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The Facial Nerve in Leprosy

2. Pathology, Pathogenesis, Electromyography and Clinical Correlations[1, 2]

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In the first paper of this series ([1]), in addition to the clinical features and operative findings, the broad objectives of this study were outlined. The emphasis in this paper will be on a discussion of the probable pathogenesis of the frequent involvement of the purely motor facial nerve, and of the selective neuritis of its zygomatic branch and consequent lagophthalmos. This is a feature both of academic interest and of practical importance. Before description of the essential pathologic changes observed in the affected branch or branches, which were biopsied in all the 11 cases, a brief account of the electromyographic observations will be presented, and a correlation will be attempted between the clinical, the electromyographic, the operative electrostimulative, and the histopathologic findings.

MATERIALS AND METHODS[4]

Electromyography was carried out preoperatively in seven of the 11 cases, and postoperatively in six. Electromyographic tracings from the frontalis, the orbicularis oculi, and the orbicularis oris muscles were recorded during maximal contraction, from both the explored and the unexplored sides of the face, including 30 muscles in all. Nerve conduction, in seven cases, was assessed from the latency of contraction; this was expressed as the time taken in milliseconds (msec.) from the moment of application of the stimulus to the start of the contraction, the tragus being the point of stimulation in each case. The latency thus measured was dependent on the distance between the tragus and the needle electrode inserted in the muscle, and hence differed in different patients, and on each side in the same patient. In normal control subjects the ratio of latency in msec. to the conduction distance (in cm.) was found to lie between 0.29 and 0.47. Hence a value of 0.5 or more was considered to indicate a prolonged latency and nerve damage.

A type IIIc R.A.F. model single channel electromyograph and concentric needle electrodes were used for recording. The stimulator provided a rectangular pulse of 300 μsec. with a maximum amplitude of 200 volts.

In the first ten cases a biopsy specimen of the affected zygomatic branches was obtained as described in our first paper ([1]). This piece of tissue, which was generally triangular in shape, with its apex pointing proximally and its base distally, consisted grossly of fibrous tissue, rarely of parotid gland tissue, containing the affected nerves embedded within it. The distalmost part near the eye often included a small portion of the orbicularis oculi muscle. This whole

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[4]The case material is described in the first paper, THE JOURNAL **34** (1966) 103-117.

piece was fixed in formalin and embedded and sectioned as one or more blocks. In the eleventh case of the series all the branches of the facial nerve were found to be severely affected on both clinical and electromyographic examination, and the trunk and the entire ramification of the nerve were excised and blocked in serial pieces. The following five staining procedures were carried out in each case: hematoxylin-eosin, picro-Mallory for connective tissue, Weil-Weight method for myelin, Holmes' silver impregnation for nerve fibers, and the Fite-Faraco method for acid-fast bacilli.

OBSERVATIONS

Electromyographic findings. The latency in the orbicularis oculi was prolonged, as expected, in all cases on the operated side; the muscle was unresponsive in one case with total facial paralysis (F-11), while the values for the frontalis and orbicularis oris were abnormal in three and four instances respectively, including the unresponsive muscles of F-11.

On the unexplored side, latency was prolonged in the frontalis in two, in the orbicularis oculi in one, and in the orbicularis oris in two cases.

The activity on moderate and maximal voluntary contraction was used to study the alterations, if any, of individual and collective motor unit patterns. The fact that fibrillations could be heard in only two cases, in spite of clinically obvious weakness in all, was due to the 50 cycle mains interference which prevented the increase of sensitivity of 100 μV/cm. and more. Evidence of denervation was obtained in the form of a decreased contraction pattern, in 17 of the 30 muscles examined, amounting in some cases (7 muscles) to only a single unit deflection, and in four muscles (F-8, F-11) to no electric activity at all. The surviving motor units were di-, tri-, or polyphasic and either within the normal range (300-1,500 μV), or of larger ampli-

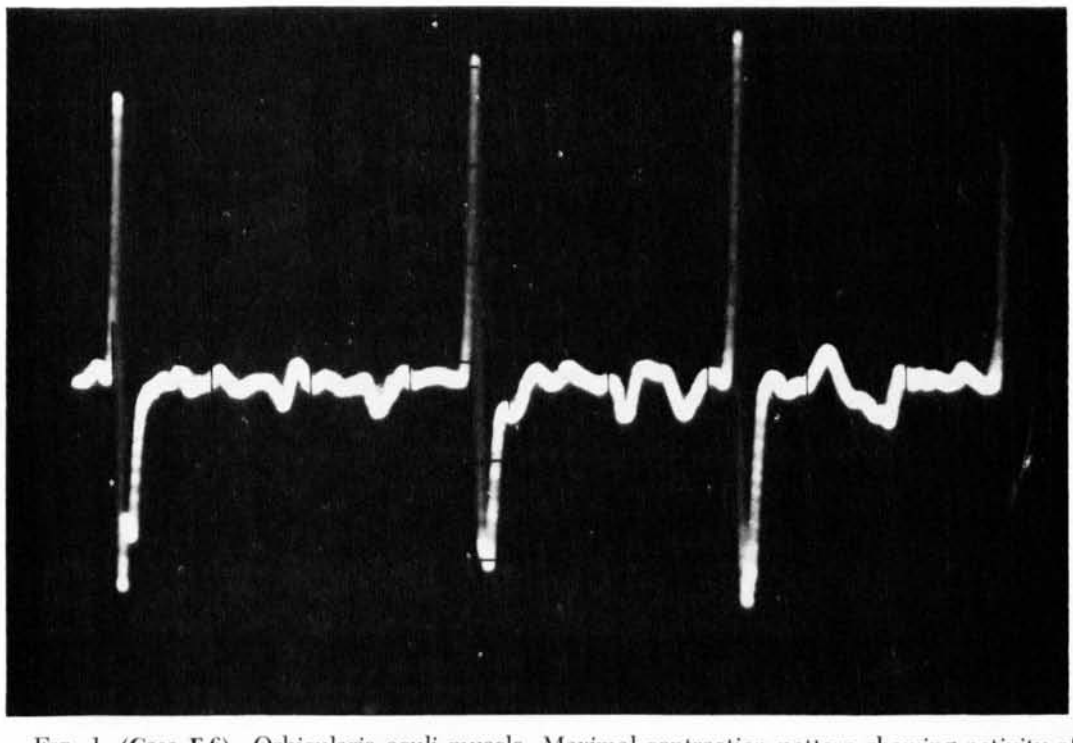


FIG. 1. **(Case F-6).** Orbicularis oculi muscle. Maximal contraction pattern showing activity of a single motor unit of normal appearance (amplitude 1,500 μV; duration 3-4 msec). This grossly reduced activity indicates advanced denervation. Scale: vertical, 1 div. = 300 μV; horizontal, 1 div. = 10 msec.

TABLE 1. *Detailed electromyographic observations*

Case No.	Clinical weakness: Frontalis	Clinical weakness: Orb. oculi	Clinical weakness: Orb. oris	Latency[a] (msec./cm.): Frontalis	Latency[a] (msec./cm.): Orb. oculi	Latency[a] (msec./cm.): Orb. oris	Electromyography: Frontalis	Electromyography: Orb. oculi	Electromyography: Orb. oris
				Operated side—postoperative findings					
F-5	+	+	−	6.5/14.0	7.4/8.0[b]	5.0/9.5[b]	Not done	Not done	Not done
F-6	−	++	−	3.5/11.4	5.6/8.2[b]	3.9/6.8[b]	Full interference pattern	Single unit interference pattern, 400 μV.	—
F-7	−	+	+	5.3/10.5[b]	3.6/7.0[b]	3.4/8.0	Incomplete interference pattern	Single polyphasic unit interference pattern, 5,000 μV.	Single unit interference pattern, 5,000 μV.
F-8	+	++	+	21.5/11.8[c]	6.3/5.6[c]	4.2/7.6[b]	Fibrillations +. Single unit interference pattern, 200 μV.	Single unit interference pattern, 400 μV.	Poor interference pattern
F-9	+	+	−	5.3/11.4	3.5/7.2[b]	3.1/8.6	Incomplete interference pattern	Single polyphasic unit interference pattern, 1,000 μV.	Complete interference pattern
F-10	−	±	−	4.3/11.6	5.3/7.0[b]	3.0/8.2	Complete interference pattern	Incomplete interference pattern	Complete interference pattern
F-11	++	++	++	No resp.[c]	No resp.[c]	No resp.[c]	No voluntary activity	No voluntary activity	No voluntary activity
				Unoperated side—preoperative findings					
F-5	±	±	−	—	6.0/8.0[c]	6.3/10.0[b]	Not done	Not done	Not done
F-6	−	±	±	3.5/11.5	4.0/9.5	3.5/7.2	—	Single polyphasic units, 1,800 μV.	Complete interference pattern
F-7	±	−	−	4.6/11.0	3.5/8.0	3.6/8.0	Complete interference pattern	Complete interference pattern	Complete interference pattern
F-8	++	+	+	9.0/11.3[c]	Previously operated	3.7/7.4[b]	Fibrillations +. No voluntary activity	—	Incomplete interference pattern
F-9	−	−	−	4.0/13.2	3.5/7.8	—	Poor interference pattern	Complete interferenece pattern	Complete interference pattern
F-10	−	−	−	4.1/12.1	2.7/7.6	2.9/9.3	Complete interference pattern	Complete interference pattern	Complete interference pattern
				Operated side—Postoperative findings					
F-5	++	excised	±	5.8/11.8	Nerve excised	4.7/8.6[b]	Single diphasic unit interference pattern	Nerve excised	Incomplete interference pattern
F-6	++	excised	++	7.3/12.0[b]	"	7.2/8.0[c]	Incomplete interference pattern	"	Single unit interference pattern, 400 μV.

F-7	++	excised	±	No response	"	3.5/7.6	No voluntary activity	"	Complete interference pattern
F-8	+++	excised	+	12.5/8.8[c]	"	7.5/7.7[c]	Single polyphasic unit interference pattern, 1,000 μV.	"	Single unit interference pattern, 150 μV.
F-9	+	excised	−	5.3/11.6	"	3.9/8.7	Incomplete interference pattern	"	Polyphasics ++, single unit interference pattern, 1,000 μV.
F-10	±	excised	+	4.1/11.7	"	3.0/9.0	Incomplete interference pattern	"	Polyphasics + Complete interference pattern
F-11	excised	excised	excised	Entire facial nerve excised			Nerve excised	"	Nerve excised

[a]Stimulation findings expressed as latency in milliseconds (numerator), over the conduction distance in centimeters from the tragus (denominator).
[b]Mild to moderate abnormality (ratio 0.5 to 0.7) as indicated in text.
[c]Marked abnormality, ratio greater than 0.7.
[d]Sign under status indicates normal muscle function.
[e]Sign implies moderate motor weakness..
±Sign indicates mild motor weakness.
+Sign indicates severe motor weakness.

tude. Clear single units of normal dimensions are illustrated in F-6 (Fig. 1). By contrast, smaller discrete units were observed in three muscles (e.g., orbicularis oculi on the unoperated side in F-6). As expected, the orbicularis oculi muscle on the operated side showed the largest number of abnormalities during voluntary contraction.

Table 1 gives the detailed electromyographic observations, the stimulation findings being expressed as latency in msec. (numerator), over the conduction distance in centimeters from the tragus (denominator).

There was good correlation between the latency and electromyographic findings for each muscle. In a number of isolated instances, however, electromyographic abnormalities were more pronounced than the corresponding latency readings. For example, the orbicularis oculi muscles in F-7 and F-9, on the operated side, showed this feature (Figs. 2a and 2b and 3a and 3b, respectively).

On comparison of the clinical evaluation of motor status with the electrophysiologic findings, a fair correlation was again apparent. There were four instances where an abnormality was detected in the electromyographic tracing, but not apparent on clinical examination, e.g., in the frontalis muscle in F-7 on the operated side, and in the orbicularis oris in F-5 on the unoperated side. The opposite situation, of a clinically affected muscle showing no electric abnormality, was noticed in only one case, the frontalis muscle of F-7 on the unoperated side.

Histopathologic findings. All the specimens examined revealed, as expected, pathologic changes in the nerves going to the orbicularis oculi muscle of the operated side. Table 2 lists the essential pathologic changes in each specimen in terms of cellular reaction, fibrosis, axon damage, myelin loss, presence of acid-fast bacilli, and changes in other tissues. It will be seen that in the majority of cases, the cellular reaction was of a chronic inflammatory nature, consisting predominantly of small mononuclear cells (Fig. 4, F-5). Perivascular polymorphonuclear reaction was seen

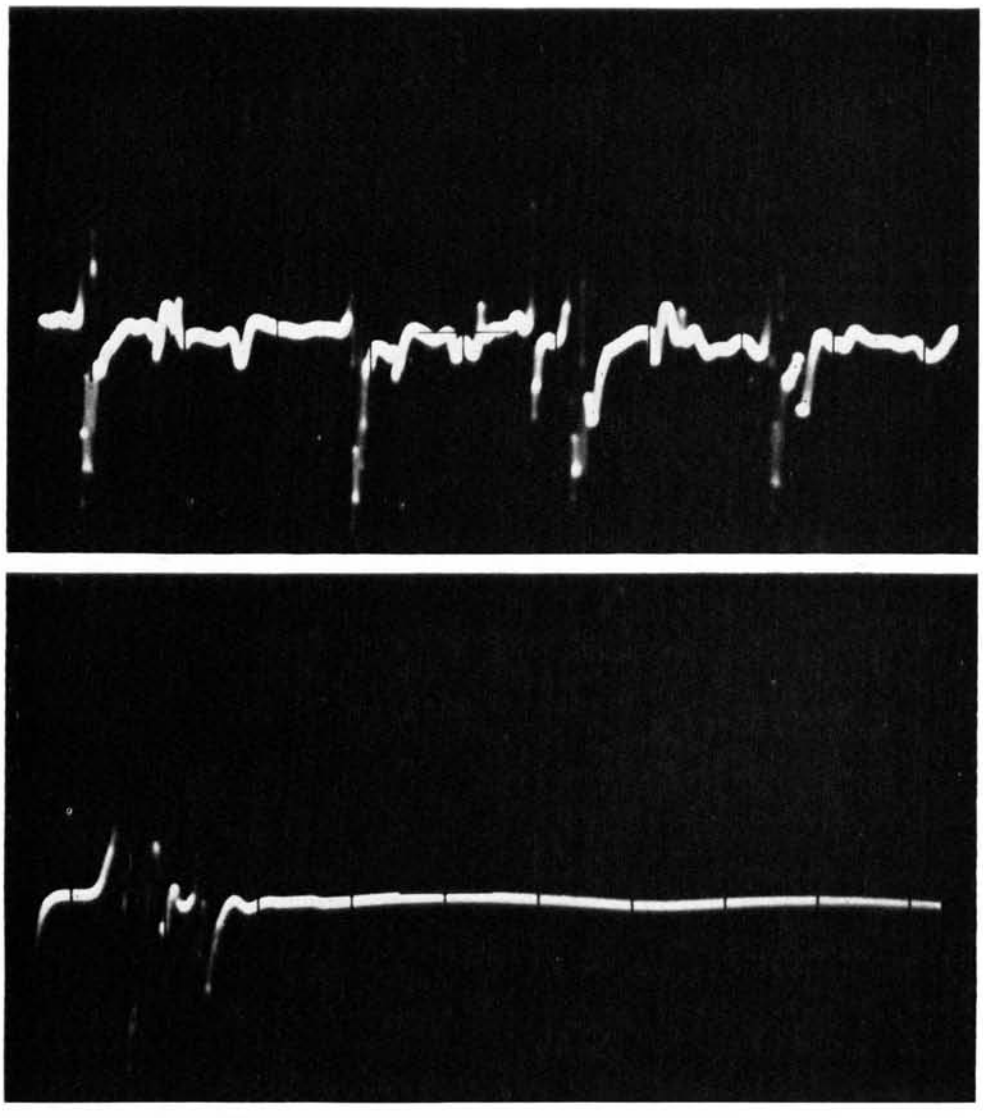


FIG. 2. **(Case F-7).** Orbicularis oculi muscle. (a) Maximal contraction in this case shows a "giant" polyphasic unit of 5,000 μV, 5 msec., again indicating a long standing neuropathic lesion. This is contrasted (b) with the mildly delayed latency in the same muscle on nerve stimulation (3.6 msec. for a conduction distance of 7.0 cm.). Scale: vertical, 1 div. = 1,000 μV; horizontal, 1 div. = 10 msec. (2b. 1 div. = 5 msec.).

in one case (F-4), and appeared to be consequent to the electromyographic needling procedure carried out the previous day on that muscle (although the recording was unsatisfactory). An epithelioid and giant cell reaction was seen in only three cases (F-1, F-5 and F-10) and localized to a few subbranches or small areas of the main nerve. One of these (F-5) was a case of dimorphous leprosy, while the others were cases of maculoanesthetic polyneuritic leprosy, this being the type of leprosy assigned to seven of the 11 cases.

Even in the one case (F-5) that showed a large number of acid-fast bacilli in the nerve, together with even larger numbers in vacuolated Virchow cells in the ear skin, there was no evidence of the presence of any histiocytes of nonneural origin harboring the organisms within the nerve. The

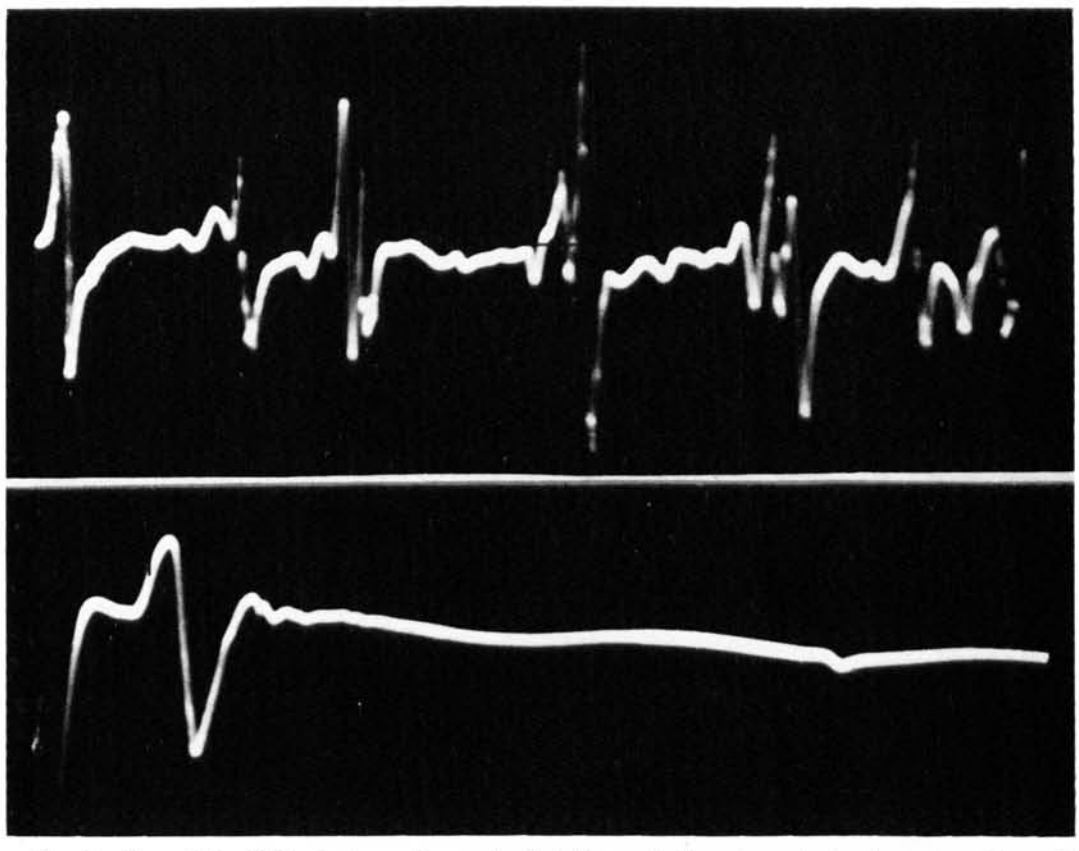


FIG. 3. **(Case F-9).** Orbicularis oculi muscle. (a) Several discrete polyphasic units of amplitudes from 2,000-4,000 μV, also illustrating denervation, which are again contrasted (b) with an almost normal latency of 3.5 msec. for a conduction distance of 7.2 cm. Scale: vertical, 1 div. = 1,000 μV; horizontal, 1 div. = 10 msec. (3b, 1 div. = 5 msec.).

acid-fast bacilli here were found within Schwann cells only, whether present in clusters or singly. In the only other case in our series (F-2) where bacilli were encountered in a facial nerve branch, a small cluster and another single bacillus detected were again in Schwann cells (Fig. 5). In the three patients (F-3, F-7, F-8) who were considered to be cases of old lepromatous leprosy, but who had been treated, no organisms were encountered within the nerve branches or in the skin. Apart from the above-mentioned two cases where Schwann cells appeared proliferated, at least in parts of the nerves examined, there were six other cases (i.e., eight of the 11), which showed a moderate increase of Schwann cells (Fig. 6, F-11). In general, parts of the nerve not severely damaged and fibrosed, and often showing inflammatory reaction, were the sites manifesting Schwann cell proliferation.

Every single nerve specimen examined showed a moderate to severe degree of fibrosis throughout, or over considerable portions of the nerves, and affecting both the perineurium and the endoneurium. In the severer cases the latter took the form of extensive eosinophilic hyalinization with reduced sheath nuclei in hematoxylin and eosin preparations (F-1 (Fig. 7), F-5, F-7), and showed dense blue collagenosis in picro-Mallory preparations. There was also prominence of interfunicular connective tissue in most of the cases. In patient F-1, where the branch going to the lower eyelid had a visible and palpable localized thickening over the zygomatic region, histologic examination revealed a peculiar oval zone of fibrosis walled in by superadded fibrous

TABLE 2. *Summary of histopathologic data for Cases F-1 to F-11.*[a]

	Cells	Fibrosis	Axons	Myelin	Acid-fast bacilli	Other nerves, muscles & skin	Assessment
F-1	Mononuclear +, ++ distally with vasculitis. Epithelioid +	+++, & fibrosed caseous area Total distal hyalinization	Degeneration +++	Loss +++	Not found	Few severely atrophic fascicles of orbicularis oculi	The only locally thickened nerve; severe chronic fibrosing neuritis; hyalinization & vasculitis more distally
F-2	Mononuclear +++, peri- & intra-funicular. Schwann +, in places −	+	Degeneration ++	Loss ++	+, one cluster in one branch		Chronic degeneration with active inflammation
F-3	Mononuclear ++	+++	Degeneration +++	Loss +++	Not found	1. Schwann cells + & minimal degeneration in accidentally cut branch 4-a going to nose. No acid-fast bacilli 2. Frontalis atrophy ++; intramuscular neural fibrosis ++ 3. Intradermal neural fibrosis ++; cells ±. No acid-fast bacilli	Chronic fibrosing neuritis still active.
F-4	Polymorphonuclear ++, perivascular because of EMG previous day; also mononuclears +. Schwann +	+ endoneurial & perineurial	Degeneration ++ Terminal branch (4a) + Stem branch (4)	Loss ++	Not found	1. Branch 5 going to side of nose & eye included in same specimen, was quite normal.	Maximal degeneration of branch to lower eyelid, distal > proximal

						2. Ear skin—perifollicular mononuclears +; nerve fibers ±; no acid-fast bacilli	
F-5	Lymphocytes, plasma cells, large mononuclear & giant cells in branches i, j, k, l, maximal proximally. Schwann +	++, especially distally	Degeneration ++ proximal +++ distal	Loss +++ throughout	++ in clusters in Schwann cells of branch i especially proximally	1. Neural atrophy orb. oculi +++; degeneration intra-muscular nerve +++ 2. Ear skin—dimorphous, lepra cells & acid-fast bacilli +++	Dimorphous histology of both nerve & skin. Distal damage more than proximal in the nerves
F-6	Mononuclear +	++, endoneurial & perineurial	Degeneration ++ except one well preserved bundle	Loss ++ except one well preserved bundle	Not found	1. Orb. oculi atrophy +, & one focus of vascular necrosis; fibrosis ++ of muscular nerves 2. Minimal atrophy digastric muscle 3. Ear skin—perineurial infiltrates +, neural fibrosis +++. No acid-fast bacilli	Severe fibrosis, including nerves in skin & muscles indicates chronicity, but the vascular necrosis indicates an exacerbating factor
F-7	Mononuclear + in intermediate part only of branch (4). Schwann +, in proximal well preserved part	Moderate hyalinization peri- & endoneurial +, intermediate; distal +++	Degeneration ± proximal; intermediate ++; distal +++	Loss corresponding to axon damage	Not found	1. Accidentally coagulated branch 3a, going to side of nose, shows changes consequent to this, otherwise well preserved	Clearly more chronic & severe nerve degeneration distally.

TABLE 2. *Summary of histopathologic data for Cases F-1 to F-11.*[a] *(Cont'd)*

	Cells	Fibrosis	Axons	Myelin	Acid-fast bacilli	Other nerves, muscles & skin	Assessment
						2. Ear skin—diffuse mononuclears & vasculitis, epithelioid cells + also; no nerves; no acid-fast bacilli	
F-8	Schwann ++ Perineurial perivascular mononuclear +	+	Degeneration + with number of normal axons	Loss & degeneration ++, with vacuolation	Not found	Skin-large granulomas in deep dermis around infiltrated & destroyed nerves	Clear tuberculoid histology in dermis but not in facial nerve branch
F-9	Schwann & mononuclear reaction ± & perineurial only	++, endoneurial & perineurial	Fiber damage ++ with sparing of thin fibers	Loss +++	Not found	Focus of calcification in dermis of ear lobule, with foreign body reaction	Very chronic fibrosing neuritis (longest duration in this series of cases)
F-10	In "spider" +++; lymphocytes, plasma, epithelioid, & rare giant cells Schwann +	++, endoneurial & perineurial	Degeneration varies from ++ to +++	Loss ++ to +++ all bundles	Not found	1. Ear skin—perivascular mononuclears superficially. No acid-fast bacilli 2. Degeneration in nerve branches in fibrous tissue over zygoma; acute post. EMG vasculitis	Still very active intraneural lesions as evidenced by cellular reaction, suggestive of tuberculoid type. Distal part of branches, >affected than proximal (on the whole)
F-11	Schwann ++; lymphocytic clusters perivascular, in the perineurium	+ to ++, more distally	+++ throughout branches pointing to orb. oculi	+++	Not found	Only case with facial nerve trunk & all branches. (i) *Trunk*: fairly well preserved in H&E & P.-M. preparations with	1. Severe & unusual total facial nerve paralysis clinically, confirmed histologically by extensive diffuse fiber degeneration

						only Schwann cell increase but with severe axon loss. (ii) The proximal portions of branches later going to zygomatic region show more severe degeneration with some inflammatory reaction & disruption. (iii) Of the branches pointing to angle of eye only one bundle showed a few well preserved axons, rest again showing degenerating, fibrotic & inflammatory changes. (iv) Orb. oculi muscle included in fibrous tissue from zygoma showed neurogenic muscular atrophy but no inflammation. (v) Skin of ear lobe showed minimal inflammation with severe nerve twig degeneration	2. Both activity (inflammatory reaction) & chronicity (hyalinization) more evident distally along all branches especially zygomatic 3. Severe trigeminal area paresthesiae for 2½ yrs. preceding facial weakness, suggesting involvement of 7th nerve territory via that of 5th.

[a]Nerve and nerve branch numbers in this table refer to diagrams for individual cases in Figure 8 of paper by Antia *et al.* The facial nerve in leprosy. 1. Clinical and operative aspects. THE JOURNAL **34** (1966) 103-117.

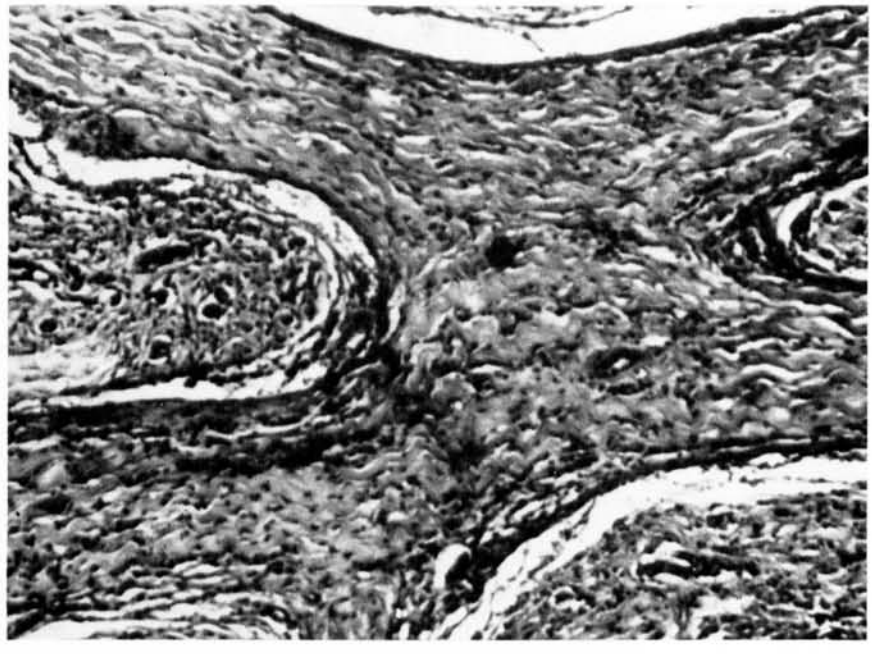


FIG. 4. **(Case F-5, NP-C-625).** Midzone of biopsied specimen showing two moderately hyalinized interconnected bundles of nerve to orbicularis oculi, with mild diffuse mononuclear cell infiltration and vascular and cellular reaction in the interfunicular tissue (H & E stain, X110).

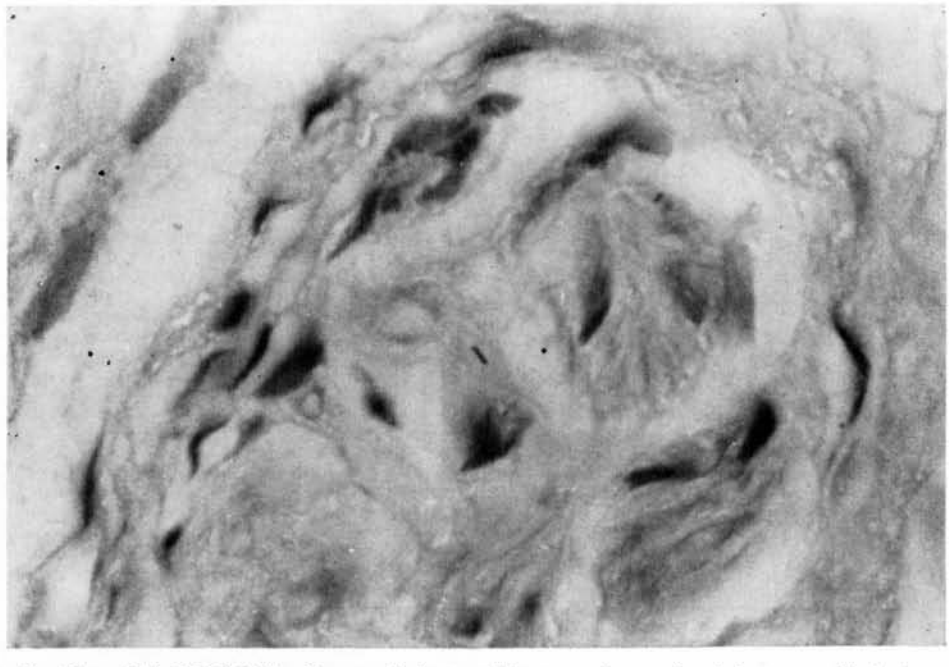


FIG. 5. **(Case F-2, NP-B-810).** One acid-fast rod in cytoplasm of a Schwann cell, in transverse section of nerve to orbicularis oculi (Fite-Faraco stain, oil immersion).

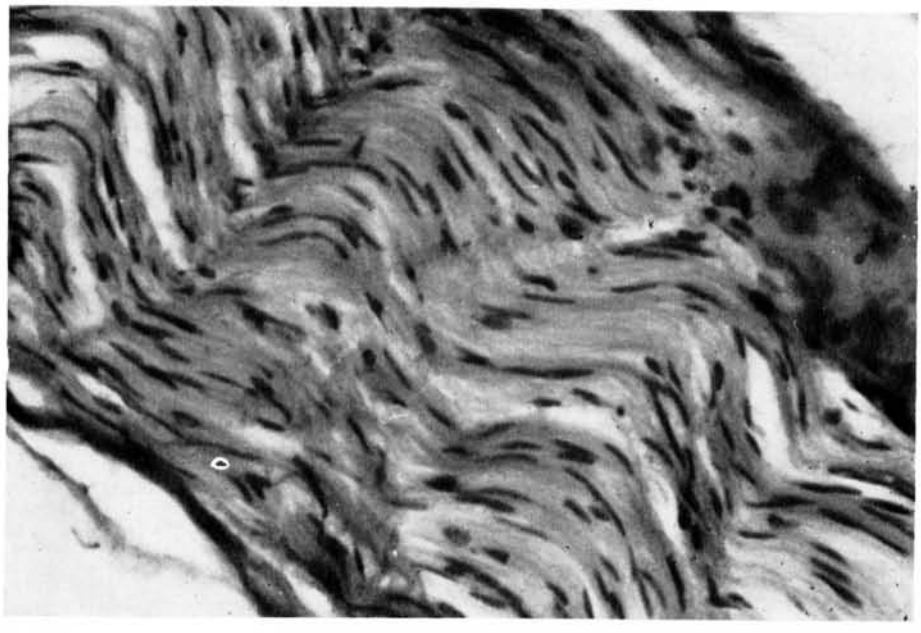


FIG. 6. **(Case F-11, NP-C-863).** Mild diffuse increase of Schwann nuclei only, in a moderately preserved nerve bundle (H & E stain, X285).

FIG. 7. **(Case F-1, NP-B-704).** Totally destroyed part of nerve to lower eyelid showing one smooth collagenosed bundle along one side, and diffuse and focal mononuclear and vascular proliferation (H & E stain, X75).

laminas, with minimal mononuclear cell reaction (Fig. 8), suggesting the end result of a possible necrotic phenomenon in the past. There was no correlation between the duration of the disease in the facial nerve and the severity of fibrosis in the biopsied nerve, as will be gathered by examining the appropriate figures of our first paper and Table 2 of this one.

While, by and large, any one region of any one nerve showed either severe inflammatory reaction and less fibrosis, or severe fibrosis and minimal inflammatory reaction, these two changes were rarely observed concurrently at the same site (Fig. 9, F-2).

As expected, axon degeneration was present in all the nerve specimens of this series, and was found to correspond roughly to the degree of fibrosis. At its mildest, the nerve fiber change was minimal, a stray degenerating fiber being found among a great majority of well-preserved axons (Fig. 10, F-7). As the degenerative change progressed, the fibrosis became more severe, and only beaded, thickened fragments of axons would be observed in a matrix of fibrous tissue (Fig. 11, F-7). At its severest, just a hyalinized cord of neural tissue, devoid of any axonal or cellular elements, was encountered.

On the whole, myelin loss too, at any one site, was at least as much as, or a little more than, the degree of axon degeneration, and was therefore encountered in all the specimens. At its mildest it took the form of a stray demyelinated fiber presenting a fish-bone appearance, among other well-myelinated fibers of a funiculus (Figs. 7, 12).

As will also be seen from the accompanying table, in three (F-3, F-4, and F-7) of the first ten cases, branches of the facial nerve other than those going to the orbicularis oculi were available for histologic examination. Since in each they were going to the muscles, at the side of the nose, which were clinically unaffected, it was not surprising to find minimal or no pathologic change in these.

A feature of note as regards the distribution of the neuropathologic changes emerged from six of the first ten cases (F-1, F-2, F-3, F-5, F-7 and F-10). This was the greater involvement of, and damage to, the more distal portions of the nerves in these few specimens at least, as compared to the

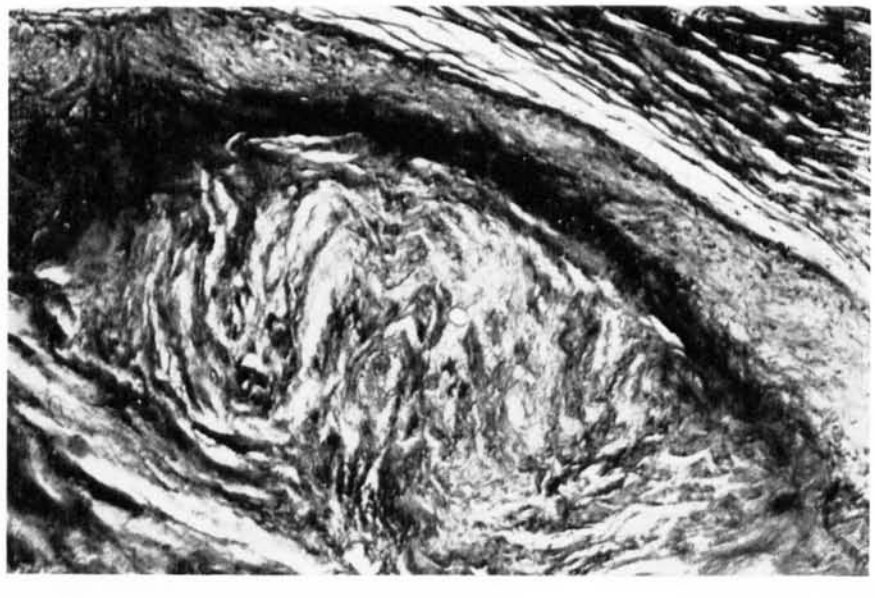


FIG. 8. Section through the thickest part of the same nerve as Figure 7, showing a fibrous wall with a few mononuclears and necrosed inner part of a possibly very chronic abscess (picro-Mallory stain, X75).

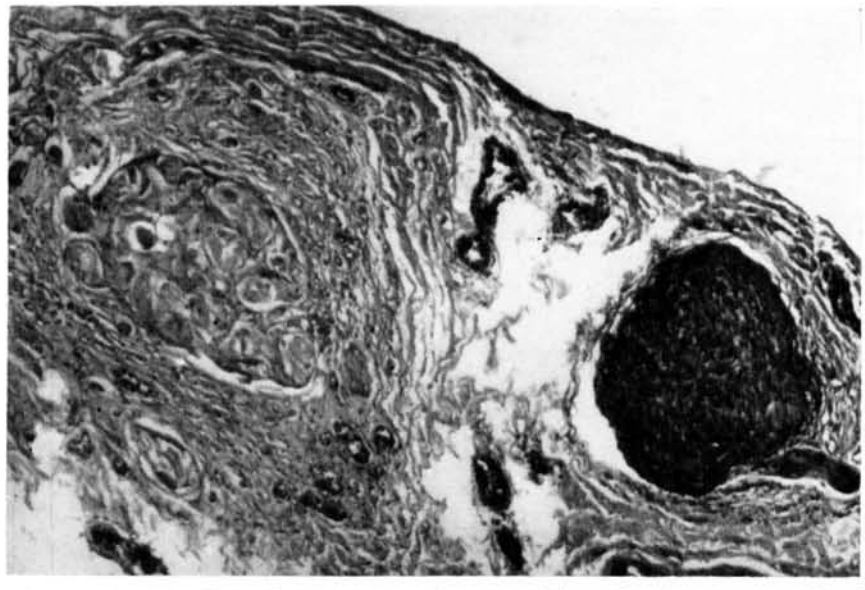


FIG. 9. **(Case F-2, NP-B-810).** Cross section of terminal branch of nerve to orbicularis oculi showing one dark necrosed bundle with matted inflammatory cells, and another paler hyalinized bundle with thickened perineurium, indicating both an active and a very chronic reaction (H & E stain, X85).

more proximal parts of the same. For example in specimen NP/C-693 (F-7), in contrast to the really well preserved proximal end of the nerve, as illustrated respectively for axons and myelin in Figures 10 and 12, the nerve in the intermediate part of the specimen showed appreciable fiber damage (Fig. 11) and fibrosis. At the distal end, the remaining nerve twigs were barely recognizable as such, being represented by totally demyelinated axonless, acellular smooth bands of collagen (Fig. 13). The same phenomenon is demonstrated by Figures 4 and 14 of Case F-5. In the eleventh case, where the trunk and the entire ramification of the facial nerve were available for examination, this feature was more clearly brought out by a gradual increase in the degenerative changes as one progressed distally from the facial nerve trunk itself, through the proximal parts or the branches going to the zygoma, up to the termination of these branches near the orbicularis oculi muscle. It was interesting to note, however, that even without actual disorganization, infiltration or fibrosis of the funiculi or the fibers of the trunk of the facial nerve, there was severe subtotal axon loss. The significance of these findings will be discussed later.

In four of the cases where a biopsy specimen of either the affected frontalis muscle (F-3) or of the affected orbicularis oculi muscle (F-5, F-6, F-11) was available for examination, clear neural muscular atrophy of a severe degree was encountered (Fig. 15, F-11). At the same time degenerating intramuscular nerve twigs, with an advanced degree of fibrosis, were observed in each of these three. In one of these muscles (in F-6) mild interfunicular mononuclear cell reaction and vascular infiltration and necrosis were detected, but there were no acid-fast bacilli in any of them.

The ear skin, which was available for examination in nine of the cases, showed varying grades of mononuclear cell reaction, predominantly perivascular, in the dermis in all. In one of these skin specimens (F-5) an interesting feature was noted. Coexistent with large clusters of vacuolated lepra cells loaded with acid-fast bacilli were a few areas of tuberculoid reaction with giant cells and mononuclears (Fig. 16), indicating a dimorphous histopathologic reaction in this case.

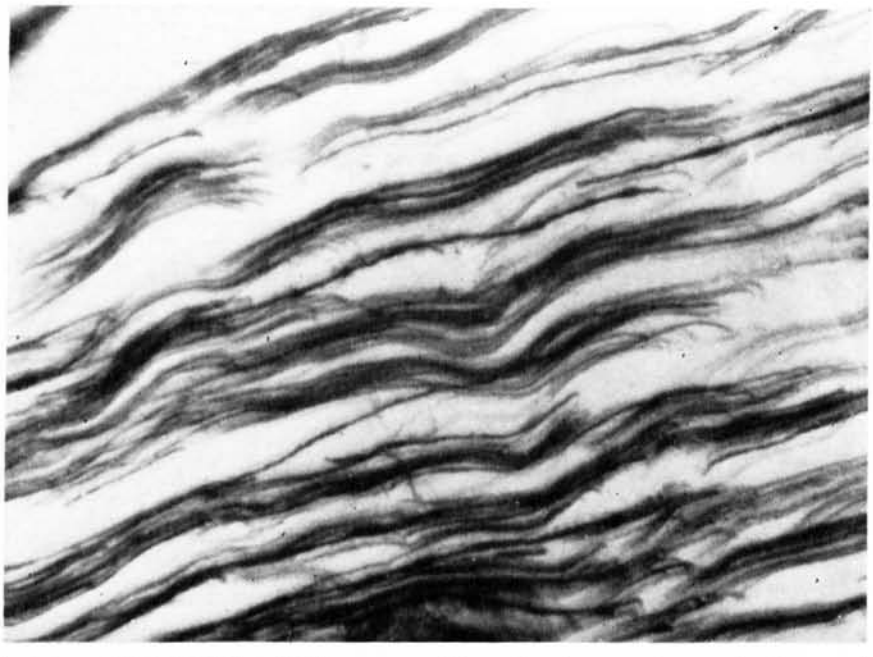
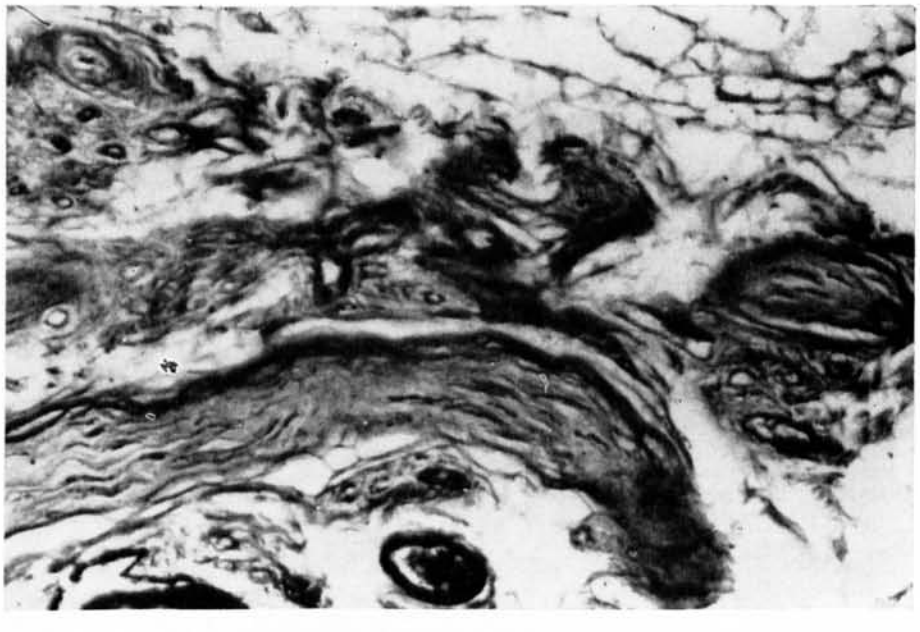


FIG. 10. **(Case F-7, NP-C-693).** Well preserved bundle of nerve in proximal part of biopsied specimen showing normal axons with only one or two beaded degenerating fibers (Holmes' silver stain, X320).



axonal loss and degeneration (Holmes' silver stain, X110).

FIG 11. Same nerve as in Figure 10 from its intermediate portion, showing fairly severe

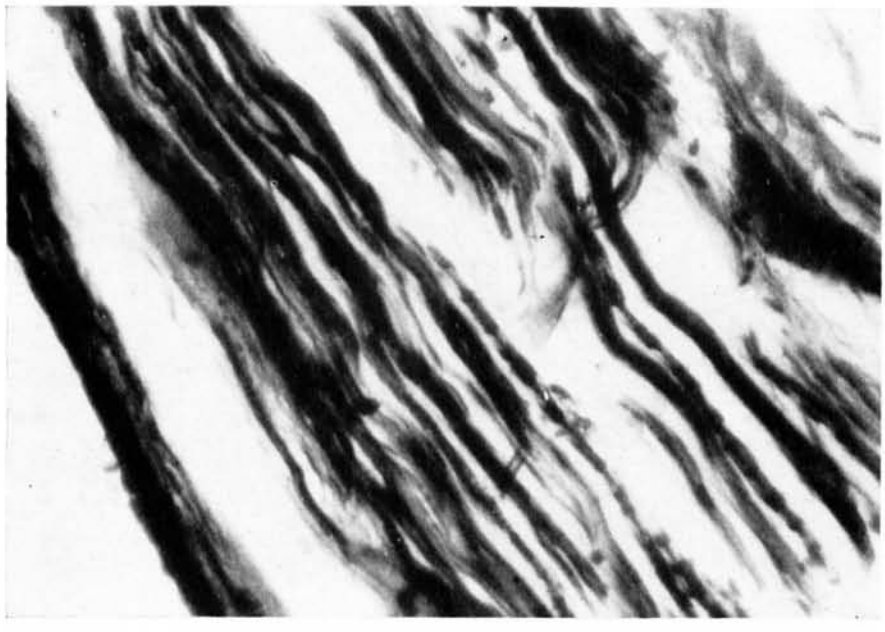


FIG. 12. Same nerve at the same site as in Figure 10, showing well myelinated fibers except for two showing degeneration and "fish bone" appearance (Weil-Weight myelin stain, X320).

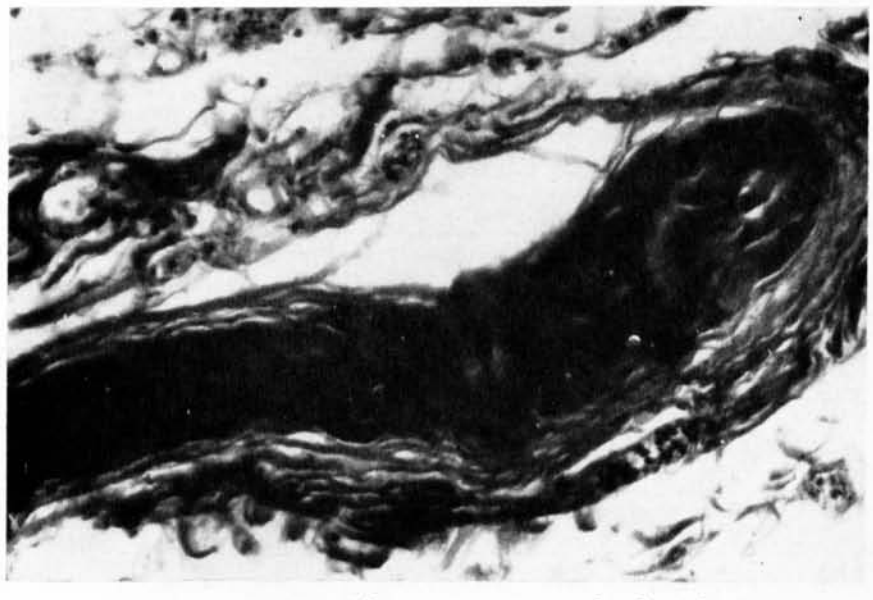


FIG. 13. Same nerve as in Figure 10 but at a site more distal to that in Figure 11, showing totally collagenosed bundle with no vestige of nerve tissue (picro-Mallory stain, X100).

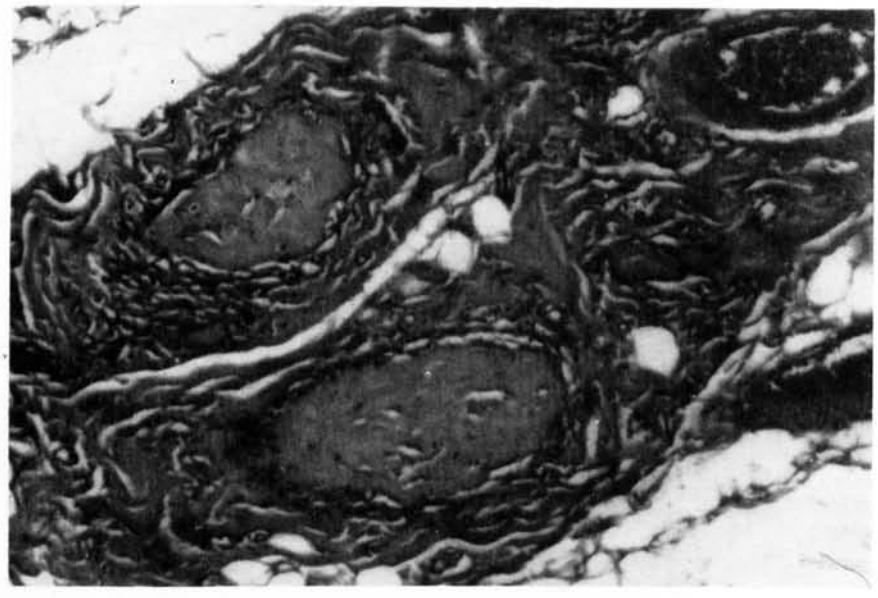


FIG. 14. Terminal part of same specimen as Figure 4, showing severe hyalinization of the distal part of the nerve to the orbicularis oculi with interfunicular fibrosis as well (H & E stain, X110).

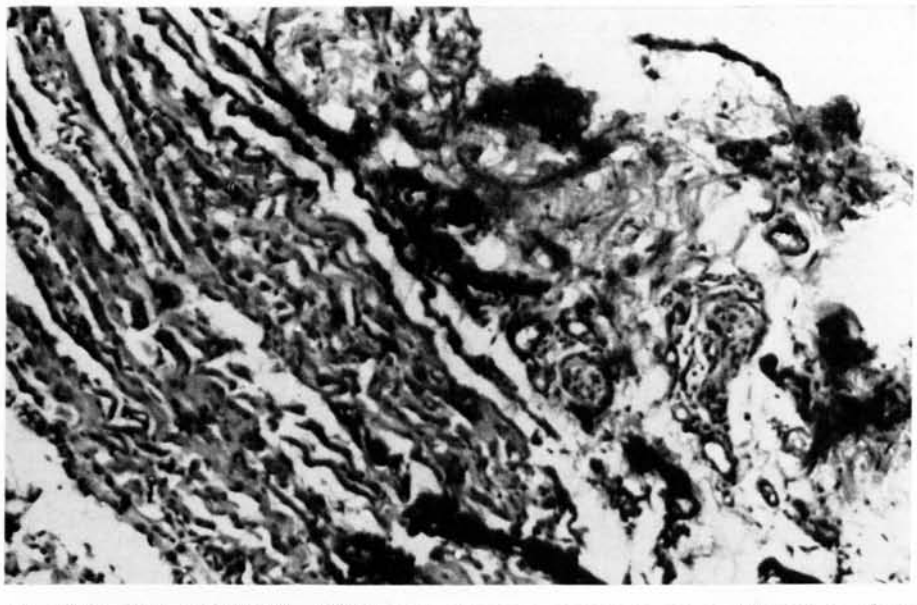


FIG. 15. **(Case F-11, NP-C-863).** Distal part of same specimen as in Figure 6, showing severely and uniformly atrophied muscle fibers of the orbicularis oculi, and mononuclear cell infiltration of the intramuscular nerve twigs (H & E stain, X115).

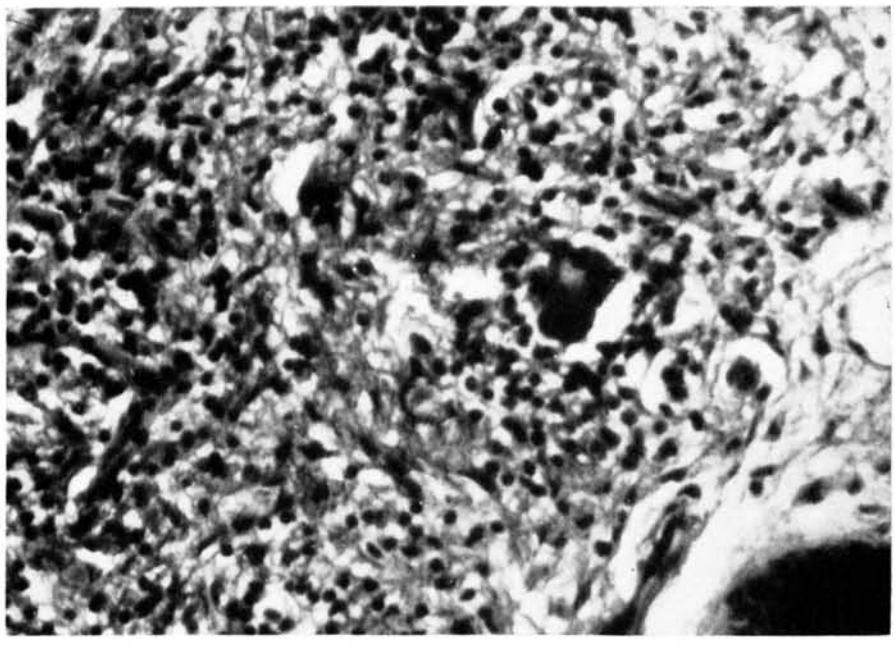


FIG. 16. Skin of hypoesthetic patch from same case as in Figure 4, showing mixed cellular reaction with mononuclears, foamy cells and giant cells (H & E stain, X250).

DISCUSSION

The histopathologic change delineated above is clearly indicative of a chronic inflammatory and fibrosing neuritis. This would be consistent with the history of leprosy of seven to 20 years' duration, and of lagophthalmos of eight months' to ten years' duration in this series of patients. As expected, and as is known in polyneuritic leprosy, there was no rigid relation between the duration of the illness and the severity of the nerve damage. The chronicity of the facial nerve involvement in our cases is brought out further by the fact that in seven of the 11 there was a polyneuritic lesion in one or more limbs antecedent to the facial nerve involvement. The widespread involvement of the nerves is revealed by the presence of polyneuritic lesions elsewhere at the time of nerve exploration in ten of the 11 patients.

There was good correlation for the group as a whole between the motor deficit clinically assessed and the severity of structural nerve damage. In only three of the 11 cases (F-7, F-8, F-10) was there a discrepancy; in one (F-8) the clinical damage was found to be more severe than the histologic, and in two the reverse was the case. The latter is more readily understandable in view of the greater accuracy of the observations possible under the microscope; the former might have resulted from the limited amount of nerve tissue (one or two branches going to the lower eyelid only) subjected to histologic examination. In this case (F-8) there was clinical and electromyographic evidence of a wider extent of involvement, the frontalis and orbicularis oris being involved as well as the orbicularis oculi.

As stated under "Observations," there was good correlation between the clinical and electromyographic findings. This was also noted in relation to the electromyographic and histologic findings in all except the three cases mentioned above. In particular, a correlation between the single unit interference pattern, when that was obtained, and severe or subtotal degenerative changes in the nerves, was fairly clear. This seems a more reliable direction in which to attempt a correlation than any other. It must be kept in mind that both the electromyographic and the neuropath-

ologic observations were restricted in our cases to motor units in the lower eyelid, while the clinical assessment of the severity of lagophthalmos was more gross, being dependent merely upon the visual impression of the patient's ability to close his eye completely or otherwise. In the movement of voluntary closure of the eyes the action or weakness of the upper eyelid is generally more conspicuous.

There was good correlation of the neuropathologic findings with the results of electric stimulation at operation, but not with the grossly visualized changes in the nerve. Thus only three cases showed macroscopic thickening of the nerves to orbicularis oculi muscles, and these were not necessarily the most damaged nerves.

The one important question arising here concerns the possible pathogenesis or, more specifically, the mechanism of involvement of this motor nerve, the facial, in a disease that afflicts the sensory nerve termination primarily ([3, 5, 7, 8]). A related question is the one raised in our first paper ([1]), in stating the objectives of this study, viz., the predilective involvement of the branch to the orbicularis oculi—the zygomatic—of the facial nerve in the majority of cases where this nerve is at all affected. A plausible mechanism that can be conceived here rests upon three observed facts. First, in each patient of the present series, and in most other cases with facial nerve involvement, a concurrent finding of sensory impairment in the territory of the trigeminal nerve, especially of its maxillary branch, was detectable. At times a hypopigmented anesthetic patch in the malar region was visible, or a history of sensory impairment was elicited ([1]). Second, in a number of our cases the distal parts of the motor branches to the orbicularis oculi were more severely affected, with more degenerative changes and at times with more inflammatory reaction, than the proximal parts of these nerves as revealed in sections of biopsied tissue blocked *en masse*. Third, it is common knowledge ([6]) that there are several anastomoses between the facial and the maxillary nerves, and particularly between the zygomatic branch of the former and the palpebral branch of the latter, in the upper malar and lower eyelid region. With all these three observations in mind, it becomes conceivable that the leprous infection entering the malar skin through its sensory nerve fibers progresses in such a way as to involve the motor branches of the facial nerve in this area, either on account of the close proximity of, or of the actual anastomotic connections between, these two nerve territories. This would account also for the almost selective affection of the orbicularis oculi muscle and the consequent lagophthalmos so characteristic of leprosy ([2, 9]). Our last case (F-11) was perhaps the exception proving the rule, in that, from the history available, the patient manifested, within the space of one year, extensive involvement of all the muscles supplied by the facial nerve, without any initial predilective involvement of the orbicularis oculi muscle. Nevertheless, histologic examination of most of these branches did reveal a more active process and more severe damage distally than proximally.

Also to be kept in mind is the possibility of secondary factors operating upon the nerve branches in the zygomatic region. As indicated in our first paper ([1]), we are impressed by the close apposition of these branches against the unyielding bony background of the zygoma and the possibility of their compression there. Increased fibrosis and fibrous tunnels sleeving these branches also seem significant in this respect. The superficial subcutaneous location of the nerve twigs in this region raises the possibility of other secondary factors operating upon them here, such as colder temperature and exposure to trauma. These and other factors have been evoked earlier to account for certain sites of predilective involvement of nerves in the limbs ([4]).

Other branches of the facial nerve do not appear subjected to the operation of secondary factors, and do not form such well recognized anastomotic connections with cutaneous sensory nerves, as the zygomatic branches do, and are therefore likely to be involved later and less frequently, as in fact does seem to happen.

SUMMARY

Electromyographic findings in seven and histopathologic observations in 11 patients, and correlation of these with the clinical and operative observations reported in our first paper, have been presented here on cases with lagophthalmos due to leprosy.

Preoperative electromyographic observations on the orbicularis oculi, the frontalis and orbicularis oris in seven of the cases, revealed increased latency of conduction and abnormal muscle activity in the form of reduced interference patterns, giant single unit patterns and polyphasic potentials.

A chronic inflammatory and fibrosing neuritis of varying severity and duration was observed in all cases. Granulomatous reaction was noted in three.

The greater involvement of distal rather than proximal parts of the nerves to the orbicularis oculi was noted in a number of cases, and suggested the possible ingress of infection in this motor nerve from the sensory branches of the maxillary nerve anastomosing with the zygomatic branch of the facial nerve. The role of secondary factors operating upon the facial nerve branches in the bony zygomatic region is discussed.

There was a good correlation in eight of the cases between the clinical, the electromyographic, the operative electric stimulative and histopathologic findings. This was more evident in severely affected cases with single unit activity in which correspondingly severe nerve damage was evident structurally.

RESUMEN

Se presentan casos de lagoftalmos debidos a lepra, con hallazgos electromiográficos en siete casos, observaciones histológicas en 11 pacientes, y su coorrelación con las observaciones clinicas y operatorias presentados en nuestro primer trabajo. Las observaciones preoperatorias electromiográficas en el orbicularis oculi, en el frontalis y orbicularis oris en siete de los casos, revelaron un aumento de la latencia de la conducción y actividad muscular anormal en la forma de cuadros de reducida interferencia, cuadros de unidades únicas gigantes y potenciales polifásicos.

En todos los casos se observaron neuritis crónica inflamatoria y fibrosanta de severidad y duración variables. En tres se observó la reacción granulomatosa.

En un número de casos se notó un mayor envolvimiento de las partes distales mas que las partes proximales de los nervios del orbicularis oculi, y sugerido como posible ingreso de la infección a este nervio motor, desde las ramas sensoriales del nervio maxilar anastomótico com la rama zigomática del nervio facial. Se discute el papel de los factores secundarios operando sobre las ramas del nervio facial en la región osea zigomática.

Hubo buena correlación en ocho casos entre los hallazgos clínicos, electromiográficos, estimulaciones operativas eléctricas y la histopatología. Esto fué mas evidente en los casos severamente afectados con actividad de unidad única en los cuales correspondientemente fué mas evidente el severo daño nervioso.

RÉSUMÉ

On a présenté ici les observations électromyographiques faites sur sept et les observations histopathologiques faites sur onze malades avec lagophtalmos du à la lèpre, ainsi que des considerations sur la relation existant entre ces observations et les observations cliniques et opératoires relatées dans notre première communication.

Les observations électromyographiques préopératoires effectuées chez sept de ces cas au niveau de l'orbiculaire de l'oeil, du frontal et de l'orbiculaire de la lèvre, ont révélé une augmentation du temps de latence pour la conduction, ainsi qu'une activité anormale des muscles s'exprimant sous la forme d'une réduction dans les tracés d'interférence, de tracés avec unité isolée géante et de potentiels polyphasiques.

Dans tous les cas on a observé une névrite inflammatoire et fibrosante chronique de gravité et de durée variables. Une réaction granulomateuse a été notée dans trois cas.

Une atteinte des nerfs de l'orbiculaire de l'oeil plus prononcée au niveau distal qu'au niveau proximal a été notée dans plusieurs cas, ceci suggérant que la porte d'entrée de l'infection dans ce nerf moteur pourrait pendre place au niveau de l'anastomose des branches sensitives du nerf maxillaire avec la branche zygomatique du nerf facial. On discute du rôle de facteurs secondaires s'exerçant sur les branches du nerf facial dans la région osseuse zygomatique.

Chez huit de ces cas, il y avait une relation satisfaisante entre les observations obtenues par la clinique, par l'électromyographie, par la stimulation électrique opératoire, et par l'histopathologie. Ceci était plus marqué dans les cas d'atteinte grave avec activité d'unités isolées, chez lesquels un sérieux dommage nerveux correspondant était structuralement évident.

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