

Pathogenesis of Extremity Deformity in Leprosy

A Pathologic Study on Large Sections of Amputated Extremities In Relation to Radiological Appearance^{1, 2}

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Crippling deformities are one of the most serious complications of leprosy, and have been extensively studied chiefly by clinical and radiologic technics. There have been a few correlative analyses of radiologic appearances and histopathologic findings relating to bone changes (^{2, 15, 25}), but the emphasis has usually been on either radiological appearance (^{20, 22, 23, 24, 26}) or on histologic analysis (^{11, 17, 18}).

The present study primarily relates to pathologic analysis but pre- and/or post-amputation X rays were available for most of the specimens. Large sections of whole, amputated hands and feet made possible the histopathologic examination of not only the involved bones but also of the neighboring soft tissues and, therefore, of the relationship of the disease processes in all the tissues. The purpose of this study was to analyze the various factors in the pathogenesis of bone changes in leprosy by correlating morphologic appearances in relation to radiologic findings utilizing the classifications of bone changes based on roentgenologic appearance as proposed by Paterson in 1961 (²⁶) and Lechat in 1962 (²²).

MATERIALS AND METHODS

Fifty-three amputation specimens from 39 leprosy patients and three control specimens from nonleprosy individuals of the same racial and socioeconomic background were studied. All patients were Chinese living either in Hong Kong or in Taiwan. Their ages ranged from 16 to 51 years in the 19 cases for which clinical information was available. Seventeen were males and two were females, and information was not available for twenty cases. Of the patients, 8 were clinically lepromatous, 14 tuberculoid, and 5 intermediate (dimorphous), and in 12 cases the clinical classification was not available. The duration of the disease ranged from 8 to 20 years in the 19 cases with reasonably adequate clinical data. There were 8 feet, 22 fore-feet, 18 toes and 5 fingers available. The technic used for the large sections was, with slight variations, that used at the Armed Forces Institute of Pathology, Washington, D.C. (¹). Each specimen was fixed in 10% formalin. After examining X-ray films, they were cut through the lesions, and decalcified by electrolysis, processed in graded alcohols and then embedded in paraffin in a vacuum oven. Paraffin-embedded tissues were sectioned at 5 to 25 micron thicknesses depending on their size by means of a Jung L-1 sliding microtome. Each specimen was stained with hematoxylin and eosin, and/or selected special stains chosen from a repertoire of Masson's trichrome, saffron trichrome, Triff (³⁰), Weigert-Van Gieson's stain and phosphotungstic acid hematoxylin. Pre- and/or post-amputation X rays were also examined in 44 specimens from 30 cases. Acid-fast staining was not generally satisfactory due apparently to electrolytic decalcification and age of some specimens.

RESULTS

The results are summarized in Table 1.

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TABLE 1. Frequency analysis of bone changes.

Case no.	Specimen	Type of diagnosis	Metatarsophalangeal osteoarthritis	Ulceration & infection	Chronic periostitis & osteitis	Pyogenic osteomyelitis	Osteoporosis	Osteochondritis deformans or ankylosis	Contracture of joint	Distal atrophy	Leprosy granuloma in bone	Fibrous nodule in bone	Leprous periostitis	Nerve	Blood vessel
4	RF		-	+	+	+	-	-	-	-	-	-	-	2	3
5	RF		+	-	+	+	+	+	+	+	-	+	-	3	5
6	LF		-	+	+	-	+	-	-	-	-	-	-	3	3
7	3Fi	L	/	+	-	-	-	-	+	-	+	-	+	5	1
8	RF	L	+	-	+	-	+	+	+	+	-	-	-	2	3
9	RF	L	+	-	+	-	-	-	-	-	-	-	-	-	4
10	LF	L	+	+	+	+	-	-	+	-	-	-	-	-	2
11	LF	L	+	+	-	-	+	-	+	+	+	-	+	5	2
13	LF	T	-	-	+	-	+	-	+	-	-	-	+	3	3
15	RF		-	+	+	-	-	-	+	-	-	-	-	-	3
16	RF	L	+	-	+	-	-	-	+	+	+	-	+	1	5
17	LF	T	+	-	+	-	-	+	-	-	-	-	-	2	2
18	RF	T	+	-	+	-	+	+	-	-	+	-	-	3	5
	LF														
19	5RT	T	-	+	+	+	-	-	-	+	-	-	-	1	3
20	2Fi	D	/	-	-	-	-	-	-	+	+	-	+	5	2
21	RF	T	+	-	+	-	+	-	-	+	-	+	-	-	5
22	RF	T	+	-	+	-	+	-	+	-	-	-	+	1	4
23	LF	T	+	-	+	-	-	+	+	-	-	-	-	4	5
24	RF	T	+	-	+	-	-	-	+	-	-	-	-	-	3
26	1LT	T	-	+	-	+	-	-	+	+	-	-	-	-	4
27	1RT	T	-	-	-	-	-	+	-	-	+	-	-	-	1
28	4LT	T	-	-	+	-	-	+	-	+	-	-	-	3	1
29	2T	D	-	-	-	-	-	-	-	+	+	-	-	-	1
30	RF	T	+	-	+	-	+	-	+	-	-	-	-	2	1
	LF														
31	2T	D	-	-	+	-	-	-	-	-	-	-	-	3	2
32	1RT	L	-	+	-	+	-	-	-	-	-	-	-	-	1
33	RF	L	+	+	+	-	-	-	+	-	-	-	-	-	3
34	RF	D	+	-	-	-	-	-	+	+	-	+	-	-	4
35	RF	T	+	-	-	+	-	+	-	-	-	-	-	3	3
36	1RT	D	-	-	+	-	-	+	-	-	-	-	-	-	1
38	1LT	T	+	-	+	-	-	-	-	+	-	-	-	-	2
49	LF		+	+	+	+	+	-	-	-	-	-	-	-	1
50	LF		+	+	+	+	-	+	-	-	-	-	-	-	4
51	RF		-	+	+	-	-	-	-	-	-	-	-	-	1
52	LF		+	+	+	+	+	-	+	-	-	-	-	1	3
54	F		-	+	+	+	-	-	-	-	-	-	-	-	4
56	F		-	-	+	-	-	+	-	-	-	+	-	3	2
57	F		-	+	+	+	+	+	-	-	-	+	-	1	2
58	F		-	+	-	+	-	+	-	-	-	+	-	-	2
Frequency*			20/37	16/37	29/37	13/37	12/37	13/37	15/37	10/37	5/37	6/37	4/37		
			(54%)	(43%)	(78%)	(35%)	(32%)	(35%)	(41%)	(27%)	(13%)	(16%)	(11%)		

T = Tuberculoid; L = Lepromatous; D = Dimorphous.

* Cases 7 and 20 are excluded in frequency analysis.

RF = Right foot; LF = Left foot.

RT = Right toe (s); LT = Left toe (s).

Fi = Finger (s).

The degree of morphologic change of blood vessels, mainly arteries, and of nerves was graded on a subjective scale of 1 (slight) to 5 (severe). The bone changes listed in Table 1 are mainly based on the classification proposed by Lechat (²²) with some modifications. The terms "metatarsophalangeal osteoarthritis" and "distal atrophy" are used in the same connotation employed by Lechat. Included under "osteomyelitis" are only the lesions that disclosed typical evidence of present or previous suppurative inflammation in the bone marrow spaces. "Nonspecific chronic periosteitis and osteitis" are terms used to designate the changes characterized by noninfectious, inflammatory cell infiltration mainly of lymphocytes and/or fibrosis in the periosteum close to the osseous cortex, or in the nutrient foramina of the cortex, or in the spongy bones, which are frequently associated with increased osteoblastic and/or osteoclastic activity ("bone turnover"). Changes similar to those categorized in "chronic periosteitis and osteitis" were often seen in the distal heads of the metatarsal bones, but these were not grouped in "chronic periosteitis

and osteitis," but were classified as "metatarsophalangeal osteoarthritis," because they are regarded as partial findings of the latter category. Fibrous nodule in the bones was usually presented as pseudocyst formation on X rays.

In the percentage analysis of the relative frequency of each change, cases 7 and 20 were excluded, as they were the specimens from the upper extremities. They were, however, noted as being good examples of leprosy specific osteitis resulting in bone absorption.

According to the classification proposed by Lechat (²²), bone changes in leprosy can be divided into two major groups: (1) specific leprosy osteitis and (2) nonspecific bone changes. From a pathologic point of view, leprosy granulomatous periosteitis, osteitis and osteomyelitis belong in the first category. Lechat classified cyst-formation and honeycomb appearance on X rays as the group of specific changes. In our study, fibrous nodule in the bones also shows cyst-formation on X rays. They may result either from chronic nonspecific osteitis or

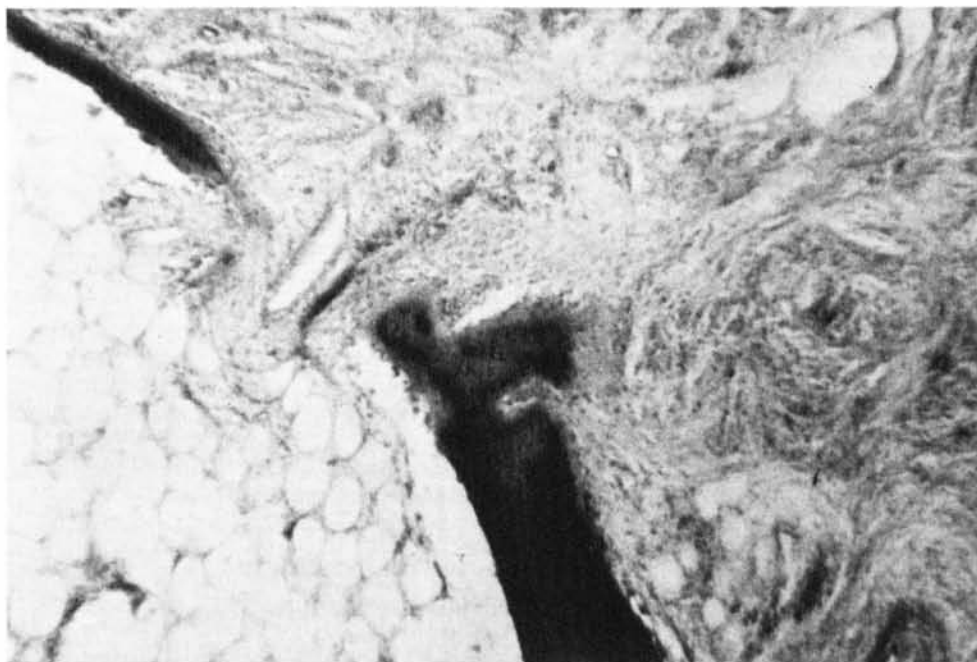


FIG. 1. Chronic nonspecific periosteitis and osteitis (case 49, H & E stain, original mag. $\times 35$). Fibrotic tissue invades bone marrow space through cortical defect. Cortex is thinned and atrophied by osteoclastic activity.

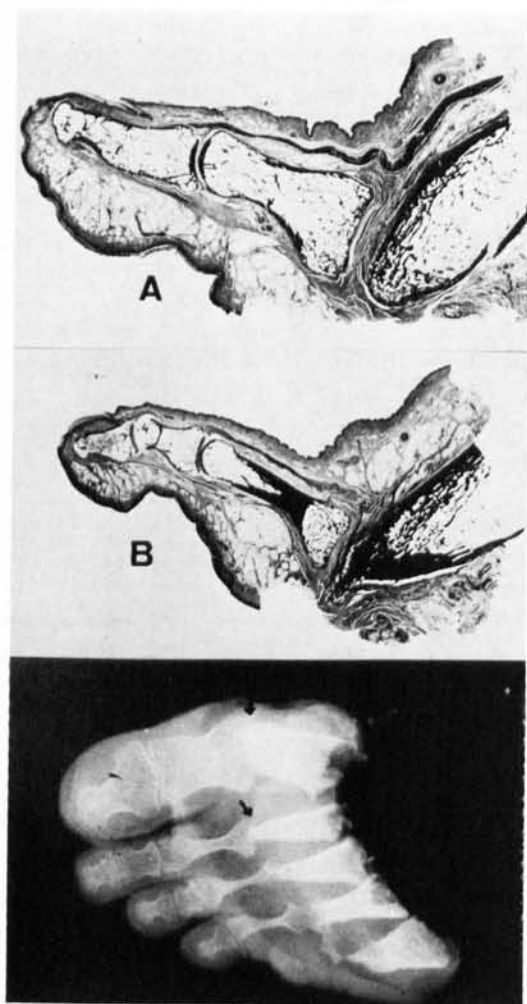


FIG. 2. Metatarsophalangeal osteoarthritis (case 23, Weigert-Van Gieson's stain). An X-ray film shows advanced bone destruction in metatarsal heads, and corresponding specimens from 1st right (A) and 2nd (B) toes reveal concentric atrophy of metatarsal heads with thickening and tapering of cortex and narrowing of bone marrow spaces.

osteoarthritis, or from inactivated healed lepromas.

In frequency analysis of each type of bone change, chronic nonspecific periosteitis and osteitis were most frequently found (78%). Most cases were associated with osteoarthritic lesions in metatarsal heads. In some instances chronic periosteitis and osteitis were seen in the shaft areas of the bones far from the joints. In such cases, the lesions were frequently found in the plantar surface

of the affected bones, and thought to be possibly caused by pressure effect without causing an ulceration (Fig. 1).

Metatarsophalangeal osteoarthritis was found frequently (54%). It is noteworthy that the bone changes appeared earlier in the metatarsal heads in our sequences of pre-amputation X rays and were more severe, as judged by histopathologic sections, than the changes seen in the proximal ends of the phalanges. In cases 22, 23, 30, 33, and 34 the metatarsal heads were severely damaged, while the phalangeal proximal basis showed only minor changes (Fig. 2). In the damaged distal ends of the metatarsal bones, concentric atrophy which is seen in many of the cases with this type of change, consists of thinning and tapering of the distal metatarsal shaft with markedly thickened and sclerosed cortex and narrowed medullary spaces. In some instances, chronic inflammation was seen in the joint membrane.

Ulceration frequently followed by secondary infection and pyogenic osteomyelitis is thought to be one of the important factors in bone destruction in leprosy. Sixteen of 37 cases (43%) had ulceration with associated infection of soft tissues, usually in the plantar surfaces of feet, presumably caused by a long-standing pressure effect and circulatory disturbances in distal parts of the extremities due to neural involvement by leprosy as well as to acute injury. Many of the cases with ulceration were associated with pyogenic osteomyelitis (Fig. 3) with bone destruction and reactive new bone formation around the lesions. Virtually total bone resorption of the foot (Fig. 4) was seen without the influence of pyogenic osteomyelitis.

In most cases there was some degree of decreased radiologic density of the affected bones; on histology this corresponded to a decreased number and thinning of the trabeculi in the medulla, and thinning of the cortex. Not only on X rays but also on corresponding histology sections, there was some degree of evidence of osteoporosis in 12 cases. Case 30 showed especially severe porotic changes in histopathologic section.

Ankylosis or osteochondritis in the joints other than the metatarsophalangeals was

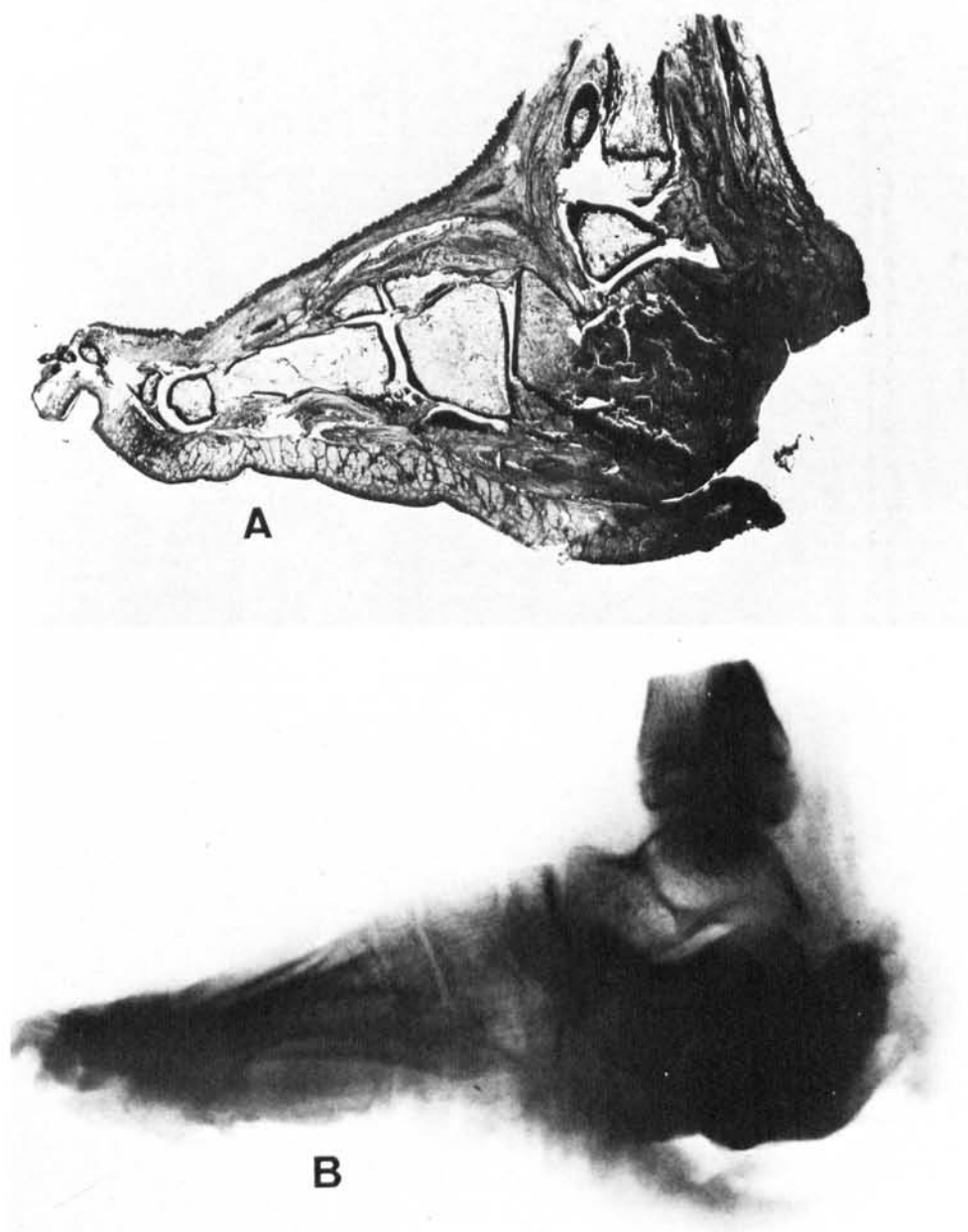


FIG. 3. Pyogenic osteomyelitis following ulceration and secondary infection in calcaneus (case 4, Masson trichrome stain, section through the 5th toe, right foot).

found in 13 cases (35%). Cases with ankylosis in the interphalangeal joints presented a perfect continuity between two phalanges on histology sections, probably representing post-osteocondritis of the joints.

Contractures of joints were seen in 15 cases (41%). These were frequently associ-

ated with dislocation of the affected joints. Contracture usually resulted from scarring in soft tissue around the affected joints, and in about half of the cases was associated with ulceration and was also frequently associated with chronic periosteitis.

Distal atrophy of phalanges was seen in

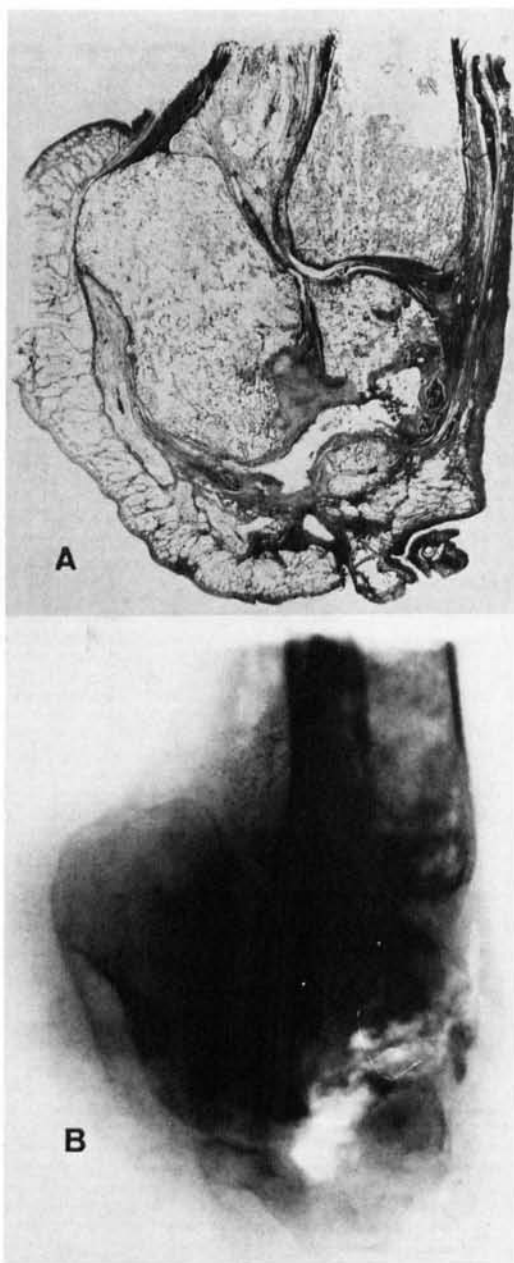


FIG. 4. Virtually complete resorption of foot, save for calcaneus which is displaced posteriorly. At time of amputation there was acute cellulitis, diffuse, but the striking bone resorption was evidently not aided by pyogenic osteomyelitis.

- A. Total long section right foot, Case 5, saffron trichrome stain.
- B. X ray of total specimen.

ten cases (27%). The lesions were histologically characterized by focal thinning and disruption of the cortex of the distal phalanges, being replaced by fibrous tissues extending from the periosteal areas to the marrow spaces (Fig. 5). Increased osteoclastic activity was also significant in the lesions.

Leprous granulomas within the bone marrow were seen in seven cases including two cases of upper extremities. In cases 7 (lepromatous) and 20 (dimorphous), the leprosy lesions were extensive both in soft tissue and bone. In both cases the distal phalanges of the fingers were severely affected and associated with marked bone absorption similar to that seen in distal atrophy on X rays (Fig. 6). Lepromatous invasion seems to extend from the soft tissue to the bone marrow spaces through the enlarged nutrient foramina. Two tuberculoid cases (18 and 27) show epithelioid

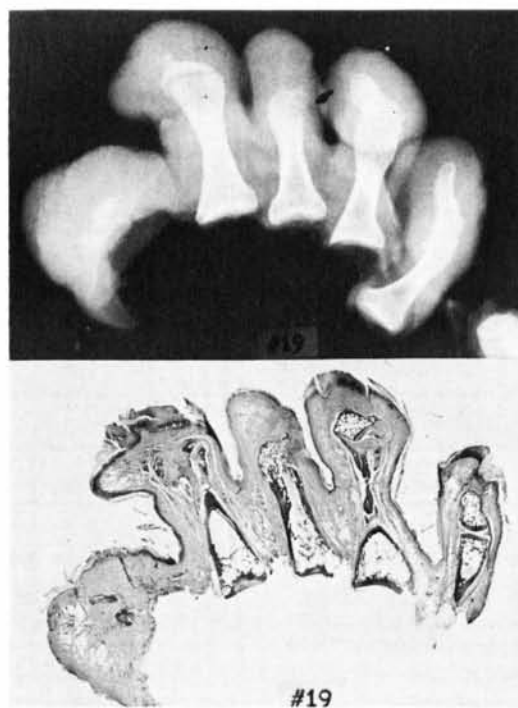


FIG. 5. Distal atrophy (case 19, Weigert-Van Gieson's stain). A post-amputation X-ray and corresponding section reveal atrophy and tapering of distal phalanges being replaced by fibrous tissues. The 3rd toe shows a small ulceration (arrow on X-ray) followed by secondary infection and osteomyelitis.

cell granulomas with Langhans type giant cells in the bones. Leprous periosteitis was seen in six cases including two cases of upper extremities and was usually associated with lepromas in the bone marrow spaces. Some cases show cortical bone absorption due to leprous periosteal invasion.

Fibrous nodules presenting pseudocyst-formation on X rays was found in six cases. The cases were usually associated with osteoarthritis of metatarsophalangeal joints as well as other joint surfaces. Fibrous tissue penetrated through cortical defects or dilated nutrient canals near the margin of articular cartilage on the plantar surface of the bones in cases with metatarsophalangeal osteoarthritis (Fig. 7).

The nerve changes ranged from peripheral fibrosis to fibrous replacement of entire bundles. Perineural, chronic nonspecific inflammatory infiltrates were found in most of the specimens. Cases 22 and 23 showed

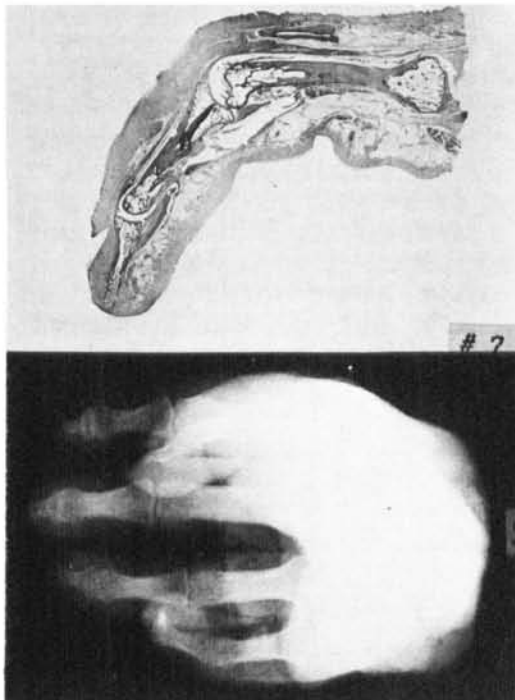


FIG. 6. Leprous granuloma in bone and leprous periosteitis (case 7, 4th finger, H & E stain). Distal phalanges are involved by leprous infiltration both in periosteum and bone marrow space. An X-ray shows atrophy of distal phalanges which simulates that seen in distal atrophy.

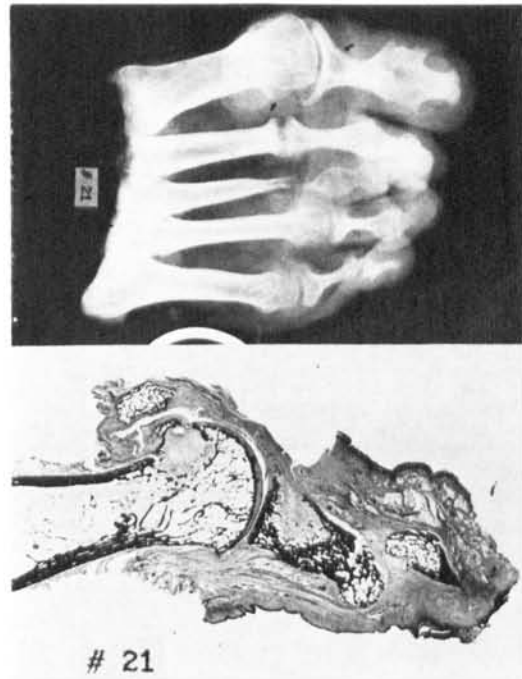


FIG. 7. Fibrous nodules in bone (case 21, 1st toe, Weigert-Van Gieson's stain). Fibrous nodules destruct and replace bones in metatarsal head and proximal phalanx. An X-ray reveals pseudocysts in corresponding locations.

tuberculoid granulomas replacing medium sized trunks.

Almost every case showed some degree of alterations in the medium sized and small arteries and arterioles. The alterations consisted of medial hypertrophy, and in advanced cases, accompanying intimal thickening. Vascular sclerosis with luminal narrowing was extreme in many instances (cases 5, 16, 18, 21, 23) (Fig. 8), which are all associated with metatarsophalangeal osteoarthritis, and chronic periosteitis and osteitis. Table 2 presents correlation between the degree of vascular changes and each type of osseous alteration. The condition of the arteries was not directly related to the age of the patients, being of severe degree in a 16 year old adolescent (case 26) and of mild degree in a 45 year old man (case 30). Severe arterial changes, graded 4 to 5, were found in 11 cases among 37 individuals (30%). Cases 10 and 21 had acute or subacute nonspecific vascu-

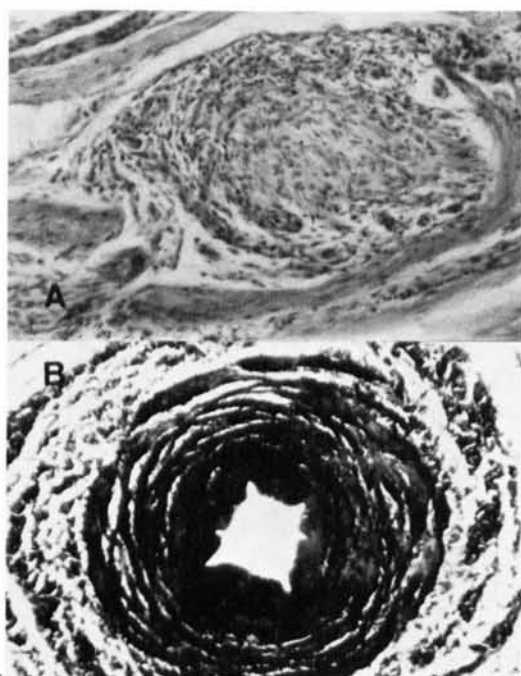


FIG. 8. Fibrotic change in peripheral nerve (A) (case 30, H & E stain, original mag. $\times 100$), and arterial alterations (B) (case 23, Weigert-Van Gieson's stain, original mag. $\times 35$) with concentric hypertrophy of media and hyaline fibrosis of intima.

litis with infiltration of polymorphonuclear leucocytes and/or plasma cells in the walls of arteries, and case 11 showed specific leprosy granulomatous arteritis.

DISCUSSION

On the basis of the radiologic studies of Paterson (²⁶) and Lechat (²²), bone changes in leprosy can be classified into two major groups: (1) specific leprosy osteitis and (2) nonspecific osteitis including pyogenic infection.

It has long been evident that direct leprosy involvement of bones is one of the factors in bone absorption. In 1934, Gass and Rishi (¹¹) found acid-fast bacilli in the bone marrow of 17 of 21 cases having mixed cutaneous and neural leprosy, and Hayashi (¹⁵) indicated that leprosy inflammation extended into bone through the Haversian canals and that both cortical absorption and periosteal thickening could be demonstrated by X-ray studies. Kozuma (²¹) and Job (¹⁷) also pointed out that direct leprosy invasion could result in bone atrophy and destruction. On X rays leprosy involvement of the Haversian canals may present as enlarged nutrient foramina, as pseudocysts and even as a honeycomb appearance (^{25, 26}). Pseudocyst may, however, also result from fibrous nodules in the bones as shown in cases 5, 21, 34, 56, 57 and 58 in our series. Erickson and Johansen (⁷) reported that pseudocysts sometimes healed under sulfone therapy, and Job (¹⁷) noted that leprosy lesions in bones may heal by fibrosis. However, it seems possible that in many cases these fibrous bone lesions may result from pressure effects, since they tend to be located close

TABLE 2. Relationship between vascular alteration and each bone change.

Bone changes	Severity of vascular change				
	1	2	3	4	5
Metatarsophalangeal osteoarthritis	2/8	4/8	5/10	4/6	5/5 ^a
Ulceration and infection, soft tissue	3/8	4/8	6/10	3/6	0/5
Chronic periosteitis and osteitis	5/8	6/8	8/10	4/6	5/5
Pyogenic osteomyelitis	2/8	3/8	5/10	3/6	1/5
Osteoporosis	2/8	2/8	3/10	1/6	3/5
Osteochondritis deformans or ankylosis	3/8	4/8	3/10	1/6	3/5
Contracture of joint	1/8	2/8	6/10	3/6	3/5
Distal atrophy	2/8	2/8	2/10	2/6	2/5
Leprosy granuloma in bone	2/8	1/8	0/10	0/6	2/5
Fibrous nodule in bone	0/8	3/8	0/10	1/6	2/5
Leprosy periosteitis	0/8	1/8	1/10	1/6	1/5

^a For example: 5/5 indicates that all five cases with degree five of vascular change have metatarsophalangeal osteoarthritis.

to articular cartilages and related to osteoarthritis. Cortical erosion or destruction by specific leprous periosteitis as seen in cases 7, 11, 13, 16, 20 and 22 occurs both in the lepromatous and tuberculoid forms.

One of the readily understandable and important factors in bone absorption is osteitis and osteomyelitis following ulceration and secondary infection as shown in Figure 3 (case 4). Ulceration of the skin and soft tissue is presumably related to a long-standing pressure or repeated trauma and circulatory disturbances in distal parts of the extremities of anesthetic patients. Even if there is no ulceration of the skin, the metatarsophalangeal joints and the calcaneus are the most effected pressure points in such patients. Prolonged pressure or repeated trauma may lead to ischemia accompanied or followed by chronic aseptic inflammation and resultant fibrosis in the metatarsal heads and plantar surfaces of the bones and periostium. Chronic vasculitis and chronic repeated pressure or traumatic effect on soft tissues of the extremities are also thought to lead to such arterial alterations as was noted in many instances in the present study. Such arterial

sclerosis in the involved extremities was considered important also by Murakami (25). Harada and Takashima (14) studied leprous vasculitis which was similar histopathologically to that in periarteritis nodosa but it seemed to be far milder in degree and chronic in course, and characterized by hyaline degeneration in the vascular walls instead of fibrinoid necrosis, and by absence of association with complete occlusion, thrombosis or aneurysm which were frequently associated with periarteritis nodosa. It is evident that vasculitis tends to occur during therapy especially as a manifestation of *erythema nodosum leprosum*.

In addition to vasculitis, reactional phases also harbor other factors which may be important in the development of extremity deformity. Edema in soft tissues, panniculitis or necrotizing *erythema nodosum leprosum* may result in sclerodermic lesions (27), and contracture of various joints (10), and the importance of prevention of deformity in such reactive phases by adequate physiotherapeutic management has been stressed by Furness *et al* (10). Another well-known phenomenon in reactive

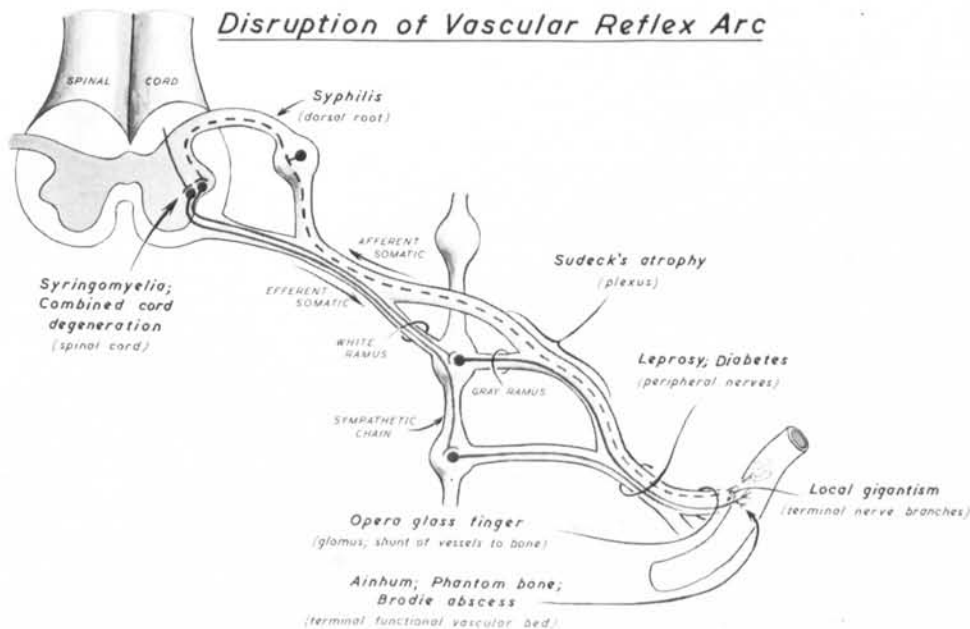


FIG. 9. Comparative locales of vascular reflex arc disruption in various bone resorption entities. Based on Johnson's suggestions (19).

phases which play a role in the development of extremity deformity is arthritis. Ramu and Balakrishnan (²⁷) studied 18 cases with recurrent attacks of arthritis in lepromatous leprosy and pointed out that in its early acute phase lepra reaction resembles acute rheumatic fever, and in its

recurrent states it simulates rheumatoid arthritis with its resulting deformities in clinical and biochemical characteristics. Innami (¹⁶) proposed the concept that the pathogenesis of *spina ventosa leprosa* has a close relation to autoimmune mechanisms, as suggested by studies of immune cross-

PERIPHERAL NERVE AFFECT

(autohomic, sensory & motor)

Interruption of vascular reflex arc:

Hyperemic bone resorption

"Fluctuant stress" vascular sclerosis

Pressure atrophy & trauma

2° to sensory loss & deformity 2° to loss of muscle support

SPECIFIC LEPROUS INFLAMMATION

(Hematogenous & direct extension. Predominantly lepromatous end of spectrum. Effect & extent of tuberculoid lesions unknown)

Inflammatory morphology reflective of leprosy type; granuloma, leproma, fibrous nodule. No sequestration.

Enlarged nutrient canals

Pseudocysts

"Honeycomb" appearance

Inflammatory vasculitis & eventual sclerosis.

BONE CHANGES

Osteoporosis & bone resorption, - concentric atrophy -

Specific leprous osteitis, periosteitis & osteomyelitis

Suppurative periosteitis, osteitis & osteomyelitis with sequestration

Metatarso-phalangeal osteoarthritis

Osteochondritis deformans

Joint contracture

IMMUNOLOGIC REACTIONS

(Predominantly lepromatous & lower borderline ~~effects~~ spectrum. Tuberculoid bone reaction & effects not documented.)

Rheumatoid arthritis-like changes with joint contracture

ENL vasculitis with eventual vascular sclerosis & ~~some~~ relative ischemia.

SECONDARY INFLUENCES

(Externally originating)

Pyogenic periosteitis, osteitis & osteomyelitis 2° to ulceration & trauma sequential to anesthesia.

Trauma 2° to sensory loss

FIG. 10. Factors initiating and sustaining progressive bone deformity.

reactions between *M. leprae*, BCG, and the human phalanx.

Møller-Christensen *et al* (²⁴) studied changes in the anterior nasal spine and alveolar process of the maxilla in seven cases and reported no sensitivity changes found in any patient which might indicate that atrophy was due to neurotrophic disturbance of bone, and they held that neurological examination did not give support to the neurotrophic theory of pathogenesis of changes in those bones. Michman and Sagher (²³) also noted that no disturbance of sensitivity was found in any of 44 cases studied with respect to changes in the nasal spine and maxillary bone in leprosy. Waller (²⁰), in a study of seven cranial specimens, attributed the changes in maxillary bones and the loss of the anterior spine to changes in the overlying soft tissues.

Circulatory abnormalities, however, have been entertained for a long time as one of the possible factors in the pathogenesis of bone absorption in leprosy.

Fite (⁹) noted that involvement of blood vessels in leprosy has been known at least since the work of Joelsohn in 1893. Fite (⁹) himself contributed a detailed study, being, however, largely concerned with leprosy infection of the blood vessels rather than the chronic effect of denervation on the vessels. In amputation specimens, such as utilized in the present study, the findings of necessity deal with long-standing changes in which it is virtually impossible to determine the initial cause of the vascular thickening. By analogy, organs such as the spleen and uterus, which undergo repeated physiologic stress and change in size, often show marked hyalin thickening of arterioles. It's possible that extremity arterioles respond similarly when stressed by chronic circulatory change due to loss of neurovascular reflex control. The vascular changes are likely, then, to be of multiple pathogenic origins. Functional disturbances, secondary to vascular innervations, have been considered important, as stressed by Lechat (²²). Barnettson demonstrated that the vasodilatation reflex, as demonstrated by immersion of the other limb in warm water, was slow or absent in

leprosy patients (³) and stressed that disturbance of reflex vasomotor response following leprosy interstitial neuritis was an important factor in pathogenesis of neurotrophic atrophy (^{2,4}). Chatterjees also pointed out that variations of extremity temperature were more prominent in leprosy patients than in normal individuals (⁶). Faget and Mayoral (⁸) performed a radiologic arteriographic study of the extremities of leprosy patients, which revealed narrowing of the arteries. Paterson (²⁶) demonstrated by angiography of the digital arteries, vascular end-loops and nutrient vessels to the phalanges of 12 leprosy patients that there was diminution in the vascular end-loops even in cases without bone absorption, and that narrowing of the caliber of digital arteries was present in the cases with osteoporosis and deformed by bone absorption. In seven cases there was a considerable increase in the circulation time of the fingers. Basu *et al* (⁵) also reported vascular changes manifested as circulatory stasis in the digits as demonstrated by an angiographic analysis of 20 cases of nonlepromatous leprosy. Statistically there is a close relationship between anesthesia and distal absorption as noted by Lechat (²²). Changes in Charcot's joint from the study of a single leprosy specimen were described by Johnson (¹⁹), who noted that in the acute phase the bone revealed three zones in the metaphysis; normal bone, porotic bone with osteoclastic resorption and telangiectasis, and new bone formation with dilated sinusoids. Such bone changes may be initiated by circulatory changes resulting from interruption of the neurovascular reflex arc at any level by a variety of afflictions including leprosy as outlined in Figure 9. The same mechanism operative at the same reflex level in neurovascular reflex is thought to be a factor in bone absorption in diabetic neuropathy (²⁰). Johnson (¹⁹) noted that hyperemia occurring as telangiectatic dilatation of sinusoids in the midst of normal fatty marrow is associated with osteoclastic bone resorption and such hyperemia is active. In contrast, hyperemia with edema and serous atrophy of fat is associated with osteoblastic bone formation and is passive.

In active hyperemia blood flows rapidly, lymphatic flow is reduced, and there is minimum loss of oxygen, sugar, proteins and all nutriment to the tissues in passage between supplying arterioles and draining venules. Active hyperemia, with its high oxygen tension and metabolic activity supports and induces osteoclastic activity. In passive hyperemia blood flow is slow, lymphatic drainage is increased and there is maximum escape of oxygen, sugar, protein and nutriment to the tissues during this same traverse. Thus, passive hyperemia with its high tissue-fluid protein supports and induces osteoblastic activity. The distinction between the two types of hyperemia and their effects on bone depends upon differences in flow rate. Thus, Coutelier^(6a) in a recent study utilizing micro-radiology and fluorescence microscopy of bone sections found that either bone destruction or bone formation may occur as isolated phenomena in leprosy. In most instances, however, the two phenomena were intermingled. The eventual result is thus a balance of these factors. These concepts are supported by the studies of Gorham and West⁽¹³⁾ who determined experimentally in mice that a very vascular tumor was associated with bone resorption, whereas a spindle-cell sarcoma blocking the arterial circulation was accompanied by marked osteogenesis. Likewise, tissue culture studies by Goldhaber⁽¹²⁾ indicate that a high concentration of oxygen (60% to 95%) stimulates osteoclastic resorption of bone and potentiates the *in vitro* action of parathyroid hormone and vitamin D on bone. Supplementing these findings Shaw and Bassett⁽²⁸⁾ determined that a somewhat lower oxygen concentration (35%) favors bone formation in culture. They also noted that oxygen deprivation blocks osteogenesis, diminishes collagen formation and favors chondrogenesis.

The pathogenesis of nonspecific bone resorption with consequent deformity in leprosy is thus a complex process (Figure 10) for which a pathophysiologic mechanism can now be postulated. The vascular changes and circulatory alterations are not, however, static but the result of alterations in response to varying factors such as the position of the

extremities and resultant effects of gravity, ambient temperature, inflammation and many other factors. Added to these are yet other mechanisms such as disuse and pressure atrophy. The sclerosis described must be slowly developing and have its modifying effect on the circulation. In balance, during the time course of the patient's affliction, the effect is that of an overbalance of osteolysis and resorption as compared with osteoblastic bone formation. The recognition that vascular denervation through interruption of the vascular reflex arc, and slowly progressive, associated, vascular sclerosis are permanent disabilities, suggests that bone resorption may be ongoing in the presence of disease arrest and may continue after cure of the disease. This recognition reiterates the desirability of achieving early therapeutic success in arresting and curing leprosy while neural involvement is yet limited.

SUMMARY

A pathologic study of 53 separate amputation specimens from 39 leprosy patients together with three normal controls was made by means of large sections paraffin histopathologic preparations correlated with pre- and post-amputation X-ray visualizations of changes in the same specimens. Utilizing the classifications proposed by Paterson and Lechat, the percentage analysis of each type of bone change found were: metatarsophalangeal osteoarthritis 54%, ulceration and infection 43%, chronic nonspecific periosteitis and osteitis 78%, pyogenic osteomyelitis 35%, osteoporosis 32%, osteochondritis deformans or ankylosis 35%, contracture of joint 41%, distal atrophy 27%, leprosy leproma or granuloma in bone 13%, fibrous nodule in bone 16%, and leprosy periosteitis 11%.

Attention is called to the vascular alterations, which were found to some degree in every case. Eleven cases had severe (graded 4 to 5) vascular changes. Cases with severe vascular changes tended to have a higher degree of metatarsophalangeal osteoarthritis, and chronic nonspecific periosteitis and osteitis. Various probable pathogenic mechanisms in extremity deformity and bone adsorption in leprosy are dis-

cussed, emphasizing the disturbance of neurovascular reflex and resulting vascular sclerosis.

RESUMEN

Se hizo un estudio anatómico-patológico de 53 muestras individuales de amputación obtenidas de 39 pacientes con lepra y de tres controles normales, por medio de preparaciones histológicas de cortes grandes en parafina, relacionándolas con los cambios observados en estas mismas muestras por medio de visualización por rayos X, efectuadas pre y post-amputación. Utilizando las clasificaciones propuestas por Paterson y Lechat, el análisis porcentual de los tipos de alteraciones óseas encontradas fue: osteoartritis metatarsofalángica 54%, ulceración e infección 43%, periostitis y osteitis crónica no específica 78%, osteomielitis piogénica 35%, contractura articular 41%, atrofia distal 27%, leproma o granuloma leproso en el hueso 13%, nódulo fibroso en el hueso 16% y periostitis leprosa 11%.

Se desea llamar la atención hacia las alteraciones vasculares, que se encontraron en cierto grado en todos los casos. Once casos mostraron alteraciones vasculares severas (graduación 4 y 5). Los casos con alteraciones vasculares severas tendían a presentar mayor grado de osteoartritis metatarsofalángica y periostitis y osteitis crónica no específica. Se sugieren varios probables mecanismos patogénicos en deformidades extremas y adsorciones de huesos en lepra, con especial énfasis en las alteraciones de los reflejos neurovasculares y la esclerosis vascular resultante.

RÉSUMÉ

Une étude pathologique de 53 échantillons provenant d'amputation chez 39 malades de la lèpre, et chez trois témoins normaux, a été menée au moyen de préparations histopathologiques enrobées dans des coupes de paraffine de grandes dimensions. Les résultats ont été mis en corrélation avec les aspects radiographiques des modifications des mêmes échantillons, constatés avant et après amputation. En utilisant les classifications proposées par Paterson et par Lechat, la répartition des différents types de modifications osseuses qui ont été trouvées est la suivante: ostéoartrite métatarso-phalangienne 54 pour cent, ulcération et infection 43 pour cent, périostite non spécifique chronique et ostéite 78 pour cent, ostéomyélite pyogène 35 pour cent, ostéoporose 32 pour cent, ostéochondrite déformante ou ankylose 41 pour cent, atrophie distale 27 pour cent, léprome ou granulome lépreux dans l'os

13 pour cent, nodule fibreux dans l'os 16 pour cent, et périostite lépreuse 11 pour cent.

L'attention a été attirée sur les altérations vasculaires, relevées à des degrés différents dans chaque cas. Onze cas présentaient des modifications vasculaires graves, de degré 4 ou 5. Les cas présentant des modifications vasculaires graves tendaient également à présenter un degré plus élevé d'ostéoartrite métatarso-phalangienne, de périostite non spécifique chronique et d'ostéite. Les divers mécanismes pathogéniques probables des difformités des extrémités et de la résorption osseuse dans la lèpre sont discutés. On souligne les troubles des réflexes neurovasculaires, et la sclérose vasculaire qui en résulte.

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