

LYMPH NODES IN LEPROSY¹

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The involvement of lymph nodes in leprosy is said to have been recorded by Gadesden in the 15th century ⁽⁸⁾, and has been included as a feature in all modern textbooks dealing with leprosy. Klingmüller ⁽¹⁴⁾, Basombrio ⁽²⁾, Schujman and Vaccaro ⁽²⁴⁾ and Furniss ⁽⁷⁾ have described the gross and microscopic appearances of the lymph nodes in leprosy. Leprologists are unanimous that the lymph nodes are invariably involved in lepromatous leprosy, but there is disagreement about the finer histologic details; and there have been differences of findings in tuberculoid leprosy. The present investigation was undertaken to study in detail the structural alterations produced in lymph nodes in lepromatous leprosy, and also to see if the nodes are at all affected in tuberculoid leprosy, and if so to what extent.

MATERIALS AND METHODS

One hundred and fifty-five leprosy patients were examined clinically for enlargement of lymph nodes. Ninety-five of these patients showed enlargement of one or several groups of nodes, and of them 40 consented to lymph-node biopsy. Of these 40 patients, 24 had lepromatous leprosy (2 of them mixed) and 16 were tuberculoid. The nodes were removed from various regions: 31 were supratrochlear, 5 were inguinal, and 4 were cervical.

The excised glands were examined in gross and then bisected. One-half of each was preserved in formalin-saline for histologic study, after making a smear for Ziehl-Neelsen staining. The other half was homogenized and inoculated into Loewenstein-Jensen medium. Facilities for animal inoculation were not available. Sections were stained in all cases with Ehrlich's hematoxylin and eosin stain, Fite's second method for the demonstration of lepra bacilli ⁽⁶⁾, the Masson-Goldner stain for connective tissue ⁽⁹⁾, and the Laidlaw silver carbonate stain for reticulin fibrils ⁽¹⁵⁾.

OBSERVATIONS

Gross appearance.—In most instances the lymph nodes were only slightly enlarged. In only 16 cases could the enlargement be called moderate, the greatest dimension 2 cm. or more. The external appearance was smooth, pink and glistening, with no evidence of periadenitis. Sectioned surfaces of the nodes from the lepromatous cases presented either a uniformly yellowish tinge or small yellowish foci irregularly distributed throughout or confined only to the cortex. The cut surfaces of the nodes from tuberculoid cases presented a uniformly pinkish-gray appearance.

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Microscopic structure of nodes from lepromatous cases.—Thickening of the capsule was present in only 25 per cent of cases in spite of the prolonged course of the disease, and there was no evidence of periadenitis. In most instances there was diffuse infiltration of the nodes by lepra cells. These were large pleomorphic cells with pale vesicular nuclei and abundant cytoplasm, which last was uniformly eosinophilic in only a few cells. Most of these cells were foamy or well filled with one or several clear vacuoles. The vacuoles sometimes attained large size, and in such cells the nuclei were hardly to be seen; the vacuoles were surrounded only by syncytial protoplasm. Giant cells were seen here and there, but they were never of the classical Langhans type. They often resembled the Touton giant cell. In a few cases the lepra cells were elongated and closely packed, resembling epithelioid cells, but there was no attempt at formation of discrete tubercles, a feature commonly seen in Boeck's sarcoid or tuberculosis.

The marginal sinuses were unaffected and did not contain lepra cells except in 3 instances. They were obliterated in some of the glands due to diffuse infiltration of the cortex by lepra cells producing marked compression of the sinus walls. These sinuses did not contain bacilli nor did they show proliferation of the littoral cells. The intermediary sinuses were grossly infiltrated with large foamy or vacuolated lepra cells. In a few glands the littoral cells in these sinuses showed hyperplasia, but they did not contain acid-fast bacilli. Medullary cords, wherever there was lepromatous infiltration, were thin and atrophic. The sinuses or the lymphoid tissue did not contain red blood cells or pigmented products of their destruction.

With the Fite technique the bacilli were easy to stain in the epithelioid cells. However, in the vacuolated cells there were great numbers of bacilli, mostly occurring at the periphery, although infrequently clumps of bacilli were seen in the center, occurring in globi. Large vacuoles were nearly always empty, and single acid-fast rods dusted the cytoplasm. Short rods as well as granular forms evidently representing the disintegrating masses of bacilli were also seen in the lepra cells. There were no bacilli in lymphocytes, endothelial cells of vessels, littoral cells, or the cells lining the peripheral sinuses. No free bacilli were seen inside the sinuses or blood vessels. Here and there a few isolated bacilli were seen lying free in the neighborhood of the areas of lepromatous infiltration, presumably representing bacilli scattered over the field as a result of disintegration of some of the lepra cells during processing of the tissue. Abundant acid-fast bacilli were seen in all the lepromatous lymph nodes except 2, in which the organisms were scarce. In only 1 lymph node the vacuoles showed no bacilli.

The capsule was not infiltrated by typical vacuolated lepra cells, nor were any bacilli demonstrated there. In none of the specimens were there noted regressive changes like fibrosis or sclerosis, hyaline changes, or deposits of calcium. There were no areas of caseation or suppuration. In this connection Case 9 is worth mentioning. The sections showed all the classical

histologic appearances of a lepromatous leprosy, but there were also large tubercles composed of epithelioid cells and typical Langhans giant cells, with no caseation. Acid-fast staining showed bacilli in the lepromatous foci, but the tubercles were conspicuous by the absence of bacilli. This case presumably represents coincidence of tuberculosis with leprosy. Unfortunately, as no guinea-pig inoculation was done this coincidence cannot be proved or disproved.

The Laidlaw reticulin stain did not show any increased formation of reticulin within or around the lepra-cell infiltration. On the contrary, the reticulin network appeared looser than normal in areas of dense lepra cell infiltration.

Microscopic findings in nodes from tuberculoid cases.—None of the 16 such nodes examined showed any significant histologic alteration. Lepra cells, the hall-mark of lepromatous leprosy, were conspicuous by their absence. Tubercles composed of small collections of epithelioid cells were not identified in any of these lymph nodes, nor were leprosy bacilli found in any case.

DISCUSSION

Frequency of lymph node enlargement.—In the present investigation an attempt was made to ascertain the frequency of lymph node enlargement and its correlation with the type of leprosy studied. We studied clinically 155 cases, and the figures compare favorably with those of Schujman and Vaccaro and of Basombrio in Argentina, as shown in Table 1.

TABLE 1.—*Frequency of lymph node enlargement.*

Authors	Type of leprosy	No. of cases	Lymph nodes enlarged	
			Number	Per cent
Schujman	Lepromatous	150	144	96
& Vaccaro	Tuberculoid	50	30	60
Basombrio	(Not stated)	173	156	90
Present	Lepromatous	82	61	76
authors	Tuberculoid	73	34	46

Frequency of enlargement of regional nodes.—There is much divergence of experience regarding the frequency of enlargement of different groups of lymph nodes, as seen by various authors. Our own figures vary from those of others, as represented by those of Basombrio, as is to be seen in Table 2.

As these findings are purely clinical, there can be much doubt as to the significance of the enlargements found. Furniss (⁷) believes that, because nonspecific glandular enlargement is so common, it is difficult to recognize clinically whether the enlargement is due to leprosy, and consequently that

clinical observations of glandular enlargement or involvement are of very little significance.

Our own observations bear out the opinion that it is not possible to determine clinically the exact nature of lymph node enlargement in a case of

TABLE 2.—*Frequency of enlargement of lymph node of different regions.*

Regional nodes	Basombrio	Authors
Inguinal	84%	45%
Cervical	47%	33%
Axillary	42%	20%
Epitrochlear	25%	62%

leprosy; histologic and other examinations are required. To rule out the discrepancy of lymph node enlargement due to associated complicating factors, in our study we included serological investigations and cultures for tubercle bacilli.

Correlation between cutaneous lesions and regional lymph node enlargement.—The study was further extended to see if there is any correlation between the extent and distribution of cutaneous lesions and the location of lymph node enlargement. The findings in the 40 cases biopsied are shown in Table 3.

TABLE 3.—*Correlation between lymph node enlargement and cutaneous lesions in areas of drainage, in the 40 cases biopsied.*

Regional nodes	Enlargement		Cutaneous lesions ^a	
	Unilateral	Bilateral	Unilateral	Bilateral
Inguinal	4	20	10	2
Cervical	3	9	8 ^b	
Axillary	2	2	2 ^c	2 ^c
Epitrochlear	4	34	20	7

^a In the areas of drainage.

^b Skin lesions mostly in the midline.

^c Excluding the lesions drained by the epitrochlear nodes.

It will be appreciated that there was no relationship between the distribution of skin lesions and the location of enlarged lymph nodes. In several cases the skin lesion was confined to one particular spot when several groups of lymph nodes were enlarged.

Gross appearance of biopsy specimens.—Hansen and Looft (¹⁰) reported an enlarged node as large as pigeon's egg, and even larger ones are said to

have been recorded. Of our specimens from lepromatous cases the enlargement was only slight, the largest specimen measuring 2.8 cm. in maximum dimension.

Very characteristic appearances of the cut surfaces of the nodes in lepromatous leprosy have been described by various authors. According to Hansen and Looft the cut surface is characteristically yellow to yellowish-brown in hue and filled with brown bodies. The capsules and the trabeculae would be thickened, but in general the structure would be preserved. Iwanowsky ⁽¹¹⁾ stated that the nodes in lepromatous leprosy range from yellowish to reddish-brown in color and sometimes show blood pigments. Jeanselme ⁽¹²⁾ describes the lymph nodes as large, whitish-pinkish and translucent on section, with an area of whitish spots at the periphery giving a variegated appearance reminiscent of adrenal cortex according to Virchow's ⁽²⁶⁾ comparison. According to this author in the first stage the lesion occupies the periphery and later on the medulla is also involved. Numerous pigmented areas can be seen and finally the tissue becomes sclerosed and the architecture of the lymph node becomes obliterated.

Wade and Rodriguez ⁽²⁷⁾ describe the lymph nodes in active cases as enlarged, rather opaque and yellowish-white and in the chronic cases tended to be rather small and very often with prominent yellow bands. Sometimes they had seen abscess formation in reaction cases, without superimposed pyogenic infection. Mitsuda ⁽²⁰⁾ believes that it is possible to tell, on naked-eye inspection, whether the lesion is old or recent. For example, when the lesion is new its surface presents a pale, pearly color, while old infiltrations are dark gray or yellow or yellowish-brown. That such a change and variety of color is related to the age of the lipid substance may be demonstrated by microscopic examinations. When the cut surfaces looks pale and translucent the vacuolated cells are not clearly visible and the bacilli are of rod forms and grouped in bundles. When vacuolated lepra cells are recognized, the lepra bacilli are few and of granular form, macroscopically imparting yellow or yellowish brown color to the cut surface.

In the present series the involved lymph nodes presented either uniformly yellow hue, or yellow cortical foci were seen standing out prominently against a pinkish-gray background of normal lymphoid tissue. Our observations are in agreement with those of other workers. Abscesses as described by Wade were not observed.

Histologic alterations of nodes in lepromatous leprosy.—Our findings in the lymph nodes removed from lepromatous cases differ significantly from those of others in several respects.

Mitsuda and Ogawa ⁽²¹⁾ stated that the sinuses are not infiltrated with lepra cells, although a small number of bacilli may be demonstrated, never enough to block them. Kobayashi ⁽¹³⁾ observed lepra cells in the lymph sinuses in 56 out of 60 cases. Miguel ⁽¹⁹⁾ states that the lymphatic sinuses become obstructed by the lining cells which change into Virchow's cells.

Schujman and Vaccaro (²⁴) found blocking of the sinuses by lepra cells in all of the 14 lepromatous cases studied. Furniss has examined 48 lymph nodes from lepromatous cases and found that the sinuses were not involved in any. Proliferation of littoral cells was present in 20 of his cases, but no lepra cells could be demonstrated. MacCallum (¹⁷) states that in lymph nodes the leprous granuloma is found to occupy the margins of the lymph cords, leaving the sinuses fairly free.

In 22 of our 24 lepromatous lymph nodes the intermediary sinuses were packed in most cases with lepra cells with a blurring or complete obliteration of the sinus outlines. In many of the cases the peripheral sinuses were obliterated due to compression from below, as the lymph follicles were enlarged as a result of marked lepromatous infiltration, but lepra cells were demonstrated in the peripheral sinuses in only 3 cases.

Besides the large vacuolated lepra cells, in 7 of the lymph nodes varying numbers of large pleomorphic cells with vesicular nuclei and abundant cytoplasm were also present. These represent earlier stages of lepra cells which in due course of time would have developed foamy cytoplasm and later on increasing sizes of vacuoles. Bacilli in these cells were abundant and easy to stain. Vacuolated lepra cells containing varying numbers of acid-fast bacilli were demonstrated in all but one of the lepromatous lymph nodes, but the histology in this case was absolutely characteristic of the lepromatous lesion. In several of his cases Basombrio (²) failed to demonstrate bacilli in sections in spite of characteristic and constant tissue changes of lepromatous infiltration. Furniss found acid-fast bacilli in all but two of the glands from lepromatous cases, and they were from patients with early macules.

Tuberculosis and leprosy in lymph nodes.—Simultaneous occurrence of leprosy and tuberculosis in lymph nodes has been observed by many workers. Mitsuda mentions that the lepra bacilli have greater affinity for areas affected by tuberculosis. Sugai (²⁵) states that if the lymph node is affected both by leprosy and tuberculosis, the former suppresses the latter. In McCoy's series (¹⁸), after culture directly from the gland onto egg media in 2 cases, and in other 8 after guinea-pig inoculation, human type tubercle bacilli were isolated. Furniss found 12 glands showing the classical histologic picture of tuberculosis, and 9 of these were confirmed as tuberculous by other necropsy evidences or by guinea-pig inoculation. The histologic picture in the other 3 cases was so characteristic that they were accepted as tuberculous although animal inoculation was not carried out.

In the present study cultures of all lymph nodes were made on Loewenstein-Jensen medium, but no growth was observed at the end of six weeks' incubation. The lymph node from Case 9 showed diffuse lepromatous infiltrate and typical tubercles composed of epithelioid cells and Langhans' giant cells, and this is regarded as tuberculous in spite of our failure to isolate tubercle bacilli. This is in consonance with the observations of Furniss.

Various authors have found evidence of fibrosis to the extent of dense sclerosis of lymph nodes in late stages of leprosy. Furniss did not observe fibrosis in any of his cases. In our series no significant fibrosis was demonstrated in any of the nodes, although the duration of the disease varied from 1 to 10 years. Only rare patchy areas of fibrosis were observed in a few nodes. Thickening of the capsule was seen only in 10 cases (25%). Periadentitis was present in only 17.5 per cent of the lymph nodes. Sclerosis of the nodes apparently does not show any relation with the duration of the disease.

Histology of nodes in tuberculoid leprosy.—The literature on visceral and lymph gland enlargement in tuberculoid leprosy is meager. Certain workers, like Arning (¹), Rabello, Jr. (²³), Lowe (¹⁶), and Schujman and Vaccaro (²⁴), have produced some evidence to suggest glandular and visceral involvement in tuberculoid leprosy, but the evidence is not unequivocal, although tuberculoid changes in biopsy specimens of the liver have been reported by de Castro (^{3, 4}) and Okada (²²). Like most workers Furniss did not observe any change in a dozen lymph nodes from tuberculoid cases. In the present series of 16 lymph nodes from tuberculoid leprosy no histologic alterations were observed.

One has to answer a moot question—why have not the tuberculoid histologic changes been described regularly in the lymph nodes and internal organs? The reason for this, presumably, is that *Mycobacterium leprae* can only invade pathologically the whole reticuloendothelial system by first passing through the skin and then becoming disseminated throughout the whole body through lymph and blood channels. In tuberculoid leprosy the bacilli are so walled off that there is little or no possibility of their widespread dissemination.

Another interesting feature noted during this study was the fact that the reticulin framework was well maintained in lymph nodes affected by lepromatous leprosy, whereas in tuberculous pathology the reticulin framework is destroyed. This histologic difference may sometimes be helpful in deciphering doubtful histology, as for example in the specimen from Case 9. In the lepromatous zone the reticulin network was intact, and whereas it was destroyed in the area affected by tuberculosis.

It will not be out of place to mention a few interesting studies on lymph nodes and our own observations thereon. Certain workers, beginning with Neisser, are said to have considered the lymph nodes as a storehouse of the bacillus in lepromatous leprosy, from where reinfection may occur. Marchoux believed that there is a latent gland leprosy which may be unrecognized. Cochrane (⁵) states that the organism may lurk in lymph nodes long after it has disappeared from the skin. We have nothing to substantiate or refute these views. These points can only be settled by the study of the same case of leprosy from early to late stages, doing skin and gland punctures at different periods. In the present series there was no case in which the skin was

negative for acid-fast organisms and the lymph node positive. In this connection Case 2 is interesting, however. Skin smears showed only rare organisms, but the lymph node was loaded with them. On the other hand, in 5 cases out of the 24 skin smears were 2+ or 3+ positive, whereas the lymph node smears were negative and the histologic sections showed very few organisms. In other cases there was a close parallelism between the numbers of organisms in the smears from the skin and the node. All our cases were well advanced in the disease, hence there would have been no point in making lymph node punctures for the purpose of demonstrating the earliest involvement of nodes in lepromatous leprosy.

SUMMARY AND CONCLUSIONS

1. Clinically 155 cases of leprosy were examined for enlargement of lymph nodes, and one or several showed definite enlargement in 95 cases.
2. In order of frequency the enlarged nodes were: epitrochlear (62%), inguinal (45%), cervical (33%) and axillary (20%).
3. There was no correlation between the site of cutaneous lesion and the regional lymph node enlargement.
4. Biopsies were made of 40 lymph nodes; 24 from lepromatous cases (2 of them mixed), and 16 from tuberculoid cases.
5. Characteristic lepromatous infiltration of the nodes was found in all the specimens from the lepromatous cases.
6. Peripheral sinuses were involved only in 3 instances, whereas intermediary sinuses were packed with typical Virchow lepra cells in almost all of the nodes from lepromatous cases.
7. Acid-fast bacilli could be demonstrated in all but one of the lymph nodes from lepromatous cases.
8. The reticulin framework in areas of lepromatous infiltration was well preserved.
9. Thickening of capsule, periadenitis, and patches of fibrosis were seen only in very few cases.
10. Sixteen lymph nodes from tuberculoid leprosy did not show any histological alteration from normal.

RESUMEN Y CONCLUSIONES

1. Se examinó clínicamente a 155 casos de lepra en busca de hipertrofia de los ganglios linfáticos, y uno o varios de éstos revelaron hipertrofia bien definida en 95 casos.
2. En el orden de su frecuencia, los ganglios hipertrofiados fueron: epitrocleares (62%), inguinales (45%), cervicales (33%) y axilares (20%).
3. No hubo correlación entre el sitio de la lesión cutánea y la hipertrofia regional de los ganglios linfáticos.
4. Se ejecutaron biopsias de 40 ganglios linfáticos: 24 procedentes de casos lepromatosos (2 de ellos mixtos) y 18 procedentes de casos tuberculoideos.
5. En todos los ejemplares procedentes de casos lepromatosos, se observó típica infiltración lepromatosa de los ganglios.

6. Los espacios periféricos no estuvieron afectados más que 3 veces, mientras que los intermedios estaban atestados de típicas células leprosas de Virchow en casi todos los ganglios procedentes de casos lepromatosos.

7. En todos, menos uno, de los ganglios procedentes de casos lepromatosos, se pudieron descubrir bacilos ácidosresistentes.

8. En las zonas de infiltración lepromatosa, estaba bien conservada la armazón de reticulina.

9. Sólo en muy pocos casos se observaron engrosamiento de la cápsula, periadenitis y placas de fibrosis.

10. Dieciséis ganglios linfáticos obtenidos de casos tuberculoideos no revelaron la menor desviación histológica de lo normal.

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DESCRIPTION OF PLATE

PLATE (10)

FIG. 1. Photomicrograph showing diffuse infiltration of lymph node by vacuolated lepra cells. Several giant forms are also present. (100 \times .)

FIG. 2. Photomicrograph showing infiltration of marginal sinus by Virchow lepra cells. (100 \times .)

FIG. 3. Photomicrograph showing diffuse infiltration by vacuolated lepra cells. Intermediary sinuses are packed with these cells, obliterating the sinus outline. Also seen is a Touton giant cell. (430 \times .)

FIG. 4. Photomicrograph showing closely packed nonvacuolated lepra cells resembling epithelioid cells. (430 \times .)

FIG. 5. Photomicrograph showing intact reticulin framework in lepromatous zone (periphery). There is condensation of reticulin around the tubercle but in its center the fibers are destroyed. (100 \times .)

FIG. 6. Photomicrograph showing thickening of capsule and fibrous adhesions, with thickened septum. Early infiltration of lymph follicle by lepra cells is also seen. (100 \times .)

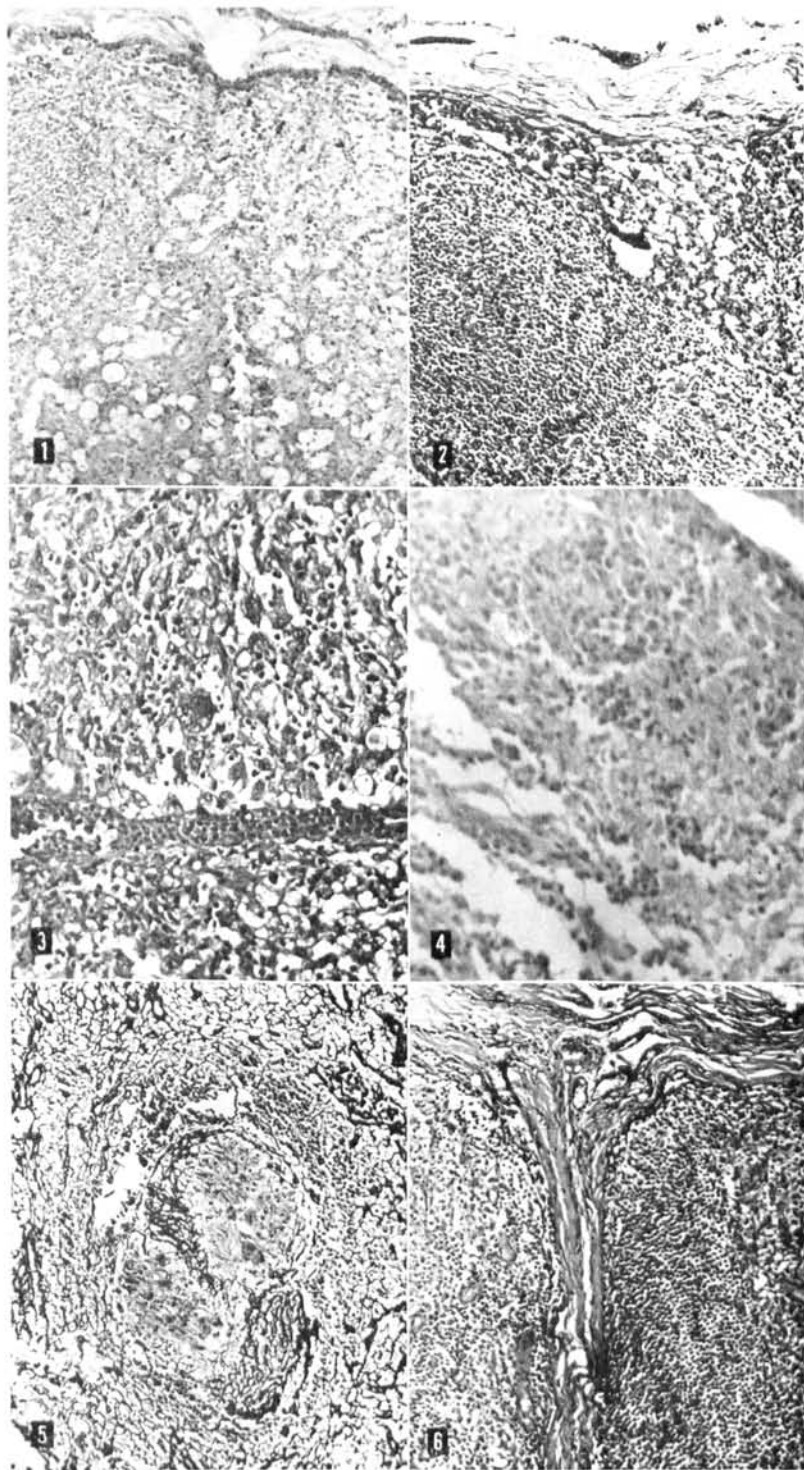


PLATE 10