SESSION 4—12 MAY 1965

Dr. Binford. I would like to introduce Dr. Robert E. Stowell, Scientific Director of the Armed Forces Institute of Pathology, who has given us much support in our leprosy program. Dr. Stowell will introduce the next speaker.

Dr. Stowell. In March 1963 it was my pleasure to travel in South India, where I visited the Christian Medical College in Vellore. I was very much impressed with the activities in the Department of Pathology there and the new professor of pathology, who had been chosen to be the future chairman of the department. I also went 14 miles away to the Scheiffelin Leprosy Research Sanatorium, where, again, I was much impressed by the work I saw, as well as by their medical superintendent, their pathologist and their chief investigator. Now all of these people, as you might guess, were one person, Dr. C. K. Job, who is our speaker this afternoon. He visited us when he was in the States, and spent two months at the Armed Forces Institute of Pathology in April and May 1964. We are glad to have him back again at this time and to speak to us this afternoon on "An outline of the pathology of leprosy."

An Outline of the Pathology of Leprosy

C. K. Job, B.Sc., M.D.

The subject assigned to me is not easy to cover within the time available. I shall try therefore to lay before you simply a bare outline of the morbid anatomy of leprosy. Leprosy is considered an infectious disease, although it has not fulfilled all of Koch's postulates. Do we have enough evidence to say that the leprosy bacillus in the form known to us is infective? The portal of entry of the infecting organism in the human body is still not known definitely. The three possible paths of entry are through the skin, the respiratory passages, and the gastro-intestinal tract. It is probable that in most cases infection is contracted through the skin.

Leprosy is essentially a disease of the peripheral nerves. Some patients are seen with involvement of peripheral nerves only, but no case is yet reported in which the nerve tissue is not involved at all.

Leprosy is manifested in a variety of forms. It may be limited to a small hypopigmented patch in the skin or it may be a generalized systemic disease. It may cause no discomfort at all, or may induce varying degrees of pain, deformity and disfigurement.

THE INDETERMINATE FORM OF LEPROSY

The most common initial symptom in leprosy is an area of numbness or a hypopigmented patch in the skin (Fig. 1). Biopsy of the skin in this area shows perivascular infiltration with small round cells, chiefly in the corium (Fig. 2). There is also obvious perineural inflammation (Fig. 3). The Schwann cells are numerous and appear swollen. Careful search in properly stained sections reveals acid-fast bacilli inside the nerve bundles. This is called the indeterminate lesion in leprosy. The indeterminate lesion is most probably the primary lesion and can be compared to the...
primary complex in tuberculosis. It may pass off unnoticed or may remain as a smouldering infection for some time, with ultimate healing, or may pass on into the other forms of the disease.

THE TUBERCULOID TYPE

The tuberculoid type of leprosy is essentially a localized disease involving a single nerve trunk or a small area in the skin. The lesion is well circumscribed, with a clearly defined border (Fig. 4). The maximum tissue reaction is seen at the edge of the lesion. There is considerable tissue resistance, and the disease is largely self-limited.

In many instances it heals without any treatment. Biopsy of the lesion shows patchy atrophy of the epidermis. There is a severe inflammatory reaction, the inflammatory cells reaching up to the epidermis. They consist mostly of epithelioid cells, with, in addition, Langhans' giant cells and collections of lymphocytes (Fig. 5). The

---

**Fig. 1.** Indeterminate leprosy. A hypopigmented patch on the right arm.

**Fig. 2.** Indeterminate leprosy. Focal collections of lymphocytes in the corium, especially around skin appendages.

**Fig. 3.** Indeterminate leprosy. Small nerve bundle in the corium showing perineural inflammation with lymphocytes.
nerve bundles are most severely infiltrated. There is marked perineural thickening and intraneural infiltration with epithelioid cells and lymphocytes (Fig. 6). In some there is total destruction of the nerve tissue, with caseous necrosis. The inflammation of the nerve may be of the Schwann cells or the axons or both, and therefore the nerve bundle itself is invaded by the inflammatory cells. Evidence now available suggests that the inflammation may be represented largely by the Schwann cells.

In some patients, for some unknown reason, the bacilli in the original lesion proliferate and become so numerous as to be demonstrable in routine smears taken from the lesion. This phase may be followed by spread through the lymph and blood streams, causing many similar lesions of varying size in different parts of the body. Histologically these lesions are not greatly different from the classic tuberculous picture. There is atrophy of the epidermis. Dense collections of epithelioid cells and giant cells forming tubercles are seen. The inflammatory reaction in these cases is marked by a pronounced increase in cellularity and tissue edema. Unlike the picture in the classic tuberculous lesions, many intracellular organisms are present.

During this phase microgranulomata are found in other parts of the body. These are composed mostly of epithelioid cells. They have been demonstrated in the liver, lymph nodes, and testis. Bacilli are present in these lesions also, but are seen only after prolonged and careful search.

The tuberculoid type of leprosy compares closely with reinfection or postprimary tuberculosis, in which the body possesses a certain capacity to limit the disease and take care of it through its own defense mechanisms. There is considerable tissue immunity, as proven by the natural history of this form of the disease.

THE BORDERLINE FORM

In the borderline group of cases, even though there is an attempt to localize the disease, it is highly inadequate. Therefore the disease spreads extensively in the skin, nerves, and other parts of the body. In many cases a large portion of the skin and most of the peripheral nerves are affected. There is a border to these lesions, but it merges gradually with the surrounding skin. The lesions are chiefly in the form of plaques, which are generalized and symmetric (Fig. 7). The peripheral nerve
FIG. 7. Borderline leprosy. Symmetric raised patches with indefinite borders over the buttocks, a very large raised patch over the back, and many small raised patches of various sizes all over the body.

FIG. 6. Tuberculoid leprosy. A nerve bundle in the corium infiltrated by epithelioid cells and giant cells and almost entirely destroyed.

FIG. 8. Lepromatous leprosy. Nodular lesions over the face and diffuse infiltration of the entire skin.
trunks, i.e., posterior tibial, lateral popliteal, radial, median, ulnar, and facial, are infected.

Biopsy of the skin lesion shows an atrophic epidermis with dense collections of inflammatory cells consisting of a mixture of epithelioid cells and collections of foamy macrophages. The small nerve bundles in the skin also show a varied picture, some with perineural and others with intraneural inflammation. In an occasional case the intraneural inflammatory reaction may be so severe as to induce caseous necrosis.

Microgranulomata, consisting chiefly of epithelioid cells, are noted in the liver, lymph nodes, and testes. Acid-fast bacilli may also be seen in these lesions.

The borderline type of leprosy may be compared to the fibrous caseous form of tuberculosis. Although there is some tissue resistance and an attempt to localize the disease, the effort by the defense mechanism is inadequate, with the result that the disease spreads locally through the lymphatics and blood stream. The inflammatory reaction is so intense and widespread that the most severe forms of deformity are seen in this type of the disease.

THE LEPROMATOUS TYPE

The lepromatous type of case is the one in which the bacilli have found the best host. There is no obvious injury to the host or the parasite for a significantly long period. Once the initial infection is established, the patient does not show any apparent defense reaction to bacilli until the disease is fully established. The organism spreads and affects every part of the skin and (Fig. 8) almost all the peripheral nerves. Except for some numbness and tingling in the extremities, the patient is apparently normal and does not complain.

Section of the skin shows an atrophic, flattened epidermis, with a clear area separating a sheet of macrophages. There are rows and rows of bacillus-filled sacs piled one over the other (Fig. 9). The small nerve bundles are surrounded by foamy macrophages and there is perineural thickening (Fig. 10). The Schwann cells appear swollen and are often distended with bacilli. Strangely enough, the Schwann cells that have engulfed the bacilli seem none the worse for it. The bacilli seem to proliferate inside them, and apparently by sheer increase in their number the Schwann cells are disrupted. The organisms thus released may be taken up by other Schwann cells or macrophages. The nerve tissue thus destroyed is replaced by fibrous tissue, giving rise to an onion peel appearance. In the course of time there is hyalinization, and the entire nerve bundle is replaced by hyalinized fibrous tissue.

Paralysis of nerves is slow in appearance and insidious, except when there is a sudden exacerbation of the disease or occurrence of erythema nodosum.

The lepromatous type of leprosy is comparable to the forms of childhood tuberculosis in which there is little resistance to the multiplication of bacilli and to extension of the disease. The infection marches on to involve the entire organs of attack, which in leprosy are the peripheral nerves and skin.

LEPROSY OF THE RETICULO-ENDOTHELIAL SYSTEM

In lepromatous leprosy the reticulo-endothelial system is extensively involved. The lymph nodes contain large collections of
foamy macrophages filled with bacilli (Fig. 11). Sometimes a large portion of a lymph node may be replaced by lepromatous granulomata. The inguinal, supratrochlear, axillary, and cervical lymph nodes are commonly involved. Occasionally lesions are seen in the external and internal iliac nodes.

The bone marrow shows infiltration with bacillus-filled macrophages. The spleen contains granulomatous lesions consisting of bacillus-filled macrophages. The Kupffer cells of the liver are prominent and contain bacilli. In addition there are many microgranulomata composed of foamy macrophages (Fig. 12). The granulomata in these lesions are growing ones, and the bacilli in them are morphologically the same as those seen in the skin.

LEPROSY OF THE NOSE

The mucous membrane of the upper respiratory tract is a very common site of inflammation. The subepithelial tissue is infiltrated with foamy macrophages and bacilli inside these cells are very well preserved. Often the infiltration of the mucous membrane may be so massive as to destroy the mucous glands. There is crust formation and ulceration of the epithelial
LEPROSY OF THE EYE

Lepromatous leprosy is properly called the "surface disease." Mostly the anterior portion of the eye is affected by the disease. Episcleritis, keratitis, and iridocyclitis are the common lesions encountered. There are nodular lesions consisting almost entirely of macrophages distended with bacilli. Repeated examination of the optic nerve has failed to show the presence of any granuloma or bacilli.

LEPROUS OSTEOMYELITIS

The small bones of the hand may show leprous osteomyelitis causing necrosis and caries of the bone. Histologically there is invasion of the bone trabeculae and osteoid tissue by foamy cells containing bacilli. In one case seen the synovial membrane of
an adjacent joint was invaded by leprous granulomata.

**LEPROUS ORCHITIS**

The testis is affected in leprosy with destruction of the parenchyma, resulting in loss of function. There is infiltration of the seminiferous tubules and interstitial tissue by bacillus-filled macrophages, plasma cells, and lymphocytes (Fig. 13). The end result is atrophy and hyalinization of the seminiferous tubules. In a small proportion of the patients the interstitial cells are preserved and apparently hyperplastic. Gynecomastia is noted in 11 per cent of the patients (Fig. 14).

**ERYTHEMA NODOSUM**

No discussion on the pathology of leprosy is complete without mentioning erythema nodosum. Nearly 30 per cent of the lepromatous cases develop painful, tender, and erythematous nodules in the skin (Fig. 15). They are transient and appear almost always during the course of antileprosy treatment. Often they are accompanied by fever, polyarthralgia, and polyneuritis. The course may be mild or severe. Histologically the lesion shows the basic lepromatous granuloma infiltrated by polymorpho-
bacilli. It is now well known that tubercle bacilli in India are much less virulent than tubercle bacilli in Great Britain.

Leprosy is a fascinating disease. It presents several unsolved problems and therefore offers a great challenge to the medical scientist.

Cultivation of M. leprae

(Cont'd)

Chairman: R. J. W. Rees

Dr. Binford. Thank you very much, Dr. Job, for this brief but compact story of the pathology of leprosy. We have to apologize for giving you such a large assignment for 20 minutes, but you accomplished it well and I am sure that those of the audience who have not had the privilege of studying this disease gained much by it.

Stability of Mycobacterium leprae and Temperature Optimum for Growth

Charles C. Shepard, M.D.

Two general areas will be discussed that need to be considered in attempts to cultivate Mycobacterium leprae: first, the stability of M. leprae at different temperatures, and second, the temperature optimum of its growth.

The stability of the organism is a matter of special concern in leprosy research. Many of the research laboratories are located far from the sources of supply in the important leprosy endemic areas, so that clinical material must be shipped long distances at considerable trouble.

In the results to be described, viability was tested by the ability of M. leprae to multiply in mice. Such multiplication is,