PATHOGENESIS OF BONE CHANGES IN NEURAL LEPROSY [1]

JAMES BARNETSON, M. D. (Pretoria); M. B., CH. B. (Edinburgh), D. T. M. & H. (Witwatersrand)
From the Institute for Pathology, University of Pretoria Pretoria, South Africa

Theories regarding the pathogenesis of bone changes in neural leprosy are numerous. An extensive review of opinion up to 1909 was made by Hirschberg and Biehler (22). Amongst early views the following are of interest. Heiberg (21) considered that several factors could be of importance, including atrophy of pure neurotrophic type and processes secondary to the anesthesia such as necrotizing periostitis, formation of ulcers and gangrene. Savtschenko (45, 46, 47) held that bone resorption is caused through disturbance in nutrition and direct bacillary influence on bone cells. Nonne (35, 36, 37) stated that the mutilations and other trophic disturbances of leprosy could not be explained solely by mechanical influences on bones and soft parts, but that a functional disturbance or disease of corresponding segments of the spinal cord was of importance. This view was contested by Lie (31), who thought that changes in the spinal cord were dependent on lesions of the peripheral nerves.

Harbitz (18, 19) pointed out that changes similar to those of neural leprosy are seen after nerve lesions of various kinds, such as gunshot wounds causing destruction of peripheral nerves. He considered that the nerve lesions in leprosy cause neurotrophic disturbance with consequent atrophy of bone and other tissues, and that ulceration and other inflammatory processes develop secondarily to the anesthesia. Numerous other authors have described atrophic changes in bone similar to those of leprosy which occurred in various nervous, vascular and other conditions. Trophic disturbances due to leprous interstitial neuritis have been stressed as the essential factor in bone atrophy by numerous writers: Tarchini (50), Chamberlain, Wayson and Garland (8), Murdock and Hutter (33), de Josselin de Jong (24), Karaseff (25), Oberdoerffer and Collier (38), Faget and Mayoral (14), Cooney and Crosby (9).

Changes in blood chemistry have been investigated in leprosy patients. Regarding serum calcium, information is confused

[1] This article has been abstracted from part of a thesis accepted by the University of Pretoria for the degree of M. D.

and diametrically opposite opinions have been expressed. Some authors, as Leman, Liles and Johansen (30), and Cruz, Lara and Paras (11), maintain that serum calcium is normal or usually so. Others, as Villela (52) and Badenoch and Byron (2), state that it is reduced. According to Wooley and Ross (53, 54), whilst total serum calcium may not be reduced there is reduction of diffusible calcium and increase of nondiffusible calcium.

Serum phosphorus in leprosy shows no significant changes, according to Wooley and Ross (53, 54). Ross (44) has found that the blood phosphatase is within normal limits in cases showing radiological evidence of bone absorption. That hyperglobulinemia is common has been reported by many workers, among them Stevenson (49), Frazier and Wu (16), Neill and Dewar (34) and Schlossman (48).

From these biochemical data it is concluded that alterations in blood chemistry have little if any effect on bone absorption in leprosy.

The importance of changes in the vascular supply to bones in neural leprosy has also been repeatedly mentioned, as by Hirschberg and Biehler (22), Murdock and Hutter (33), Oberdoerffer and Collier (38) and Cooney and Crosby (9); whilst infection, trauma, or altered mechanics in anesthetic extremities have been regarded as significant secondary factors, for example by Chamberlain, Wayson and Garland (8), Murdock and Hutter (33), Faget and Mayoral (14), Cooney and Crosby (9) and Rogers and Muir (43).

Before discussing their pathogenesis it is necessary to describe briefly the nature of the bone changes. The "basic bone lesion" will be described first. This is a convenient term to denote the pure form of atrophy occurring in the hands and feet in the early stages of evolution of the disease, before secondary factors have altered the picture. The radiological evolution of the basic bone lesion will be described, followed by a description of the corresponding histopathological changes. The pathogenesis of the basic bone lesion will then be discussed. After this, secondary bone changes will be described and their pathogenesis discussed. These are changes occurring in hands and feet due to fairly obvious secondary factors such as repeated trauma, infections, etc.

THE BASIC BONE LESION IN NEURAL LEPROSY

RADIOLOGICAL FINDINGS

The bone changes in neural leprosy as seen radiologically have been described repeatedly and have recently been summa-

rized by me (5), with a description of the pattern of evolution of these changes. Bone atrophy in neural leprosy is confined almost exclusively to small bones of the hands and feet. The earliest appreciable change is the development of minute nicks occurring always on distal margins of terminal phalanges. The nicks enlarge and the distal margin of the tuft of the phalanx becomes frayed in appearance. Later the tuft disappears, and the phalanx then consists of the base and part of the shaft. The shaft and finally the base undergo gradual resorption, and when they have disappeared the process starts in the more proximal bone. These changes take place without periosteal reaction, osteosclerosis or sequestrum formation unless there is secondary infection.

The basic process in bone atrophy in neural leprosy is thus seen to be a pure atrophy beginning at the most distal portions of terminal phalanges and proceeding proximally, slowly and undramatically, until phalanges and finally complete digits disappear.

Osseous changes in neural leprosy are almost always bilateral, but they are rarely symmetrical in the sense that corresponding digits on both sides are not always affected, and if affected are rarely found in the same stage of evolution. This lack of symmetry is obvious and can readily be appreciated by anyone who carefully studies roentgenograms of these cases.

HISTOPATHOLOGICAL FINDINGS

Few articles are available which describe the histopathological changes of the bones in neural leprosy. Harbitz (18, 19) described active osteoclastic absorption with depressions on the surface of the bone reaching deep into its substance. He found no sign of leprous osteomyelitis or periostitis, and noted that leprosy bacilli were not present in bone. de Josselin de Jong (24) investigated the tarsal bones of a neural case and stated that the cortex and spongiosa contained very few and very small trabeculae, irregularly distributed in an excess of fatty tissue. Somewhat similar changes were also described by Häupl (20).

I have recently (6) attempted to correlate the radiological and histopathological findings and to trace the evolution of the latter. In normal phalanges small gaps can frequently be seen in the cortical bone, and these are filled with connective tissue. In the stage of neural leprosy associated with fraying of the distal margins of phalanges, similar but larger and more numerous gaps, also filled with connective tissue, can be seen extending from the periosteum to the marrow cavity. The trabeculae of

the spongy bone become gradually scantier and more slender than normal. Later the marrow becomes myxomatous and finally undergoes progressive fibrosis, until little or no fatty marrow may be present. In bones which have undergone partial resorption the cortex remains of normal width up to the distal margin of the bone, except in the rare cases where there is a diffuse osteoporosis affecting several bones. Although Harbitz (19) described active osteoclastic resorption in his cases, I have only found it in a minority of mine.

PATHOGENESIS OF THE BASIC BONE LESION

After perusal of the literature and as a result of my own investigations I conclude that the significant factors in the pattern of the basic bone lesion are as follows: (*a*) The most peripheral parts of the most peripheral bones are affected primarily. (*b*) Only bones of the hands and feet are affected (with very few exceptions). (*c*) Bone lesions are bilateral but very rarely symmetrical. (*d*) Similar bone changes are seen in numerous other conditions, including lesions of peripheral nerves.

An invariable precursor of leprous osseous atrophy is leprous interstitial neuritis, and the degree of bone change is dependent on the extent and duration of the nerve damage. The precise relationship between nerve damage and bone atrophy is, however, a controversial matter. The pattern of the basic bone lesion and the nerve involvement suggest that circulatory disturbances might be of prime importance, and I have recently investigated this problem (3, 4).

Several authors have reported the results of sympathectomy for trophic ulcers of the feet in leprosy. Hyperemia and a feeling of warmth in the affected limbs were noted after the operation by Osawa and Nojima (39), Cruz, Abuel and Samson (10), Black (7), Marty (32) and Kirkaldy-Willis (26), and in some instances healing of the ulcers had occurred. Leitner (29), however, injected radio-opaque material into the anterior tibial artery of a female with leprous mutilation and perforating ulcer of the foot and demonstrated a rich and patent arterial network even as far as the ulcer. Faget and Mayoral (14), as a result of arteriographic studies in all types of leprosy, stated that arterial supply in extremities is not materially disturbed in neural leprosy. Various observers, by the means of the capillaroscope, have noted anomalies of skin capillaries in leprosy, as Tedesco and Mazzolenis (51), Komatsu (27) and Rivelloni (42).

By oscillometric methods, I failed to find any evidence of organic occlusion of arteries and larger arterioles of the wrist

and ankle regions in 37 neural cases presenting evidence of bone absorption (3). Using the skin-temperature thermometer, however, I found very definite circulatory anomalies. The vascular responses of the hands and feet to local cooling and local warming, as shown by the skin-temperature thermometer, corresponded closely to normal controls, but there was a marked failure of reflex vasodilatation (4). Reflex vasodilatation is measured by immersing a limb in water at 110-115°F. According to Richards (41), rise of skin temperature due to reflex vasodilatation will normally occur in the nonimmersed limbs in 7 to 20 minutes. The mechanism of this reflex response is still under discussion; cf. Gibbon and Landis (17), Pickering (40), Duthie and Mackay (12), Richards (41) and Allen, Barker and Hines (1). Warm blood returning from the heated limb may, however, be regarded as the afferent pathway of the reflex arc, and the sympathetic nerve fibers to limbs as the efferent pathway. As said, I have shown that, whereas dilatability of peripheral vessels in neural cases in response to local stimulation (warming or cooling) is not impaired, there is failure of reflex vasodilatation corresponding in degree to the extent of leprous neuritis and bone absorption.

This failure of reflex vasodilatation is assumed to be due to destruction of vasomotor fibers in the peripheral nerves by leprous neuritis, and it is of fundamental importance in the causation of the bone atrophy. The health and normality of the structure of any tissue depend not only on the basic circulation —which is assumed to be normal in the presence of a healthy general circulation and in the absence of organic occlusion of vessels—but also on the power of its blood channels to accommodate themselves to continual variations in the circumstances of the tissues. Changes in metabolism and in the amount of work done, changes evoked by trauma or by alteration of environment —these and many others require rapid and sometimes prolonged variations in the flow of blood to the tissue. These changes result normally from reflex vasomotor control of the vessels, and it is just this function which is impaired in neural leprosy. The degree of loss of vasomotor control depends on the degree of destruction of vasomotor fibers by the neuritis.

Bone atrophy has been shown to occur as result of various types of alteration of the blood flow. It is seen, for example, as a result of hyperemia as in Südeck's atrophy, as shown by Fontaine and Hermann (15). It has also, however, been shown to occur as a result of relative ischemia, as in senile atheroscle-

rosis and thromboangitis obliterans by Allen, Barker and Hines (1), in scleroderma by Edeiken (13), and in Raynaud's disease by Kornblum (28).

Bone atrophy in neural leprosy thus probably occurs as a result of failure of the blood vessels supplying the bones to adapt themselves to the everchanging requirements of an extremely active and labile tissue. This circulatory anomaly so alters the bone tissue that absorption becomes a more dominant process than deposition, and consequently the bone becomes gradually absorbed. The lack of symmetry in the bilateral lesions is obviously due to the chance involvement of some and sparing of other vasomotor nerve fibers by the bilateral leprous neuritis.

As bone absorption is always due to osteoclasts, an explanation must be found for the fact that osteoclasts are not always seen in partially absorbed bones. That they are found in some cases has been shown by Harbitz (19) and myself (6) and others. Bone atrophy in neural leprosy is an extremely slow and undramatic process. Probably on account of this extreme chronicity, osteoclastic resorption occurs either intermittently or on such a small scale that osteoclasts are frequently very scanty or even absent for varying periods.

SECONDARY BONE CHANGES AND THEIR PATHOGENESIS

Apart from the basic bone lesion already described, other bone changes are common in neural leprosy, and they can usually be related to fairly obvious secondary factors.

Although bone absorption invariably begins along distal margins of distal phalanges, it is frequently more advanced in more proximal bones even in the absence of secondary infection. In the feet this is seen in bone surfaces adjacent to the metatarsophalangeal joints. This is one of the areas of the foot which has to bear the brunt of the body weight in standing or walking. As has been indicated by several authors this leads to innumerable minor traumata which, in insensitive tissues, lead to bone absorption. A similar process is seen in the hands when flexion deformities have occurred. The bone surfaces adjacent to rigid, insensitive, flexed joints undergo repeated traumatism due to continual knocking against various objects. This leads to absorption of bone surfaces adjacent to interphalangeal or metacarpophalangeal joints.

The fact that absorptive changes are usually more advanced in the bones of the foot than those of the hands can be explained by the fact that trauma of weight bearing is more constant and

more intense than the trauma to which the fingers are subjected.

Pathological fractures occur in neural leprosy, but they are uncommon. They are probably due mainly to concentric atrophy of shafts of short long bones, or to trauma. An appearance closely simulating pathological fracture and possibly at times confused with it is, however, frequent. This appearance is due to absorption of bone at adjacent surfaces of joints. When the articular surfaces and parts of the shafts of the two bones forming a joint have been absorbed, the appearance closely simulates a fracture. It occurs in connection with interphalangeal or metatarso- or metacarpophalangeal joints.

Concentric atrophy of shafts of metatarsals, metacarpals and proximal phalanges is common. It is characterized by gradual narrowing of the shaft but without osteoporosis demonstrable radiologically or histologically. The precise histogenesis of this condition and of the rather rare finding of diffuse osteoporosis in multiple bones of hands or feet is not clear.

Disuse or relative disuse of a limb resulting from varying degrees of paresis of muscles of hands and feet has also been suggested by various writers as a causal factor in bone atrophy. Oberdoerffer and Collier (38) suggested that inactivity of the related muscles may result in decreased blood supply to bones.

The alleged bilateral symmetry of osseous changes in neural leprosy has occasionally evoked arguments in favor of the view that lesions of the central nervous system are the prime factor concerned, as by Nonne (35, 36, 37), Hirschberg and Biehler (22), and Cooney and Crosby (9). As has already been indicated the lesions, although nearly always bilateral, are rarely symmetrical. The fact that peripheral neuritis in neural leprosy is nearly always bilateral is sufficient to account for the bilaterality of bone changes. The relative asymmetry is, as said, due to chance destruction of various fibers in affected peripheral nerves.

Secondary infection frequently causes further bone changes in neural leprosy. Such changes as acute periostitis, osteomyelitis and sequestrum formation can commonly be seen radiologically or histologically.

Secondary infection is of common occurrence in the soft tissues of the insensitive hands and feet, and even when there is no sign of secondary infection of bone it is possible that prolonged hyperemia caused by the infection may lead to some bone resorption similar to that seen in Südeck's atrophy. A remarkable series of cases characterized by advanced absorption of bones of the feet and apparently related in some instances to

pyogenic infection of the soft tissues but not of the bones has recently been published by Hodgson, Pugh and Young (23), and lends some support to this view.

SUMMARY

The literature of the pathogenesis of bone atrophy in neural leprosy is briefly reviewed.

Alterations in blood chemistry are probably of no importance in the causation of the bone changes.

The pattern of bone atrophy as seen by the author is discussed. It is indicated that there are two principal types of pattern: (1) the "basic bone lesion," where atrophy always begins on distal margins of the most distal bones of hands or feet and proceeds proximally, this being essentially the so-called "neurotrophic" atrophy, and (2) secondary bone lesions, in which further bone absorption can usually be related to fairly obvious secondary factors such as trauma.

The pathogenesis of bone atrophy in neural leprosy is discussed. It is indicated that the atrophy of the basic bone lesion varies in accordance with the degree and duration of peripheral nerve damage due to leprous interstitial neuritis, which leads to destruction of vasomotor fibers. As shown by the author this causes failure of reflex vasomotor responses in vessels supplied by these nerves, and it is considered that this failure is the essential factor in the bone atrophy.

The factors concerned in the secondary bone changes are discussed. It is indicated that repeated trauma to insensitive bones and joints is of major importance, and that pyogenic infection of soft tissues, as well as and apart from pyogenic osteomyelitis, may be of consequence.

RESÚMEN

El autor hace un breve análisis de la literatura relaciónada con la patogénesis de la atrofia ósea en lepra del tipo neural.

Alteraciones en la química de la sangre probablemente no juegan papel de importancia en la causa de los cambios óseos.

El autor discute su interpretación de los cambios en el cuadro de atrofia ósea e indica que hay 2 tipos principales: 1) la "lesión básica" donde la atrofia siempre comienza en el margen distal de los huesos distales de las manos y los pies, y progresa proximálmente, causando el cambio conocido como "atrofia neurotrófica," y 2) lesiones óseas secundarias en las cuales reabsorción subsiguiente del hueso puede relacionarse fácilmente con factores secundarios tales como trauma.

El autor discute la patogénesis de la atrofia ósea en lepra neural y observa que la atrofia ósea del tipo básico varía de acuerdo con el grado y la duración de los daños a los nervios periferales como ocurre en la neuritis leprosa interesticial, la que culmina con la destrucción de las fibras vasomotoras. El autor demuestra como ésto cáusa la falla en los reflejos vasomotores en los vasos enervados por éstas fibras nerviosas, y considera que éste es el factor esencial en la atrofia ósea.

También discute los factores relacionados con los cambios óseos secundarios. Trauma a los huesos y articulaciones insensibles es de la mayor importancia, y la infección piogénica de los tejidos blandos ademas de la osteomielitis, pueden ser también de gran consecuencia.

REFERENCES

1. ALLEN, E. V., BARKER, N. W. and HINES, E. A. Peripheral Vascular Diseases. Philadelphia and London; W. B. Saunders Company, 1946.
2. BADENOCH, A. G. and BYRON, F. E. The calcium content of the blood serum in some cases of leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **26** (1932) 253.
3. BARNETSON, J. Oscillometric studies in neural leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **43** (1950) 535.
4. BARNETSON, J. Skin temperature studies in neural leprosy. Trans. Roy. Soc. Trop. Med. & Hyg. **43** (1950) 539.
5. BARNETSON, J. Osseous changes in neural leprosy; radiological findings. Acta Radiol. **34** (1950) 47.
6. BARNETSON, J. Osseous changes in neural leprosy; correlation between histopathological and radiological findings. Acta Radiol. **34** (1950) 47.
7. BLACK, K. Periarterial sympathectomy for the ulcerations of leprosy. Malayan Med. J. **8** (1933) 60 (*abstract*, Trop. Dis. Bull. **30** (1933) 558).
8. CHAMBERLAIN, W. E., WAYSON, N. E. and GARLAND, L. H. The bone and joint changes of leprosy; a roentgenologic study. Radiology **17** (1931) 930.
9. COONEY, J. B. and CROSBY, E. H. Absorptive bone changes in leprosy. Radiology **42** (1944) 14.
10. CRUZ, M. C., ABUEL, J. I. and SAMSON, J. G. Periarterial sympathectomy in trophic ulcers of leprosy. J. Philippine Islands Med. Assoc. **11** (1931) 474 (*abstract*, Trop. Dis. Bull. **29** (1932) 549).
11. CRUZ, M. C., LARA, C. B. and PARAS, E. Blood calcium in leprosy. J. Philippine Islands Med. Assoc. **8** (1928) 216 (quoted by Villela).
12. DUTHIE, J. J. R. and MACKAY, R. M. I. Vasomotor reflexes in the control of body temperature in man. Brain **63** (1940) 295.
13. EDEIKEN, L. Scleroderma with sclerodactylia. American J. Roentgen. **22** (1929) 42.

14. FAGET, G. H. and MAYORAL, A. Bone changes in leprosy; a clinical and roentgenologic study of 505 cases. Radiology **42** (1944) 1.

15. FONTAINE, R. and HERRMANN, L. G. Post-traumatic painful osteoporosis. Ann. Surg. **97** (1933) 26.

16. FRAZIER, C. N. and WU, H. Blood serum globulin in leprosy. American J. Trop. Med. **5** (1925) 297.

17. GIBBON, J. H. and LANDIS, E. M. Vasodilatation in the lower extremities in response to immersing the forearms in warm water. J. Clin. Invest. **11** (1932) 1019.

18. HARBITZ, F. Om die Patologisk-anatomiske foranderinger af neurotrofisk oprindelse. Christiania, A. W. Brøggers Bogtrykeri, 1900.

19. HARBITZ, F. Trophoneurotic changes in bones and joints in leprosy. Arch. Int. Med. **6** (1910) 147.

20. HAÜPL, C. Beitrag zur Kenntnis des Knochenschwundes bei Lepra. Acta Path. et Microbiol. Scandinavica (1930) Suppl. 5, p. 35.

21 HEIBERG, H. Om lepra mutilans og trophoneurotiske forandringer ved spedalskhed. Klin. aarborg 1886 iii (quoted by Harbitz, 1900).

22. HIRSCHBERG, M. and BIEHLER, R. Lepra der Knochen. Dermat. Ztschr. **16** (1909) 415 and 490.

23. HODGSON, J. R., PUGH, D. G. and YOUNG, H. M. Roentgenologic aspect of certain lesions of bone; neurotrophic or infectious. Radiology **50** (1948) 65.

24. DE JOSSELIN DE JONGH, R. Over tropo-neurotische atrofie in beenderen (naar aanleiding van een onderzoek van organen bij een lijder aan lepra mutilans). Nederländsche Tijd. v. Geneesk. **78** (1934) 1720.

25. KARASEFF, J. Aspect radiographique des manifestations osteo-articulaires dans la lèpre. J. de Radiol. et d'Electrol. **20** (1936) 373.

26. KIRKALDY-WILLIS, W. H. Sympathectomy in leprosy. East African Med. J. **22** (1945) 88.

27. KOMATSU, S. Dermatoscopische Untersuchungen über die Kapillarschlinge in der leprosen Haud. Japanese J. Dermat. & Urol. **41** (1937) 13 (*abstract*, Internat. J. Leprosy **5** (1937) 542).

28. KORNBLUM, K. Bone changes in Raynaud's disease as revealed by the roentgen ray. American J. Roentgen. **21** (1929) 448.

29. LEITNER, A. J. Les osteo-arthropathies lèpreuses du pied. Internat. J. Leprosy **6** (1938) 471.

30. LEMAN, I. I., LILES, R. J. and JOHANSEN, F. A. Blood serum calcium in leprosy. American J. Trop. Med. **7** (1927) 61.

31. LIE, H. P. Lepra im Rückenmark und den peripheren Nerven. Bergen, 1904 (quoted by Hirschberg and Biehler).

32. MARTY, J. La sympathectomie péri-artérielle dans le traitement des ulcères de la lèpre nerveuse. Bull. Soc. Path. exot. **31** (1938) 199 (*abstract*, Trop. Dis. Bull. **35** (1938) 556).

33. MURDOCK, J. R. and HUTTER, H. J. Leprosy; a roentgenological survey. American J. Roentgen. **28** (1932) 598.

34. NEILL, M. and DEWAR, M. Plasma proteins in leprosy. Publ. Hlth. Bull. **168** (1927) 4.

35. NONNE, M. Jahrb. d. Hamburger. Stadtkrankenhausen 1892, Bd. VI (quoted by Hirschberg and Biehler).

36. NONNE, M. Fortschr. a.d. Geb. D. Röntgenstr. 1900-1901, Bd. V. (quoted by Hirschberg and Biehler).

37. NONNE, M. Lepra **5** (1905) 22-69 (quoted by Hirschberg and Biehler).

38. OBERDOERFFER, M. J. and COLLIER, D. R. Roentgenological observations in leprosy. American J. Roentgen. **44** (1940) 386.

39. OSAWA, Y. and NOJIMA, T. Sympathektomie an Leprakranken. Deutschen Med. Wchnschr. **53** (1927) 65.

40. PICKERING, G. W. Vasomotor regulation of heat loss from human skin in relation to external temperature. Heart **16** (1932) 115.

41. RICHARDS, R. L. The Peripheral Circulation in Health and Disease. Edinburgh: E. & S. Livingstone Ltd., 1946.

42. RIVELLONI, G. Ricerche morfologiche a funzionali sul sistema capillare cutaneo nella lepra. Giorn. italiana Dermat. e Sifilol. (1938) 281.

43. ROGERS, L. and MUIR, E. Leprosy. Bristol: John Wright & Sons Ltd., 1946.

44. ROSS, H. Serum phosphatase in leprosy. Internat. J. Leprosy **9** (1941) 57.

45. SAVTSCHENKO. Wratsch, 1887, No. 17 (quoted by Hirschberg and Biehler).

46. SAVTSCHENKO. Centralbl. f. Bakteriol. (etc.) 1889, No. 18 (quoted by Hirschberg and Biehler).

47. SAVTSCHENKO. Beitr. z. path. Anat. 1890 (quoted by Hirschberg and Biehler).

48. SCHLOSSMANN, K. Ueber Gleichwichtstorungen der Eiweisskorper im Bludserum Leproser. Ztschr. Immunitf. **68** (1930) 154 (quoted by Villela).

49. STEVENSON, W. D. H. Complement deviation and globulin content in the blood of the lepers. Indian J. Med. Res. **12** (1925) 583.

50. TARCHINI, P. Contributo allo studio delle lesioni osee nella lepra anestetica. Giorn. italiana Dermat. e Sifilol. **66** (1925) 451.

51. TEDESCO, P. A. and MAZZOLENIS, U. Prime ricerche di capillariscopia nella lepra. Giorn. Clin. Med. **6** (1925) 175 (*abstract*, Trop. Dis. Bull. **22** (1925) 579).

52. VILLELA, G. G. The biochemistry of leprosy; a review. Internat. J. Leprosy **6** (1938) 61 and 223.

53. WOOLEY, J. G. and ROSS, H. Phosphorus, total calcium and diffusible calcium content of the blood sera of lepers and their relation to bone changes. Publ. Hlth. Rep. **46** (1931) 641.

54. WOOLEY, J. G. and ROSS, H. Calcium, phosphorus and protein metabolism in leprosy. Publ. Hlth. Rep. **47** (1932) 380.