COMPARATIVE STUDY OF THE NERVE BRANCHES OF THE SKIN IN TUBERCULOID AND LEPROMATOUS LEPROSY

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During examinations of numerous histologic sections of leprosy lesions of the skin my attention has been struck by the different changes to be seen in the nerves and their relation to the clinical picture.

In tuberculoid leprosy the nerve injury is serious, and the sheath and the neurofibrils disappear rather early (Fig. 1), ending in complete destruction of the nerve. Of 50 tuberculoid cases involved in a previous study (1), no nerves whatever could be detected in the sections of 8 (16%) of them. In lepromatous leprosy, on the other hand, the damage is less marked, and it is exceptional to find a specimen in which nerves cannot be found. Both bacilli and infiltrating cells are often present within the nerves in this type of the disease. These facts show that the nerve branches in the skin behave differently in the different types of leprosy. The present paper is intended to analyze this behavior.

In the lepromatous type the nerve sheath, as well as the other nerve elements, can be found for a long time. It may be detached or shifted by the infiltration (Figs. 2, 3 and 4), but it is rarely destroyed. Sometimes Virchow cells are seen between the sheath and the nerve fibers, pushing the former outwards, and in a more advanced condition veritable cysts may be present (Fig. 5). Furthermore, nerves in which cellular infiltration is absent may show vacuoles of various sizes (Fig. 6), due to fatty degeneration and intraneural globi (Fig. 7).

In order to ascertain the degree of destruction in the two types of leprosy, a histologic analysis of all nerve branches in a series of skin specimens from lepromatous and tuberculoid cases was undertaken. The study involved a total of 12 specimens, 6 of tuberculoid and 6 of lepromatous lesions.

Every nerve observed in the histological section was outlined in a diagram drawn from the projected microscopic image, and the condition with respect to the following features was tabulated: (1) Situation of the nerves with reference to the infiltrates, they being sometimes without infiltration whereas at other times they were partially or entirely surrounded by infil-

tration. (2) Condition of the various nerve elements, namely, the perineurium or nerve sheath, the endoneurium, and the neurofibrils; sometimes they were present and of normal appearance, while at other times they were partly or completely destroyed. Special attention was given to nerve sheaths, which were often detached, or thickened (hyperplastic), or partially or completely destroyed. (3) Presence of bacilli in the same nerves studied, though in other sections stained by the Ziehl-Neelsen method. At times they appeared in large numbers, sometimes in globi, while in certain cases they were scarce. There were specimens in which not all of the nerves found in ordinarily stained sections could be detected after this method of staining.

RESULTS

The number of nerve branches found in these twelve specimens, and the numbers with and without infiltration, are shown in summary in Table 1.

(1) *Number of nerve branches found.*—In the lepromatous specimens a total of 120 branches was found, whereas in the tuberculoid specimens only 69—57.5 per cent as many—were identified, though these specimens averaged materially larger than the others. This fact supports the earlier evidence that nerve destruction is more common in tuberculoid than in lepromatous leprosy.

(2) *Proportion of branches in the infiltrates.*—It is also to be seen in Table 1 that only one-half of the branches found in the tuberculoid specimens (35 of 69, or 51%) were present in areas of infiltration, whereas in the lepromatous specimens more than three-quarters (94 of 120, or 78%) were so located. Evidence is seen here that nerve branches located in the infiltrates are more seriously affected in tuberculoid than in lepromatous leprosy.

(3) *Analysis of the nerve elements.*—The data on the three principle nerve elements, the perineurium, the endoneurium and the neurofibrils, are consolidated in Table 2. From the data there given it is evident that in the tuberculoid lesion there predominate destructive processes which affect all of the principal elements, in varying degrees. In the lepromatous lesions, on the other hand, persistence of these elements is the rule, their partial or complete destruction occurring with relative infrequency.

TABLE 1.—*Number and condition of nerve branches found in specimens examined.*

Specimen Number	Length of specimen	Total nerve branches	Without infiltration	With infiltration
Lepromatous				
1	1.3 cm.	27	1	26
2	0.9 cm.	7	0	7
3	1.2 cm.	10	4	6
4	1.5 cm.	23	2	21
5	1.1 cm.	19	1	18
6	1.0 cm.	34	18	16
Total	7.0 cm.	120	26	94
Average	1.2 cm.	20	4.3	15.7
Tuberculoid				
7	1.0 cm.	5	3	2
8	1.5 cm.	8	0	8
9	1.6 cm.	20	7	13
10	1.8 cm.	6	4	2
11	1.5 cm.	10	3	7
12	1.5 cm.	20	17	3
Total	8.9 cm.	69	34	35
Average	1.5 cm.	11.5	5.7	5.8

TABLE 2.—*Condition of the elements of the nerves in the specimens examined.*

Type of lesion	Infiltration	Condition of the nerve element, and numbers	
Perineurium:			
Tuberculoid	Absent	Perineurium present	34
	Present	Perineurium present	3
		Perineurium partially destroyed	7
		Perineurium completely destroyed	25
Lepromatous	Absent	Perineurium present	26
	Present	Perineurium present	67
		Perineurium partially destroyed	15
		Perineurium completely destroyed	12
Endoneurium:			
Tuberculoid	Absent	Endoneurium present	34
	Present	Endoneurium present	9
		Endoneurium partially destroyed	10
		Endoneurium completely destroyed	14
		Sclerosed	2
Lepromatous	Absent	Endoneurium present	22
		Endoneurium partially destroyed	4
	Present	Endoneurium present	58
		Endoneurium partially destroyed	34
		Endoneurium completely destroyed	2
Neurofibrils:			
Tuberculoid	Absent	Neurofibrils present	34
	Present	Neurofibrils present	5
		Neurofibrils partially destroyed	16
		Neurofibrils completely destroyed	14
Lepromatous	Absent	Neurofibrils present	21
		Neurofibrils partially destroyed	3
		Neurofibrils completely destroyed	2
	Present	Neurofibrils present	50
		Neurofibrils partially destroyed	37
		Neurofibrils completely destroyed	7

(4) *Bacilli within the nerves, in lepromatous cases.*—The findings in the sections of lepromatous lesions stained for bacilli are summarized as follows: Of the 26 nerve branches free from cellular infiltration, no less than 20 (77%) revealed bacilli; they were absent in 2 branches, and the condition of 4 was uncertain. Of the 94 branches with infiltration, 63 (67%) had bacilli;10 were without them, and 21 were recorded as uncertain. From these findings it appears that, in lepromatous lesions, most of the nerves contain Hansen bacilli whether infiltration is present or not; and from this fact it may be concluded that the nerves are constantly damaged in that form of the disease.

DISCUSSION

The changes which have been considered are of different degrees of importance. The most important are the relation of the nerves with the infiltrates, the condition of the perineurium, and absence or presence of bacilli. Less important are the condition of the endoneurium and the neurofibrils; in fact, for evaluating them one must compare them with the perineurium. However, when that structure has been displaced or has disappeared, one has no base point for determining the degree of conservation or destruction of the nerve.

The data which have been presented are taken to indicate that injury to the nerves is always present in both types of leprosy, with infiltration and destruction in the tuberculoid form, and infiltration and common presence of bacilli in the lepromatous form.

The disproportion of nerve branches found in the tuberculoid specimens (69) and those found in the lepromatous specimens (120) is all the more striking when it is considered that in total the tuberculoid specimens were larger than the lepromatous ones (average length 14.8 mm. as against 11.7 mm.), and also that every tuberculoid specimen included an area of normal skin whereas the lepromatous specimens were from areas with the diffuse involvement typical of that type of lesion.

The fact that bacilli are constantly present in the nerves in lepromatous lesions, with much less serious damage than is suffered by the nerves in tuberculoid lesions, where the finding of bacilli is exceptional, presents an interesting problem. It seems evident that nerve destruction in tuberculoid leprosy is accomplished by the infected organism itself—in other words, by an allergic reaction of the body.

This important fact can be explained by either of two hypotheses according to which the injury would be regarded either as

a consequence of allergy or as a factor of that condition. (*a*) Considering the nerve damage as a consequence of an allergic condition, it is an incidental or secondary effect of a rather violent reaction of the organism to the presence of the leprosy bacillus in an effort to destroy it. (*b*) Considering the damage as a causative factor of the allergic process, it would represent a histo-physio-pathological element of the whole allergic process. I do not have enough evidence to determine which of these hypotheses is correct; were it the second one, a new field for therapeutic experimentation would lay open.

In the lepromatous type, contrary to the fact in the tuberculoid type, nerve damage is serious only in advanced cases, in early cases the nerves remain present, though they contain bacilli. This finding may prove useful in solving the problem of prognosis of the indeterminate form of leprosy. There are cases of that group whose lesions show marked nerve damage, and one must suppose that they are inclined to evolve toward the tuberculoid form and should therefore be of benign prognosis. This matter needs further investigation, from the clinical and pathological points of view.

SUMMARY AND CONCLUSIONS

A comparative study of the cutaneous nerve branches in 6 specimens of tuberculoid and 6 of lepromatous leprosy has given evidence of severe nerve damage in tuberculoid cases, and less marked damage in the lepromatous ones. But nerve injury is constantly present in both types of the disease, since most of the nerves in the lepromatous specimens contain bacilli in spite of their apparently good condition. The observations here recorded lead to the following conclusions:

1. Nerve injury is constant in both tuberculoid and lepromatous leprosy.

2. The perineurium, endoneurium and neurofibrils remain present and recognizable for a long time in lepromatous leprosy, whereas in the tuberculoid form they tend to be destroyed at a relatively early stage of progression of the disease.

3. Nerve destruction in tuberculoid leprosy is a manifestation of an allergic process, but it cannot be said whether it is a consequence of or one of the causative agents of allergy.

4. Further study is required to determine if indeterminate cases with severe nerve destruction evolve toward the tuberculoid form.

REFERENCE

CASTAÑÉ DECOUD, A. Estudio histopatológico de las neuritis en la lepra tuberculoide; su valor diagnostico. Tesis de Doctorado, 1942.

DESCRIPTION OF PLATES

PLATE 26

FIG. 1. Tuberculoid leprosy. Epithelioid cells are invading the nerve, tending to destroy it.

FIG. 2. Lepromatous leprosy. The perineurium is detached and separated from the nerve bundle by infiltrating cells, but it is not destroyed.

FIG. 3. Lepromatous leprosy. A few infiltrating cells are present between the perineurium and the nerve itself on one side. The endoneurium presents a homogeneous appearance. Three spongy neurofibrils are visible.

FIG. 4. Lepromatous leprosy. The perineurium is hyperplastic and separated from the nerve itself by Virchow cells. The endoneurium and neurofibrils in this instance are regarded as "partially destroyed."

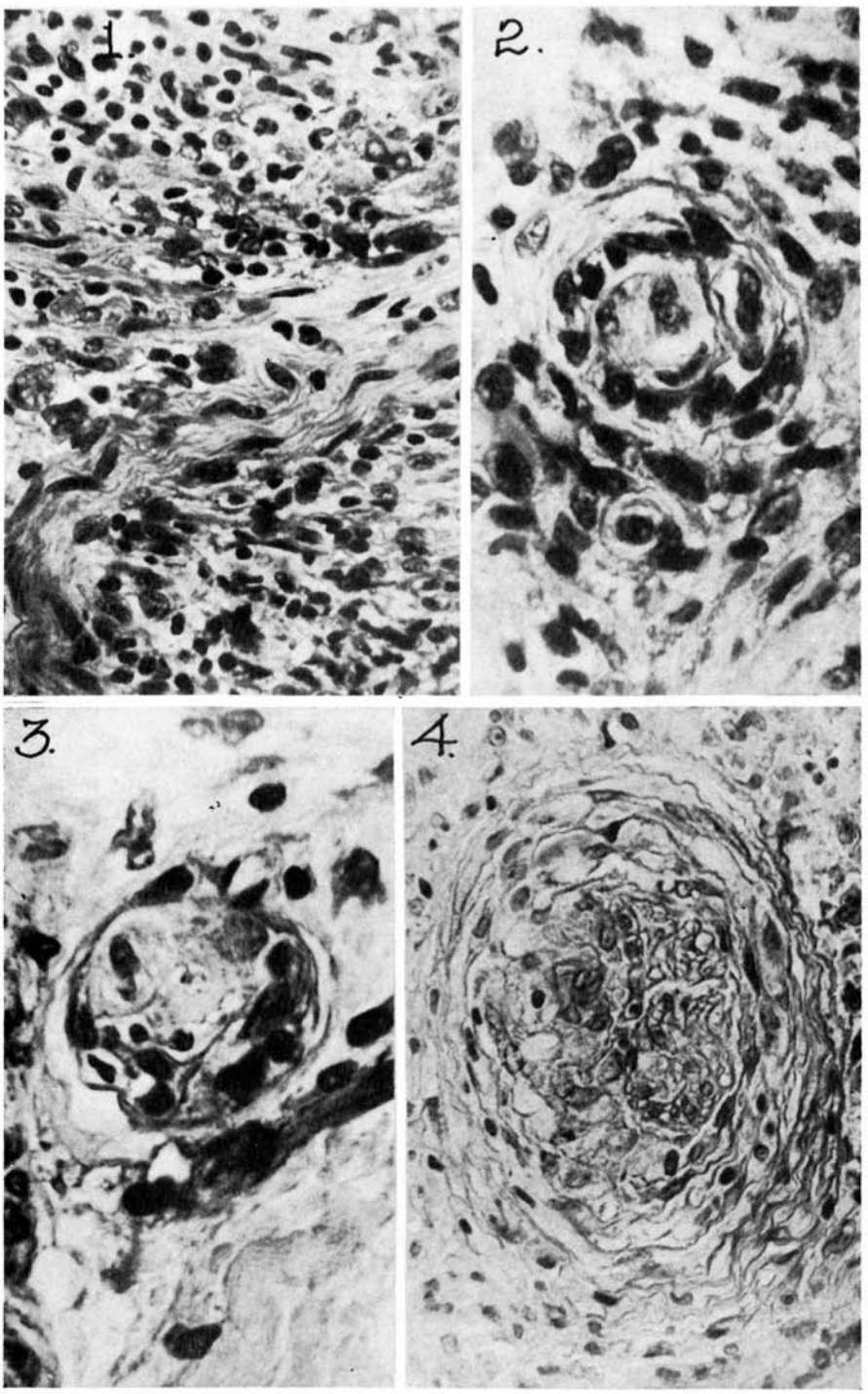


PLATE 26

PLATE 27

FIG. 5. Lepromatous leprosy. The hyperplastic perineurium is displaced by cellular elements, and there is a cystic space between it and the nerve.

FIG. 6. Lepromatous leprosy. This nerve shows no cellular infiltration, but there are vacuoles of various sizes. The perineurium is hypertrophic.

FIG. 7. Lepromatous leprosy. A nerve stained by the Ziehl-Neelsen method, containing numerous groups of bacilli and globi but no infiltrative cells.

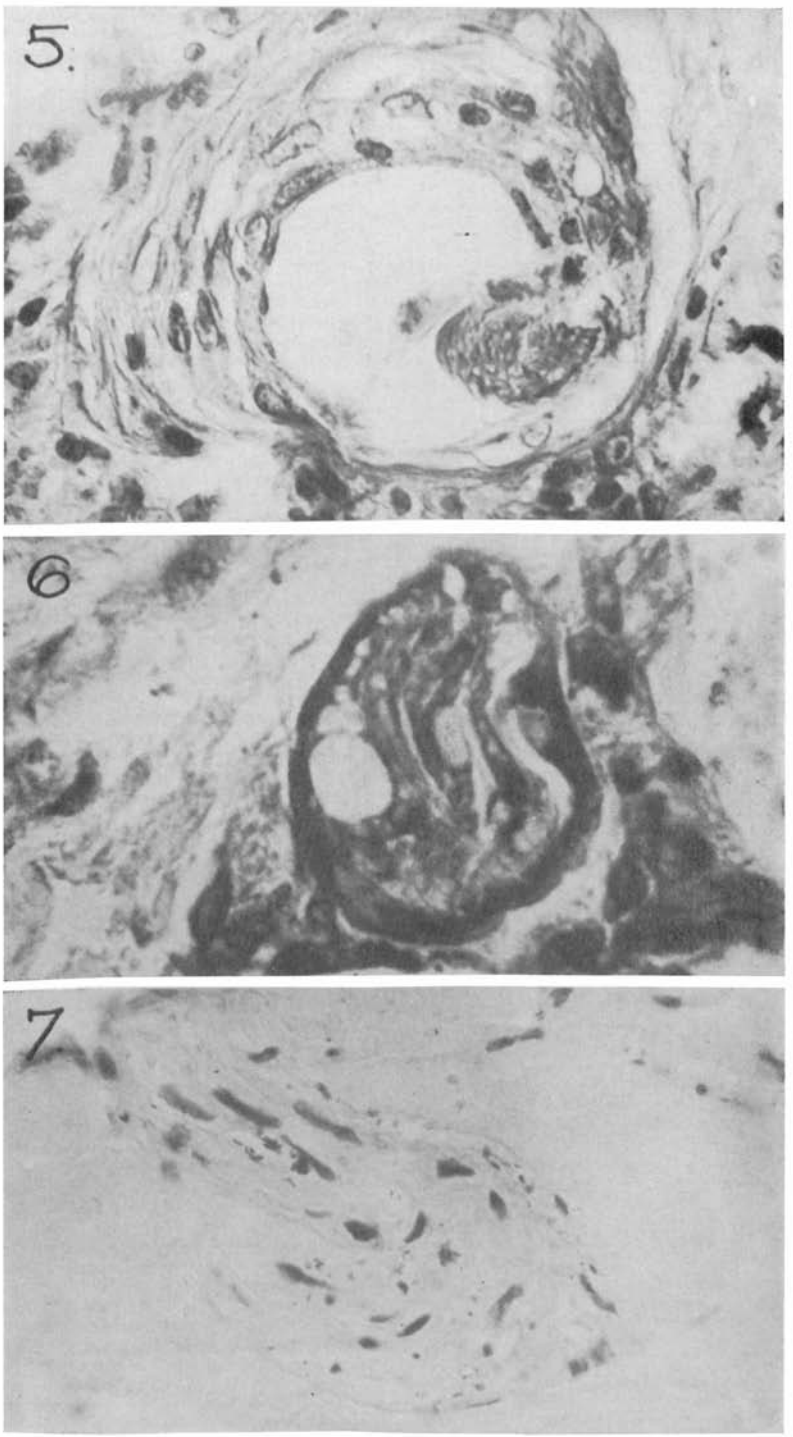


PLATE 27

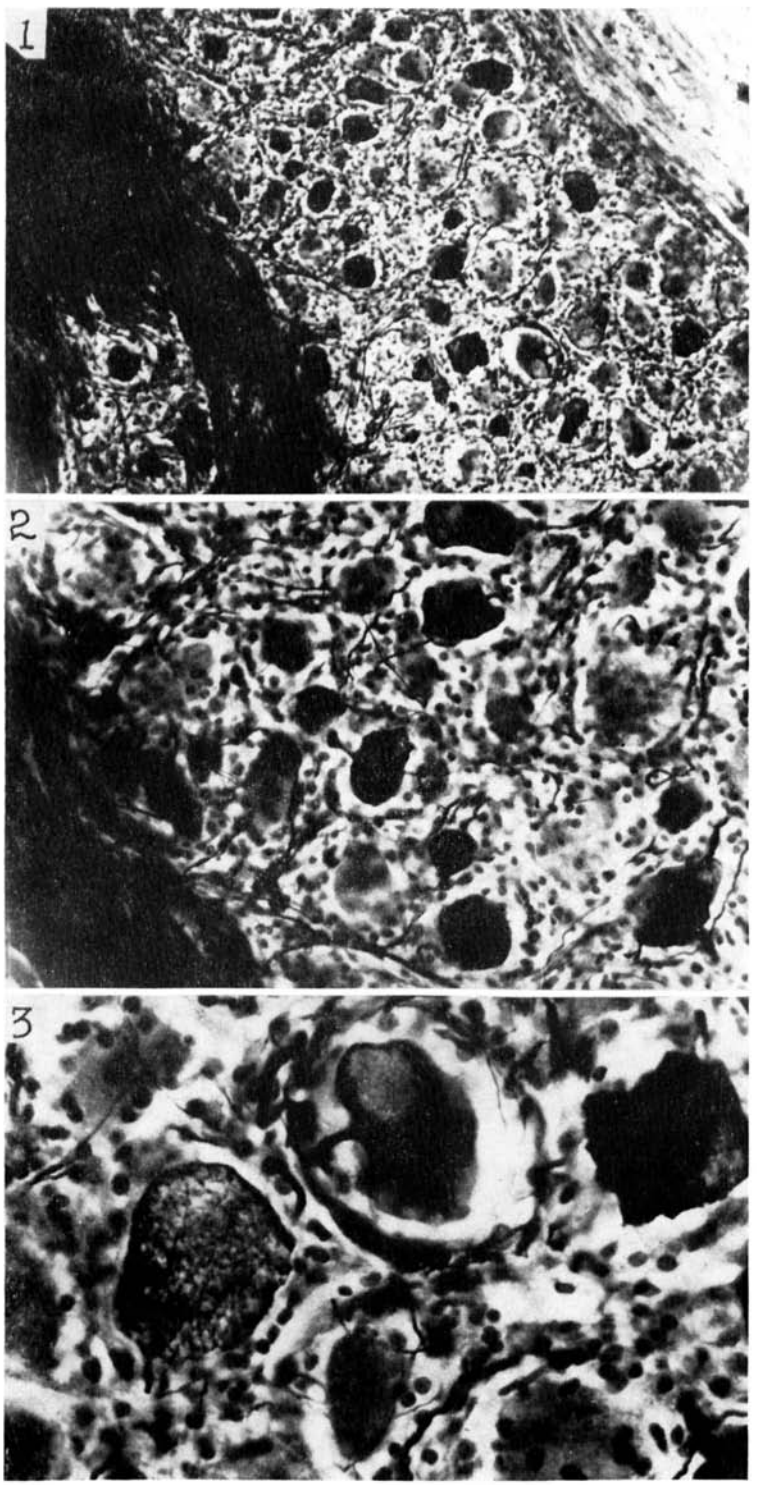
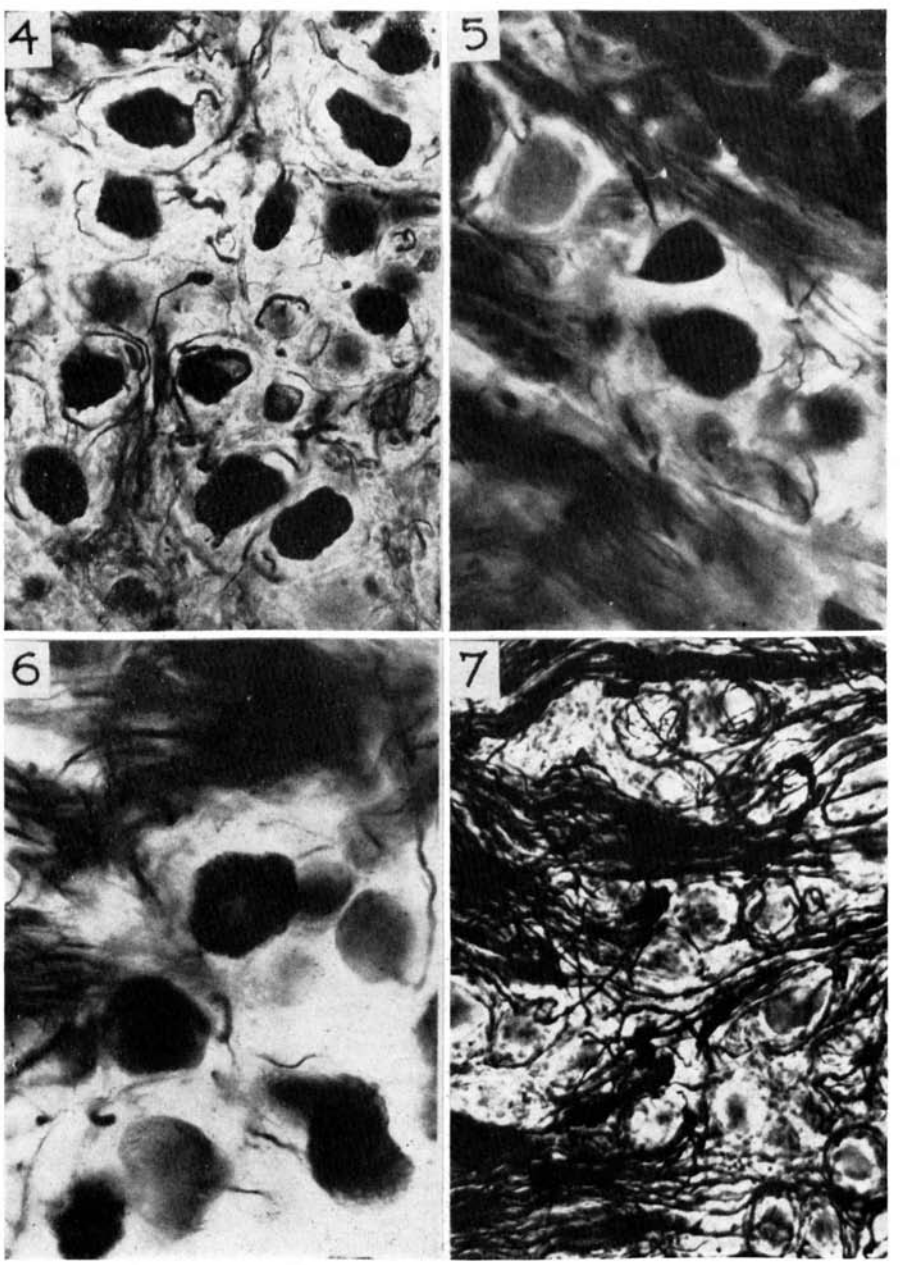


PLATE 28



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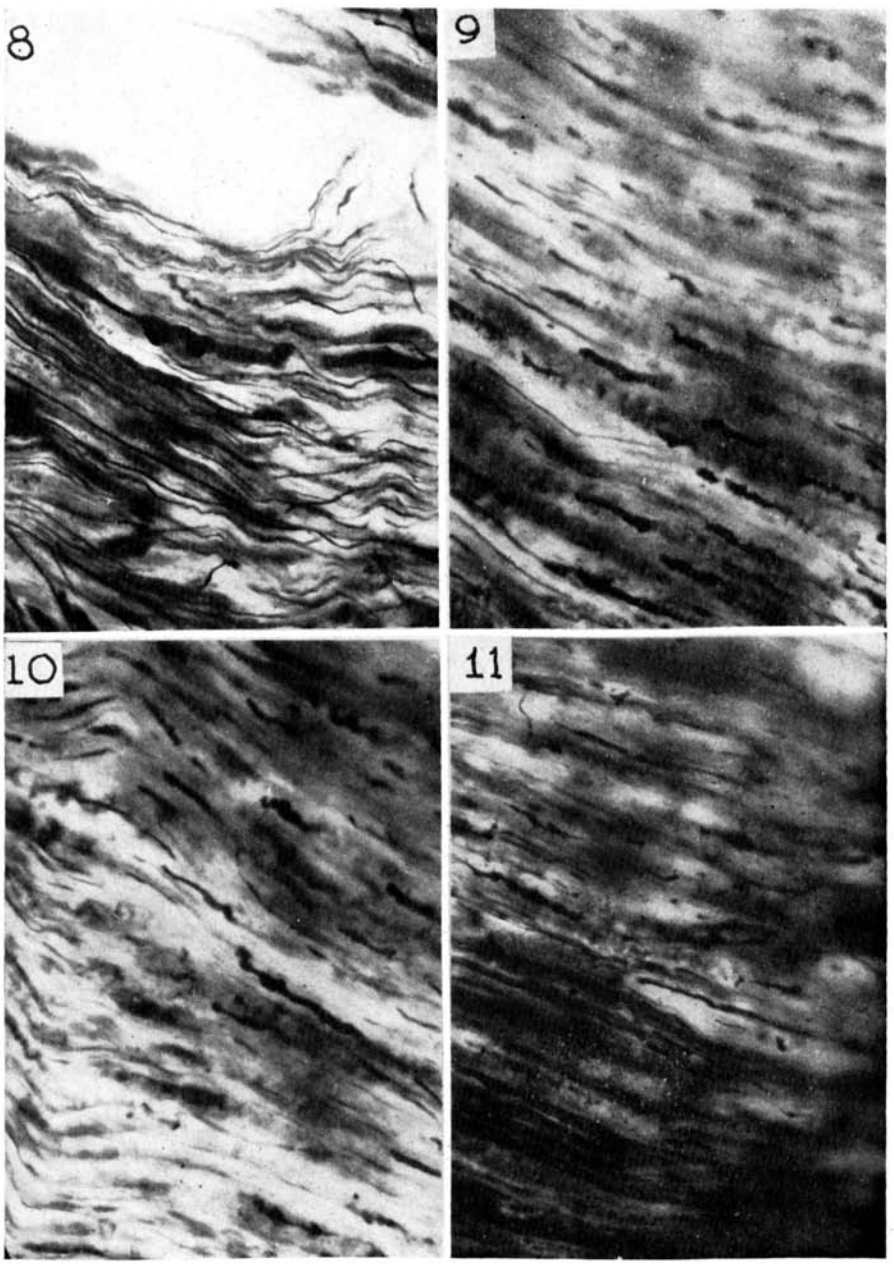

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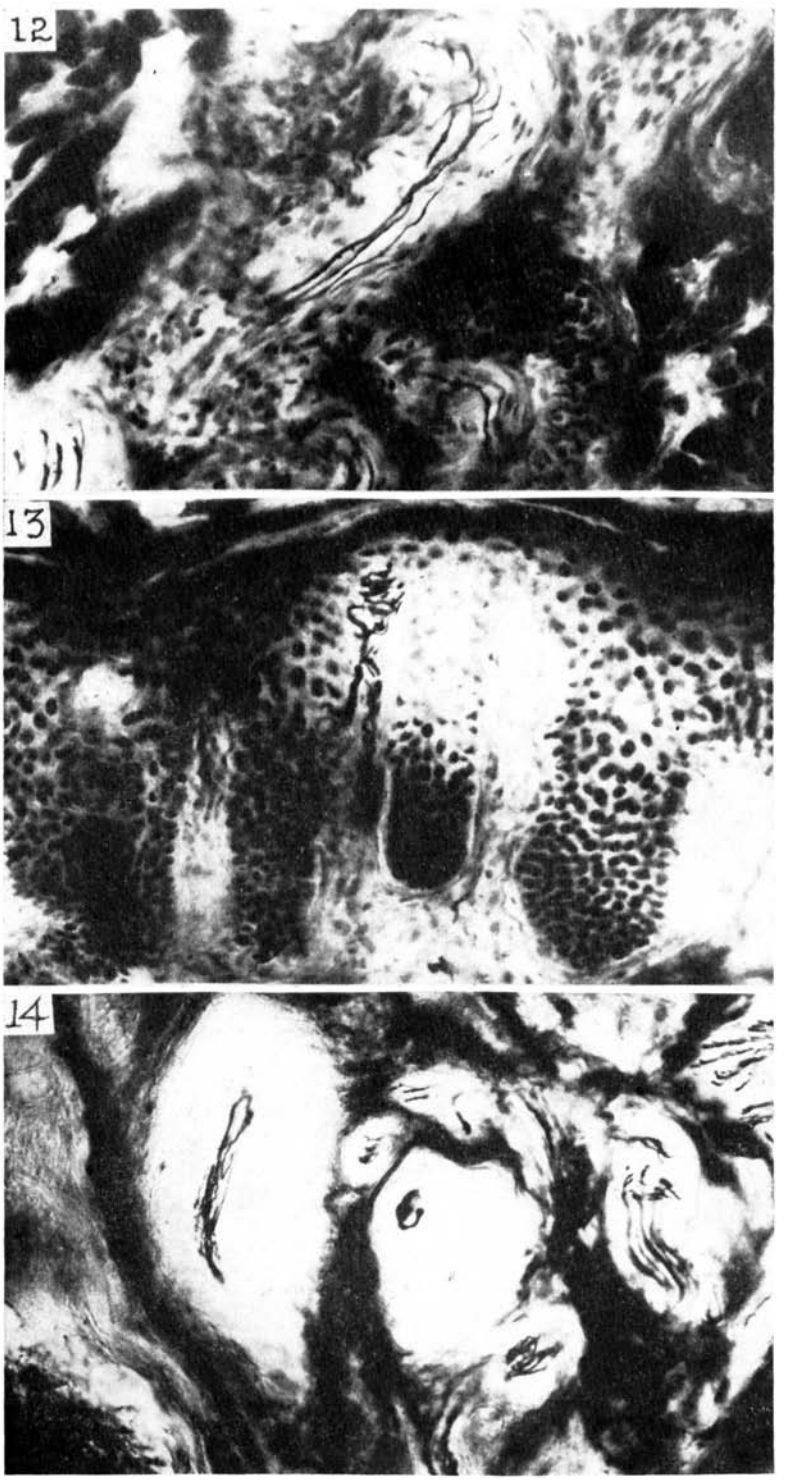

PLATE 31

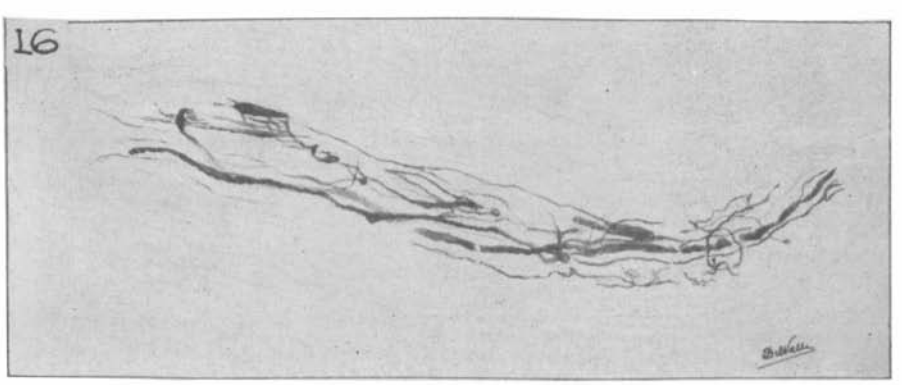

PLATE 32