithelioid cell granulomatous reaction including a rim of lymphocytes. One Langhans' glant cell is seen amidst the epithelioid cells. Hematoxylin and eosin, x 115. AFIP neg. 64-2427.



FIG. 3. Tuberculoid leprosy with conspicuous involvement of dermal nerves and with focal necrosis. Lesion on forearm of 50-year-old woman in Guam. AFIP Acc. 116067. (A) Profile of epidermis and infiltrate. The only nerve seen is indicated by the dot at the point of the horizontal arrow. The vertical arrows indicate the sites of two bacilli which were seen in one acid-fast stained section. One in the nerve and the other in a necrotic center of a granuloma. Hematoxylin and eosin, x 9. AFIP neg. 65-3920. (B) Epithelioid cell infiltrate at B' in A, x 115. Dark shaded center of infiltrate represents necrosis. Hematoxylin and eosin, AFIP neg. 65-3918. (C) Infiltrate at C' in A, x 115. Horizontal arrow indicates the remaining fibers of a damaged nerve. Hematoxylin and eosin. AFIP neg. 65-3917. (D) Nerve at D' in A, x 995. Vertical arrow indicates a beaded acid-fast bacillus within the damaged nerve. Fite-Faraco acid-fast stain. AFIP neg. 3919.

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FIG. 4. Tuberculoid leprosy with conspicuous involvement of dermal nerves and with extensive necrosis. Lesion on cheek of 20-year-old Surinam man. AFIP Acc. 1122520. (A) The entire dermis is replaced by inflammatory infiltrate. The cleft is an artifact. Dermal nerves are not preserved. Vertical arrow indicates the site of two bacilli in an acid-fast stained section. Hematoxylin and eosin, x 7. AFIP neg. 65-1642. (B) Part of infitrate at B' in A, x 130. Necrotic area surrounded by epithelioid cells and occasional Langhans' giant cells. Hematoxylin and eosin. AFIP neg. 65-1644. (C) Area at C' in A, x 1,000. Vertical arrow indicates two bacilli in immediate vicinity of hair follicle. Fite acid-fast stain. AFIP neg. 67-6181.



sections. Examination of several acid-fast stained sections revealed occasional bacilli in necrotic areas and in subepithelial free zones.

The total destruction of dermal nerves in this massive inflammatory infiltrate is suggestive but not diagnostic for leprosy. The occurrence of acid-fast bacilli in the subepidermal free zone is strong additional support for a diagnosis of leprosy. Epithelioid cell inflammatory infiltrate, fewness of acidfast bacilli, and damage of nerves are consistent with tuberculoid leprosy.

If the biopsy had included the margin of the lesion with a small part of normal skin, perineural focalization of inflammatory infiltrate and damaged nerves with acidfast bacilli would most likely have been present between the normal skin and the massive infiltrate and have given the pathologist more confidence to make a diagnosis of leprosy.

Focal necrosis of epithelioid cell inflammatory infiltrates of the skin is not inconsistent with leprosy. The necrosis is usually confined to the centers of few infiltrates of the mid-dermis. The necrosis apparently occurs at the sites of dermal nerves. In tuberculoid leprosy we have never observed massive superficial necrosis and ensuing ulceration in lesions of the skin. Massive necrosis of epithelioid cell granulomas of peripheral nerve trunks with the formation of a so-called nerve abscess is not uncommon in tuberculoid leprosy.

Inconspicuous nerve involvement in tuberculoid leprosy.

Case 5. Figure 5 demonstrates a lesion on

the thigh of a Filipino woman who came to the U.S.A. two years before the biopsy was taken. The lesion was described as an erythematous, annular plaque that was anesthetic to pinprick. There was also anesthesia of the fingers. Both the consultant dermatologist and the pathologist felt that the woman had leprosy.

In the superficial dermis there is a cordlike, inflammatory infiltrate composed of epithelial cells and Langhans' giant cells enveloped by lymphocytes. Several infiltrates are also noted in the mid- and lower dermis.

Twelve nerves are identified. Two nerves are not related to inflammatory infiltrate. The other ten nerves are located in the peripheral parts or in the margins of inflammatory infiltrates. No nerve is surrounded by epithelioid cells. All nerves appear well-preserved.

One acid-fast stained section reveals 11 bacilli in six different locations. Seven bacilli are noted in the subepidermal zone. Four bacilli are observed in two nerves.

The presence of acid-fast bacilli in nerves convincing evidence of leprosy. The appearance of the epithelioid cell inflammatory infiltrate and paucity of bacilli are features of tuberculoid leprosy.

Case 6. Figure 6 demonstrates a biopsy specimen, from the margin of a macule on the left buttock of a 35 year old female Bush Negro in Surinam. She also had a lesion on the skin of one of her feet. The macule of the buttock was hypopigmented in the center and it had somewhat infiltrated margins. There was no loss of sensitivity

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FIG. 5. Tuberculoid leprosy; inconspicuous involvement of dermal nerves. Lesion on thigh of Filipino woman. AFIP Acc. 1225637.

thigh of Filipino woman. AFIP Acc. 1225637. (A) Profile of epidermis and infiltrate. The horizontal arrows indicate 12 well-preserved nerves marked by dots. Ten nerves are situated in the margins of inflammatory infiltrates. Two nerves are not connected with inflammatory infiltrates. Six vertical arrows indicate sites of 11 bacilli observed in one acid-fast stained section. Seven bacilli occur in the subepidermal zone. Hematoxy-lin and eosin, x 5. AFIP neg. 67-4182. (B) Area B' in A, x 250. The inflammatory infiltrate is composed of epithelioid cells, lymphocytes and a Langhans' giant cell. A small nerve, indicated by horizontal arrow, is not involved. Hematoxylin and eosin, AFIP neg. 67-4190. (C) Area at C' in A, x 65. This inflammatory infiltrate is connected with branching nerve, indicated by three horizontal arrows. Hematoxylin and eosin, AFIP neg. 67-2209. (D) Subepidermal zone at D' in A, x 1,000. Vertical arrow indicates seemingly dividing bacillus. Fite-Faraco acid-fast stain. AFIP neg. 67-4201. (E) Subepidermal zone at E' in A, x 1,000. Vertical arrow indicates acid-fast bacil-lus. Fite-Faraco acid-fast stain. AFIP neg. 67-4196. (F) Subepidermal zone at F' in A, x 1,000. Vertical arrow indicates acid-fast bacillus. Fite-Faraco acid-fast stain. AFIP neg. 67-4205. Subepidermal zone at G' in A, x 1,000. Vertical arrow indicates three acid-fast bacilli. Fite-Faraco acid-fast stain. AFIP neg. 67-4107. (H) Small nerve at H' in A, x 1,000. Vertical arrow indicates beaded acid-fast bacillus within a nerve. Fite-Faraco acid-fast stain. AFIP neg. 67-4200. (I) Small nerve at I' in A, x 1,000. Vertical arrow indicates two opposed acid-fast bacilli within a nerve. Fite-Faraco acid-fast bacillus. The nerves illustrated in Area I and Area J are the same. but photographed in different focus. Fite-Faraco acid-fast stain. AFIP neg. 67-4199. tical arrow indicates acid-fast bacillus. The nerves illustrated in Area I and Area J but photographed in different focus. Fite-Faraco acid-fast stain, AFIP neg. 67-4199.





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demonstrable in the affected areas of the skin and bacteriologic examination of the margin of the lesion on the buttock was negative for acid-fast bacilli.

A cord-like inflammatory infiltrate occupies the superficial dermis. On the left side it touches the epidermis at several places but on the right side a subepidermal free zone is preserved. Several inflammatory infiltrates are present in the mid-dermis and a few infiltrates occur in the lower dermis.

Fourteen nerves are noted in one section. Nine nerves are connected with, or situated within, inflammatory infiltrates. Most nerves appear well-preserved.

Search of five acid-fast stained sections reveals five bacilli. One bacillus is identified in an apparently undamaged nerve. Three bacilli occur in the subepidermal zone. One bacillus is located in an inflammatory infiltrate.

Although involvement of dermal nerves is not conspicuous the observation of an unmistakable acid-fast bacillus in a nerve is considered diagnostic for leprosy. The epithelioid inflammatory infiltrate and paucity of acid-fast bacilli are features of tuberculoid leprosy.

Case 7. Figure 7 demonstrates a hypopigmented macular lesion on the forearm of a 21 year old Bush Negro of Surinam. At the time of biopsy the patient had similar macules on the left cheek, the right upper arm, and the volar side of the right forearm. The margins of the macules were elevated.

A massive epithelioid cell inflammatory infiltrate replaces part of the superficial and mid-dermis. The infiltrate extends to the basal layer of the epidermis which, above the infiltrate, is somewhat stretched. Small inflammatory infiltrates occur in other parts of the dermis. Twenty-eight nerves are present. Ten nerves are noted in the left part of the profile and 18 nerves are noted in the right part. On the left of the profile seven nerves are related to or situated within inflammatory infiltrates, and three nerves are surrounded by unaltered dermal connective tissue. In the right part of the profile five nerves are related to or situated within inflammatory infiltrates and thirteen nerves are surrounded by unaltered connective tissue. The nerves appear well-preserved.

The examination of two acid-fast stained sections reveals three bacilli in nerves. The demonstration of bacilli in these nerves justifies the diagnosis of leprosy in this epithelioid cell granuloma.

Absence of nerve involvement in sarcoidosis and non-leprotic mycobacterial granulomas.

Case 8. Figure 8 demonstrates an epithelioid cell granuloma of the skin in a 27 year old man with sarcoidosis.

The distribution of the inflammatory infiltrate is not unlike that in Figure 7. The large infiltrate is composed of well-defined circular clusters of epithelioid cells with very few lymphocytes. Such a distinct nodular pattern of epithelioid cell granulomas with only few lymphocytes would not be expected in leprosy.

There are 16 nerves. Nerves are not present in the large inflammatory infiltrate. Five nerves are connected with small infiltrates. All nerves are well-preserved. Bacilli are not observed in several acid-fast stained sections. The patient had several other signs of sarcoidosis.

Case 9. This illustrates how diagnostic difficulties may be encountered in epithelioid cell granulomas of the skin caused by mycobacteria other than *M. leprae*. Figure 9 demonstrates a lesion on the right leg of an 85 year old woman, born in Norway

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FIG. 6. Tuberculoid leprosy with inconspicuous involvement of dermal nerves. Lesion on buttock of 35-year-old Surinam woman. AFIP Acc. 1122499.

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⁽A) Profile of epidermis and infiltrate. Horizontal arrows indicate 14 nerves marked with dots. Vertical arrows indicate sites of five bacilli observed in five acid-fast stained sections. Hematoxylin and eosin, x $6\frac{1}{2}$. AFIP neg. 65-1638. (B) Subepidermal zone at B' in A, x 1,000. Vertical arrow indicates acid-fast bacillus. Fite-Faraco stain. AFIP neg. 67-1922. (C) Area at C' in A, x 65. Epidermis, subepidermal zone and superficial inflammatory infiltrate are illustrated. Hematoxylin and eosin. AFIP neg. 67-2209. (D) Area at D' in A, x 75. Hematoxylin and eosin, x 75. AFIP neg. 67-2213. (E) Subepidermal zone at E' in A, x 1,000. Vertical arrow indicates acid-fast bacillus. Fite-Faraco acid-fast stain. AFIP neg. 67-1924. (F) Nerve and inflammatory infiltrate at F' in A, x 1,000. Horizontal arrow indicates nerve and vertical arrow indicates acid-fast baciltory infiltrate at G' in A, x 260. Horizontal arrow indicates damaged nerve. Hematoxylin and eosin. AFIP neg. 67-2215.





Sarcoidosis. Lesion on forearm of 27-year-old man. AFIP Acc. 516640. FIG. 8. (A) Profile of epidermis and infiltrate. Fifteen horizontal arrows indicate 16 nerves marked by dots. Hematoxylin and eosin, x $4\frac{1}{2}$. AFIP neg. 67-1683. (B) Area at B' in A, x 42. Nodular, epithelioid cell inflammatory infiltrate. Nerves not present. Hematoxylin and eosin. AFIP neg. 67-1741. (C) Inflammatory infiltrate at C' in A, x 100. Horizontal arrow indicates well-preserved nerve. Hematoxylin and eosin. AFIP neg. 67-1740.

and, since her 20th year, living in the U.S.A.; presently in Minnesota. Her physician thought that she might have had contact with leprosy patients in her youth or during visits to her native country.

Subcutaneous nodules, varying from pinpoint to 3 cm in diameter, were present on the posterior aspect of the right calf. The largest nodule was bluish-red, slightly warm, and moderately tender. The skin surface was intact. Similar lesions were present at the skin of the right patella and on the left wrist.

On histopathologic section a large, massive, inflammatory infiltrate has replaced

the greater part of the dermis. Small infiltrates occur in the remaining part of the dermis. The inflammatory infiltrates are composed of lymphocytes and plasma cells with clusters of epithelioid cells.

Nine nerves are present. Six nerves are located within inflammatory infiltrates and three nerves are surrounded by unaltered dermal connective tissue. Nerves are not observed within foci of epithelioid cells.

Acid-fast stained sections reveal numerous bacilli. Most bacilli are situated within inflammatory cells. Bacilli are not observed in nerves.

If this were a case of leprosy many

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Fig. 7. Tuberculoid leprosy; inconspicuous involvement of nerves. Lesion on fore-

<sup>Fig. 7. Tuberculoid lepiosy; inconspicuous involvement of nerves. Lesion on fore-arm of 21-year-old Surinam man. AFIP Acc. 1122510.
(A) Profile of epidermis and infiltrate. Horizontal arrows indicate 28 nerves marked with dots. Two vertical arrows indicate sites of three bacilli observed in two acid-fast stained sections. Hematoxylin and eosin, x 4. AFIP neg. 67-2218. (B) Epithelioid cell inflammatory infiltrate at B' in A, x 225. Small nerve indicated with horizontal arrow. Hematoxylin and eosin. AFIP neg. 67-2223. (C) Nerve at C' in A, x 1080. Vertical arrow indicates acid-fast bacillus. Fite-Faraco acid-fast stain. AFIP neg. 67-2225. (D) Inflammatory infiltrate at D' in A, x 225. Horizontal arrows indicate two small nerves. Hematoxylin and eosin. AFIP neg. 67-2222. (E) Nerve at E' in A, x 1080. Vertical arrows indicate two beaded acid-fast bacilli. Fite-Faraco acid-fast stain. AFIP neg. 67-2226.</sup> 67-2226.



FIG. 9. Unclassified mycobacterial infection of skin. Nodular lesion on leg of 85-

FIG. 9. Unclassified mycobacterial infection of skin. Nodular lesion on leg of 85-year-old woman. AFIP Acc. 1159132.
(A) Profile of epidermis and infiltrate. Nine horizontal arrows indicate nerves, marked with dots. Sites of numerous acid-fast bacilli not indicated. Hematoxylin and eosin, x 5. AFIP neg. 67-4927. (B) Area at B' in A, x 1190. Numerous, mostly intracellular acid-fast bacilli indicated with vertical arrows. Fite-Faraco acid-fast stain. AFIP neg. 65-1481. (C) Area at C' in A, x 250. Horizontal arrow indicates damaged nerve. Epithelioid cell infiltrate in lower part of picture. Bacilli were not observed in nerves. Hematoxylin and eosin. AFIP neg. 67-4924.

bacilli should be present in nerves. In the absence of nerve involvement we excluded leprosy as a possible diagnosis. Further laboratory studies failed to identify the mycobacteria causing this lesion and further clinical studies did not confirm a diagnosis of leprosy.

Epithelioid cell granuloma of the skin in reactional tuberculoid leprosy.

Case 10. Figure 10 demonstrates a representative example of a lesion of the skin in a patient with tuberculoid leprosy in reaction. The biopsy was taken from the margin of a large maculoanesthetic lesion on the right arm of a 25 year old Cantonese Chinese woman who lived in Malaysia, North Borneo. The right ulnar nerve was thickened. Scrapings from the lesion of the skin were negative for acid-fast bacilli. The clinical diagnosis was dimorphous leprosy.

The distribution of the inflammatory infiltrate follows the pattern of distribution of dermal nerves. The infiltrates are composed of foci of epithelioid cells surrounded by lymphocytes intermixed with few plasma cells. Lymphocytes are very numerous in the infiltrates of the lower dermis. Nerves are not observed. Acid-fast bacilli are numerous.

If this were not a case of leprosy, several nerves should have been noted in the large areas of uninvolved dermal tissue between the inflammatory infiltrates. The total absence of dermal nerves in this focalized, mycobacterial inflammatory lesion supports a diagnosis of tuberculoid leprosy in this mycobacterial granuloma. The large number of acid-fast bacilli and lymphocytes indicate a reactional phase of the infection.

Epithelioid cell granuloma of the skin in dimorphous leprosy.

Case 11. Figure 11 demonstrates a typical example of a borderline lesion of the skin. The biopsy was taken from a nodule on the right forearm of a four year old Surinam boy.

The distribution of the inflammatory infiltrate is perineural. The infiltrates are composed of ill-defined epithelioid cell foci and lymphocytes. The infiltrate approaches but does not encroach on the basal layer of the epidermis.

There are 11 nerves. All nerves are surrounded by infiltrates. The nerves are only slightly damaged by infiltrate. Acid-fast bacilli are abundant. Most bacilli occur in nerves where they are often aggregated in clusters. Several bacilli are also noted in inflammatory cells.

The extensive, loosely arranged, epithelioid cell inflammatory infiltrate of the dermis which does not encroach on the basal layer of the epidermis, and the slight damage of dermal nerves notwithstanding the presence of numerous bacilli are features that lead to a diagnosis of borderline leprosy.

DISTINCT HISTOPATHOLOGIC CHARACTERISTICS OF THE VARIOUS LEPROTIC EPITHELIOID CELL GRANULOMAS OF THE SKIN OBSERVED IN BIOPSY SPECIMENS

Review of the biopsy material. The cases presented illustrate a variety of leprotic epithelioid cell granulomas of the skin encountered in biopsy specimens that were forwarded to the Armed Forces Institute of Pathology during the years 1963-1966. The biopsies were taken specifically for diagnostic purposes, not for research. It can be assumed that most patients consulted the physicians at the time they became concerned about their skin diseases and that, in several instances, the local pathologists consulted the Armed Forces Institute of Pathology because of the diagnostic difficulties. The presented cases, therefore, illustrate the histopathology of epithelioid cell granulomas of the skin that occur in active lesions of untreated patients with tuberculoid or borderline leprosy, and they include several uncommon variants. Caseous necrosis in epithelioid cell granulomas of the skin is rarely seen in biopsies taken for observing progress in tuberculoid leprosy. It is not infrequently encountered in biopsy specimens taken for the initial diagnosis. The clinical changes in the lesions with necrosis may have disturbed the patient so much that medical attention was sought. In fact, one of the first descriptions of epithelioid cell granulomas in skin lesions of leprosy patients mentions the occurrence of coagulation necrosis (Jadassohn) (6). Furthermore, epithelioid cell granulomas of the skin with inconspicuous involvement of nerves, although uncommon in patients with tuberculoid leprosy, are not infre-



quently encountered in diagnostic biopsy specimens because such lesions, in particular if they are small, often do not present anesthesia, the clinical hallmark for the diagnosis of leprosy. Therefore, the clinician is more apt to seek the assistance of a pathologist. With the exception of the specimen illustrated in Figure 4 all specimens chosen for illustration were taken from the margins of active lesions and, in addition, included the entire thickness of the dermis. Superficial biopsy specimens or biopsy specimens taken from inactive lesions or inactive parts of lesions are often insufficient for making a histopathologic diagnosis of leprosy. In such instances, the pathologist in his report should mention the inadequacy of the specimen.

The outlined selection of the illustrated varieties of leprotic epithelioid cell inflammatory lesions of the skin implies certain restrictions for their use as a reference in the practice of laboratory pathology. Tuberculoid leprosy is a disease with an unpredictable course. Long periods of arrest often alternate with relatively short periods of activity. During disease arrest, anesthethypopigmented macules ic. may be present. Such macules do not increase in size, their margins are not infiltrated, and microscopically there is, at the most, only minor chronic nonspecific inflammatory infiltrate. Acid-fast bacilli usually cannot be demonstrated. Such atypical inflammatory lesions are often observed in biopsy specimens that were taken from lesions of the skin in persons who were examined because they had been in close contact with leprosy patients, or in which macules were noted during an examination for another illness. A different picture of the histopathology of lesions of the skin in tuberculoid leprosy will also be obtained when biopsy specimens are taken from a group of patients with an established diagnosis of tuberculoid leprosy, and perhaps have been

under treatment already for considerable time (7).

From the foregoing, it is evident that for proper evaluation of a biopsy specimen the pathologist should be informed about the nature of the disease of the patient, the type and activity of the biopsied lesion, and the site from which the specimen was taken. This information is of particular importance in case leprosy is suspected clinically, but not supported by the findings in a biopsy specimen. Such negative findings can be interpreted as evidence against leprosy only if the biopsy specimen was taken from the margin of an actively growing skin lesion.

Leprotic nerve involvement versus secondary nerve involvement. Epithelioid cell inflammatory dermal lesions usually cause severe and often permanent damage to the skin regardless of their etiology. This damage, resulting in atrophy or scarring, involves the epidermis altering its pigmentation, the blood vessels, the appendages, and connective tissue. The dermal nerves, protected as they are by sheaths of epineurium and perineurium, are more resistant to damage than the other elements of the skin. But massive inflammatory infiltrates may overwhelm the dermal nerves. In such inflammatory lesions, it is not unusual to find the number of nerves decreased, to observe nerves amidst inflammatory cells, and to note actual inflammatory infiltration and damage of occasional nerves.

In severe, nonleprotic, mycobacterial infection of the skin, phagocytic cells carrying bacilli may have migrated into a nerve through a damaged perineurium.

When comparing nerve involvement in animals experimentally infected with the human leprosy bacillus with those infected experimentally with the murine leprosy bacillus (*Mycobacterium lepraemurium*), we found that, while the human leprosy bacillus regularly selectively invades intact

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FIG. 10. Tuberculoid leprosy in reaction. Lesion on arm of 25-year-old Cantonese Chinese women in Malaysia, North Borneo. AFIP Acc. 1132582.

⁽A) Profile of epidermis and infiltrate. Nerves not present. Numerous acid-fast bacilli not indicated. Hematoxylin and eosin, x 11½. AFIP neg. 65-2393. (B) Area at B' in A, x 225. Epithelioid cell inflammatory infiltrate surrounded by broad rim of lymphocytes. Hematoxylin and eosin. AFIP neg. 65-1656. (C) Area at C' in A, x 1080, including part of epithelioid cell infiltrate shown in Figure B. Clusters of acid-fast bacilli indicated by vertical arrows. Fite-Faraco acid-fast stain. AFIP neg. 65-1657.



FIG. 11. Dimorphus leprosy. Nodule on arm of 4-year-old Surinam boy. AFIP Acc. 1080913.

1080913.
(A) Profile of epidermis and infiltrate. Horizontal arrows indicate 11 nerves marked with dots. Numerous acid-fast bacilli not indicated. Hematoxylin and eosin, x 11. AFIP neg. 66-9321. (B) Area at B' in A, x 265. Horizontal arrow indicates nerve. Hematoxylin and eosin. AFIP neg. 67-1674. (C) Area at C' in A, x 875, with same nerve as in Figure B. Vertical arrows indicate bacilli. Fite-Faraco acid-fast stain. AFIP neg. 67-1672. (D) Nerve at D' in A, x 875. Vertical arrows indicate clusters of bacilli. Fite-Faraco acid-fast stain. AFIP neg. 67-1673.

nerves, the murine bacillus only involved nerves when there had been a massive infection of all tissues including nerves. In searching for nerve involvement in skin lesions caused by mycobacteria, the pathologist therefore must distinguish primary from secondary nerve involvement.

In massive, typical epithelioid cell inflammatory lesions of tuberculoid leprosy most, and sometimes all, dermal nerves are destroyed beyond recognition. If remnants of incompletely destroyed nerves are present, acid-fast bacilli usually are not difficult to find. The number of bacilli observed in nerves is usually in inverse relation to the extent of damage of nerves.

In massive, atypical epithelioid cell inflammatory lesions of the skin in borderline leprosy, many dermal nerves are partially preserved and contain acid-fast bacilli. Outside of nerves in this form of leprosy acid-fast bacilli are often noted in macrophages.

In massive mycobacterial epithelioid cell inflammatory lesions of the skin that are not caused by M. leprae, some well-preserved nerves are usually found easily in the lower dermis but they do not contain bacilli. Only, as was observed in our experimental studies of murine leprosy, nerves overgranulomatous whelmed by massive infiltrate may contain acid-fast bacilli but they are more numerous in the infiltrate outside the nerve than within the nerve. In fact, even in such severe cases, the observation of acid-fast bacilli within the nerves is very rare.

Conspicuous leprotic nerve involvement versus inconspicuous leprotic nerve involvement. Although nerves apparently are the *loci minores resistentiae* for *M. leprae* in tuberculoid leprosy, histologic nerve involvement is not conspicuous in all biopsy specimens of otherwise typical tuberculoid leprosy skin lesions. The lesions of tuberculoid leprosy in which dermal nerves generally appear well-preserved and the inflammatory infiltrate is not obviously localized around nerves are probably relatively young (Figs. 5, 6, 7).

In cases of inconspicuous involvement of dermal nerves, the greater part of the inflammatory infiltrate is observed in the superficial dermis, above the level of the sebaceous glands. A narrow rim of uninvolved dermal tissue is usually noted at several places between the inflammatory infiltrate and the overlying epidermis. Acid-fast bacilli, often solidly stained, are usually easily found in these subepidermal zones. Some nerves, adjacent to or surrounded by inflammatory infiltrates but usually appearing well-preserved, contain occasional acid-fast bacilli.

In cases of tuberculoid leprosy with prominent involvement of dermal nerves, inflammatory infiltrate is usually noted in all levels of the dermis. In contrast to lepromatous leprosy, superficial inflammatory infiltrates do not spare the subepidermal zone but typically encroach on the basal cells of the epidermis. A subepidermal clear zone is usually observed focally in borderline leprosy. In most instances the largest inflammatory infiltrates are located in the lower dermis around the nerves.

Klingmüller (7) reported the occurrence of acid-fast bacilli in the immediate subepidermal zone of the skin of patients with tuberculoid leprosy. He also suggested that in leprosy the bacilli from active lesions are seeded by the bloodstream and lodge in small vessels of the skin particularly those around small nerves and appendages.

Binford $(^3)$ demonstrated that inoculation of the dermis of ears of golden hamsters with *M. leprae* frequently produced histologic evidence of leprotic involvement of dermal nerves but generally not before one year after inoculation, although inflammatory infiltrate and evidence of multiplication of *M. leprae* was noted much earlier in several experiments. The invasion of nerves by *M. leprae* is a slow process.

To us it is resonable to assume that inconspicuous involvement of nerves in lesions of the skin of patients with tuberculoid leprosy may occur if *M. leprae* are seeded in the superficial, papillary dermis. Local proliferation of *M. leprae* will soon provoke a rather severe inflammatory response in the superficial dermis of persons who are allergic to the bacilli. In the meantime, *M. leprae* may have invaded tiny nerve twigs of the superficial dermis but the twigs cannot be recognized in routine tissue sections. At the time the superficial inflammatory infiltrate has become clinically visible, most nerves of the mid- and lower dermis are still not invaded. In a biopsy specimen of such a lesion, leprotic involvement of nerves will not be conspicuous.

On the other hand, lesions with evident histologic involvement of nerves at the time of biopsy may have originated from hematogenous seeding of M. leprae in the lower levels of the dermis, close to well recognizable dermal nerves, for example in the vicinities of the lower portions of hair follicles. Or, M. leprae may even have reached the skin by spreading along nerve twigs from a focus in a subcutaneous nerve trunk. In case of progression of a local infection of the skin the distinction between the two types may be obscure, as for example in Case 4. The observation of acid-fast bacilli in the subepithelial zone suggests however, that the infection orginated in the superficial dermis.

Tuberculoid leprosy versus borderline leprosy. Once the pathologist has recognized leprotic involvement of nerves in a biopsy specimen of the skin, the distinction between tuberculoid leprosy and borderline leprosy is usually not difficult in epithelioid cell inflammatory lesions.

In tuberculoid leprosy, nerves invaded by M. leprae are severely damaged and soon destroyed beyond recognition; epithelioid cells with occasional Langhans' giant cells form the centers of most inflammatory infiltrates. There are varying numbers of lymphocytes in the peripheral portions of the inflammatory infiltrates; bacilli are difficult to find, except during phases of severe reaction characterized by conspicu-OUS plasmacellular and lymphocytic infiltrate around epithelioid cell foci. Typically in tuberculoid leprosy which is not reactive, the inflammatory infiltrates are usually well-circumscribed with clear-cut boundaries.

In borderline leprosy, the dermal nerves, although invaded by *M. leprae*, are usually not destroyed beyond recognition; infiltrates of nonspecific histiocytes are often noted next to the epithelioid cell infiltrates; bacilli are easily found in nerves and often also in inflammatory cells; occasional globi may occur; the inflammatory infiltrate is often massive with vague borders; lymphocytes and plasma cells are not numerous.

The pathologist, however, should realize that his interpretation of a small portion of a lesion may not be in full agreement with the opinion of the clinician, who must make his classification on the sum total of all data available on the case.

LEGAL, SOCIAL, AND MEDICAL IMPLICATIONS OF A DIAGNOSIS OF LEPROSY

The pathologist who makes a definite diagnosis of leprosy on the examination of a biopsy specimen should be aware that several countries still enforce laws that limit the opportunities for work and for movements of leprosy patients and compel their treatment in leprosaria. A diagnosis of leprosy may therefore incur severe financial loss to the patient even if he is not disabled. It is a general practice that a diagnosis of leprosy may require immediate discharge from a military service.

In spite of the greatly improved prognosis for the leprosy patient that has resulted from the use of effective sulfone drugs and the efforts of enlightened health officials to integrate leprosy with other controllable infectious diseases, the social status of a known leprosy patient, or a patient suspected of having leprosy, is not enviable in many communities.

Once a definite diagnosis of leprosy has been made, treatment with drugs is indicated and lifetime use of the drug is often recommended in order to prevent relapse of the disease.

A pathologist should never make or confirm a suspected diagnosis of leprosy upon evidence other than that obtained from his own examination. In case of doubt, proposal of the examination of another biopsy specimen or consultation of another pathologist is often far better for the sake of the patient than to report a diagnosis as "consistent with leprosy." Suspicion of leprosy can be reported verbally to the clinician. Both the pathologist and the clinician should not be reluctant to consult their colleagues with experience in leprosy if they are inexperienced in the disease, even if there is little or no doubt about the diagnosis.

Pathologists, of course, should be aware of the possible legal implications that may arise from 1) missing an obvious diagnosis of leprosy, and 2) making an erroneous diagnosis of leprosy.

SUMMARY

Increasing awareness among pathologists that international travel requires that leprosy be considered as a diagnostic possibility in lesions of the skin or nerves, results in a significant number of cases of possible leprosy being sent in consultation to the Armed Forces Institute of Pathology.

When leprosy is considered as a clinical possibility a specimen of active lepromatous leprosy should present no great problem to the pathologist. Lesions demonstrating an epithelioid cell granulomatous reaction, however, require very careful histopathologic study in order to differentiate leprosy from other skin conditions characterized by an epithelioid cell granulomatous reaction.

In an effort to pinpoint the histopathologic characteristics of tuberculoid leprosy and compare it with sarcoidosis and nonleprotic mycobacterial granulomas of the skin, histopathologic lesion profiles from low power photomicrographs were prepared from illustrative cases to depict the pattern of infiltration and the relationship of the infiltrate and bacilli to nerves.

In our study two patterns of distribution of the histopathologic changes in tuberculoid leprosy emerged. In one the distribution of the infiltrate followed the large and small dermal nerves which were usually totally or subtotally destroyed and bacilli, if found, were usually at sites of destroyed nerves or in remnants of persisting nerves. In the second in which the infiltrate was prominent in the superficial dermis bacilli were usually seen in the subepidermal zone and in nerves that were not yet involved by infiltrate; perineural distribution of the infiltrate was not conspicuous.

The study emphasizes the peculiar predilection of *Mycobacterium leprae* for nerves.

RESUMEN

El hecho de que los patólogos estén cada día más conscientes de que los viajes internacionales requieren que la lepra sea considerada como una posibilidad diagnóstica en lesiones de la piel o de los nervios, ha dado como resultado el que un número significativo de casos posibles de lepra sean enviados en consulta al Armed Forces Institute of Pathology.

Cuando se considera que la lepra es una de las posibilidades clínicas, una biopsia de lepra lepromatosa activa no debiera significar un gran problema para el patólogo. Sin embargo, las lesiones que muestran una reacción granulomatosa de células epitelioides requiren un estudio histopatológico muy cuidadoso para poder diferenciar entre lepra y otras enfermedades de la piel caracterizadas por una reacción granulomatosa con células epiteliodes.

Con el propósito de describir minuciosamente las características histopatológicas de la lepra tuberculoide, comparándola con la sarcoidosis y granulomas no lepróticos de la piel producidos por micobacterias, se prepararon esquemas de lesiones histopatológicas a partir de microfotografías con pequeño aumento de casos ilustrativos, para demostrar el tipo de infiltración y la relación del infiltrado y de los bacilos con los nervios.

De nuestro estudio se obtuvo evidencia de que existían dos modelos de distribución de las alteraciones histopatológicas producidas por la lepra tuberculoide. En uno de ellos la distribución del infiltrado seguía los nervios dérmicos mayores y menores, que por lo general estaban destruídos en forma total o subtotal, los bacilos, si se encontraban presentes, por lo general se ubicaban en los sitios donde habían estado los nervios destruidos, o en los restos de nervios que aún persistían. En el segundo modelo, en el cual el infiltrado era prominente en la dermis superficial, se observaban por lo general bacilos en la zona subepidérmica y en los nervios que aún no estaban atacados por el infiltrado; la distribución perineural del infiltrado no era demasiado evidente. Este estudio pone de relieve la especial predilección del Mycobacterium leprae por los nervios.

RÉSUMÉ

Les pathologistes sont de plus en plus conscients du fait qu'à la suite des voyages internationaux, la lèpre doit être considérée comme un diagnostic possible en cas de lésions nerveuses ou cutanées. En conséquence, un nombre notable de cas suspects de lèpre sont envoyés en consultation à l'Institut de Pathologie des Forces Armées. (Armed Forces Institute of Pathology).

Lorsque la lèpre est considérée comme un diagnostic clinique possible, l'examen d'une préparation de lèpre lépromateuse active ne devrait pas soulever de grave problèmes pour le pathologiste. Toutefois, la présence de lésions indiquant une réaction granulomateuse à cellules épithélioides, exige une étude histopathologique très soigneuse, afin de distinguer la lèpre des autres conditions cutanées caractérisées par une réaction de ce type.

Une étude a été menée, afin de mettre en évidence les caractéristiques histopathologiques de la lèpre tuberculoide, et de les comparer avec celles relevées dans la sarcoidose et dans des granulomes cutanés d'origine mycobactérienne non lépreuse. Les caractéristiques histopathologiques des lésions, telles quelles apparaissent sur des photomicrographies à faible agrandissement, à partir de cas démonstratifs, ont été passées en revue, afin de montrer le schéma d'infiltration, de même que la relation entre l'infiltrat des bacilles d'une part et les nerfs d'autre part.

Au cours de cette étude, deux schémas sont apparus en ce qui concerne la distribution des modifications histopathologiques dans la lèpre tuberculoide. Dans l'un de ces schémas, la distribution des infiltrats suivait les nerfs dermiques, gros et petits, qui étaient généralement totalement, ou presque totalement, détruits. Les bacilles, quand ils étaient présents, se trouvaient généralement à l'endroit des nerfs détruits, ou dans les vestiges des nerfs encore présents. Dans le second schéma, caractérisé par le fait que l'infiltrat prédominait dans le derme superficiel, les bacilles étaient généralement observés dans la zone sousépidermique et dans les nerfs qui n'étaient pas encore atteints par l'infiltrat. La distribution périneurale de l'infiltrat n'était pas bien marquée.

Cette étude souligne la prédilection particulière de Mycobacterium leprae pour les nerfs.

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