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IMMUNOLOGICAL SIGNIFICANCE OF CHANGES IN LYMPH NODES ACROSS THE LEPROSY SPECTRUM

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SUMMARY

Seventy-seven lymph nodes were examined histologically from sixty-two leprosy patients representing the whole range of the disease spectrum from the high resistance form (tuberculoid) to the specific immunity deficiency form (lepromatous). At the lepromatous end of the spectrum paracortical areas were infiltrated with undifferentiated cells of the histiocyte–macrophage series which failed to eliminate mycobacteria. As resistance to infection increased across the leprosy spectrum, histiocytes became more differentiated eventually appearing epithelioid. This was paralleled by increasing numbers of small lymphocytes in the paracortical areas. In the borderline tuberculoid form of the disease an appearance was seen similar to that found in sarcoidosis. In polar tuberculoid leprosy where there is a high degree of cellular immunity, paracortical areas were well developed and populated with lymphocytes and immunoblasts. The immunological significance of these findings are discussed, especially the relation of the changes in morphological appearance of cells of the histiocyte series to the ability of the patient to develop cell-mediated immune reactions.

INTRODUCTION

The varied manifestations of the disease spectrum associated with infection by *Mycobacterium leprae* have been considered to be a function of the immunological reactivity of the host (Turk, 1969). Much of the work that has led up to this concept derives from the observations of Ridley & Jopling (1966) who correlated the clinical appearance of patients in the various forms of the disease with the histological appearance found in their skin lesions, paying particular attention to the degree of lymphocytic infiltration and the appearance of cells of the histiocyte–macrophage series.

There have been a number of descriptions in the past of the changes which occur in lymph nodes in leprosy (for review see Desikan & Job, 1966). However, there has been little attempt

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to correlate these with the immunological status of the patient, or to interpret the findings in the context of modern immunological concepts. In a recent preliminary study (Turk & Waters, 1968), note was made particularly of the depletion of lymphocytes from the paracortical areas in patients with lepromatous leprosy. Also, it was observed that there was evidence of repopulation of these areas with lymphocytes in a patient who regained cell-mediated immunity during anti-mycobacterial therapy.

The present report is a continuation of this study in sixty-two patients placed critically on the leprosy spectrum according to the criteria of Ridley & Jopling (1966), as modified by Ridley & Waters (1969). An attempt has been made to correlate the changes observed in the lymph nodes with other clinico-pathological evidence of the immune status of the patient.

MATERIALS AND METHODS

The study was based on the examination of seventy-seven lymph nodes obtained from sixty-two patients (including Malays, Chinese, Southern Indians and Gurkhas) receiving in-patient treatment at Sungei Buloh Leprosarium. In seventy-six instances palpable nodes were biopsied under local anaesthesia, the sites being supratrochlear seventy-four, inguinal one, axillary one; one node (mesenteric) was obtained at post-mortem examination. Seven patients underwent a second (serial) lymph node biopsy, usually from the opposite arm, 2 weeks to 15 months after the primary biopsy. On eight occasions, both left and right supratrochlear lymph nodes were biopsied simultaneously. The great majority of the nodes were fixed in Carnoy's solution. A small number of the earlier biopsies were fixed in formol saline, but this method gave less satisfactory results and was soon discarded. Triplicate sections from the lymph nodes were stained one each by the pyronin-methyl green, the haematoxylin and eosin, and the Ziehl-Neelsen methods.

Patients underwent full clinical and chest X-ray examinations, and the leprosy status of each was classified clinically and by skin biopsy according to the modified Ridley-Jopling scale (Ridley & Jopling, 1966; Ridley & Waters, 1969), which groups the patients round a number of points on the spectrum and can be related to their degree of specific cell-mediated immunity against the organism. These points are referred to as:

TT tuberculoid
BT borderline tuberculoid
BB borderline
BL borderline lepromatous
LI indefinite lepromatous
LL lepromatous

However, it must be realised that these are no more than arbitrary points on a spectrum extending from TT to LL and patients may exist at any point in time in an intermediate position on the spectrum to those described, (i.e. BT/BB, BB/BL, BL/LI). The presence of erythema nodosum leprosum (ENL) or reversal reactions at the time of lymph node biopsy was also noted carefully, and its type (Ridley, 1969), severity and treatment recorded. Current and past leprosy treatment was also recorded. Slit-skin smears from both ear lobes and from active skin lesions were examined for acid-fast bacilli, and scored for the bacterial index (Ridley's logarithmic scale, Ridley, 1958) and the morphological index (Waters, Rees & Sutherland, 1967). Intradermal testing with lepromin (Wade-Mitsuda) and with tuberculin

(RT 23,1 TU and if negative, subsequently 20 TU) were carried out if no recent results were available. Lepromin tests were all recorded at 3 weeks. In addition, thirty-three of the patients were tested by the method of Turk & Waters (1969) for their ability to become sensitized to DNCB.

A summary of the classification of the sixty-two patients, and of their length of treatment at the time of biopsy is given in Table 1.

RESULTS

Infiltration with cells of the macrophage–histiocyte series was detected in all lymph nodes studied, save those obtained from patients with single or few localized typical tuberculoid skin lesions, graded TT or BT close to TT. In general, the character of the infiltrate varied according to the classification of the patient. Just as the clinical and histological appearances of skin lesions form a continuous spectrum, so too did the lymph node infiltrate form a spectrum from BT to LL.

1. *Tuberculoid lymph nodes*

These nodes were obtained from patients showing clinically only one or very few localized typical tuberculoid skin lesions classified histologically TT, BT (close to TT) or indeterminate whose smears were negative, and whose lepromin reactions were mostly strongly positive. Two different varieties of lymph node were seen, although in neither were any acid-fast bacilli detected.

(*a*) *No evidence of immunological stimulation.* The lymph nodes were tiny, the germinal centres were not conspicuous, and the paracortical areas and medulla were nondescript, with normal numbers of plasma cells present in the latter area. However, a few subcapsular macrophages and a few sinus histiocytes could usually be found. Supratrochlear lymph nodes were not usually palpable in this category of patient, and therefore only four were available for study. Only one of these could have been a lymph node draining a skin lesion.

(*b*) *Evidence of stimulation of cell-mediated immunity* (*CMI*). Lymph nodes from two tuberculoid patients were slightly enlarged and showed mild hyperplasia of the paracortical area lymphocytes (Fig. 1), among which very occasional immunoblasts could be seen. In one patient, left and right supratrochlear nodes were biopsied, and immunoblasts were found in both, despite the fact that only a single tuberculoid annular lesion was visible, situated on the right forearm.

2. *BT* (*generalized*), *BT/BB and BB lymph nodes*

Nine lymph nodes were studied from eight patients from this unstable part of the leprosy spectrum. All patients had multiple skin lesions. Seven biopsies were obtained when patients were in an active phase of their disease; two patients were in downgrading reaction, whereas five were in reversal reaction. Two untreated patients were not considered to be in reaction at the time of biopsy; one of these was graded BB, and when he was rebiopsied after only 2 weeks' treatment he was already in reversal reaction and the new skin biopsy was graded BT/BB. Skin smears were variable, with the BI ranging from 0 to 3·0, although acid-fast bacilli were always present in the skin biopsies. Lepromin reactions varied from 0 to 8 mm in diameter. One patient with a reversal reaction showed an increase in lepromin reactivity from 3 to 8 mm.

TABLE 1. Classification of patients undergoing lymph node biopsy, and duration of effective treatment at time of biopsy

Leprosy classification	No. of patients	No. of lymph nodes	No. of simultaneous bilateral biopsies (L and R supra-trochlear)	No. of serial biopsies*	No. of biopsies performed at different lengths of effective treatment				
					None	<3 months	<6 months	<2 years	2 years and over
TT and BT (localized)	7	8	1	0	5	2 (1B†)	0	0	0
BT (generalized), BT/BB and BB	8	9	0	1	2	5 (1S‡)	2	0	0
BB/BL	4	6	0	2	4	0	1S	1S	0
BL	7	9	0	2	4	3	2S	0	0
BL/LI	3	3	0	0	2	0	0	1	0
Reversal from BL/LI to borderline (BB or BT)	2	2	0	0	0	0	0	2	0
LI	26	32	5	1	8 (1B)	7 (3B)	2 (1B)	3 (1S)	7
LL	5	8	2	1	3 (2B)	1	1	1S	0
Total	62	77	8	7	28 (3B)	18 (1S, 4B)	8 (3S, 1B)	8 (3S)	7

* Each serial (second) biopsy has been included in the same classification group as the corresponding first biopsy, whether or not the patient changed classification during the intervening period as a result of downgrading or reversal lepra reactions.

† B = bilateral biopsy—i.e. left and right supratrochlear lymph nodes were biopsied together.

‡ S = serial (second) biopsy.

The lymph nodes themselves were all infiltrated and enlarged, but varied considerably in size. Acid-fast bacilli were either not detected, or else were present only in small numbers singly or in small groups in occasional infiltrate cells. Germinal centres either appeared normal or were moderately prominent; plasma cells were slightly or moderately increased in numbers.

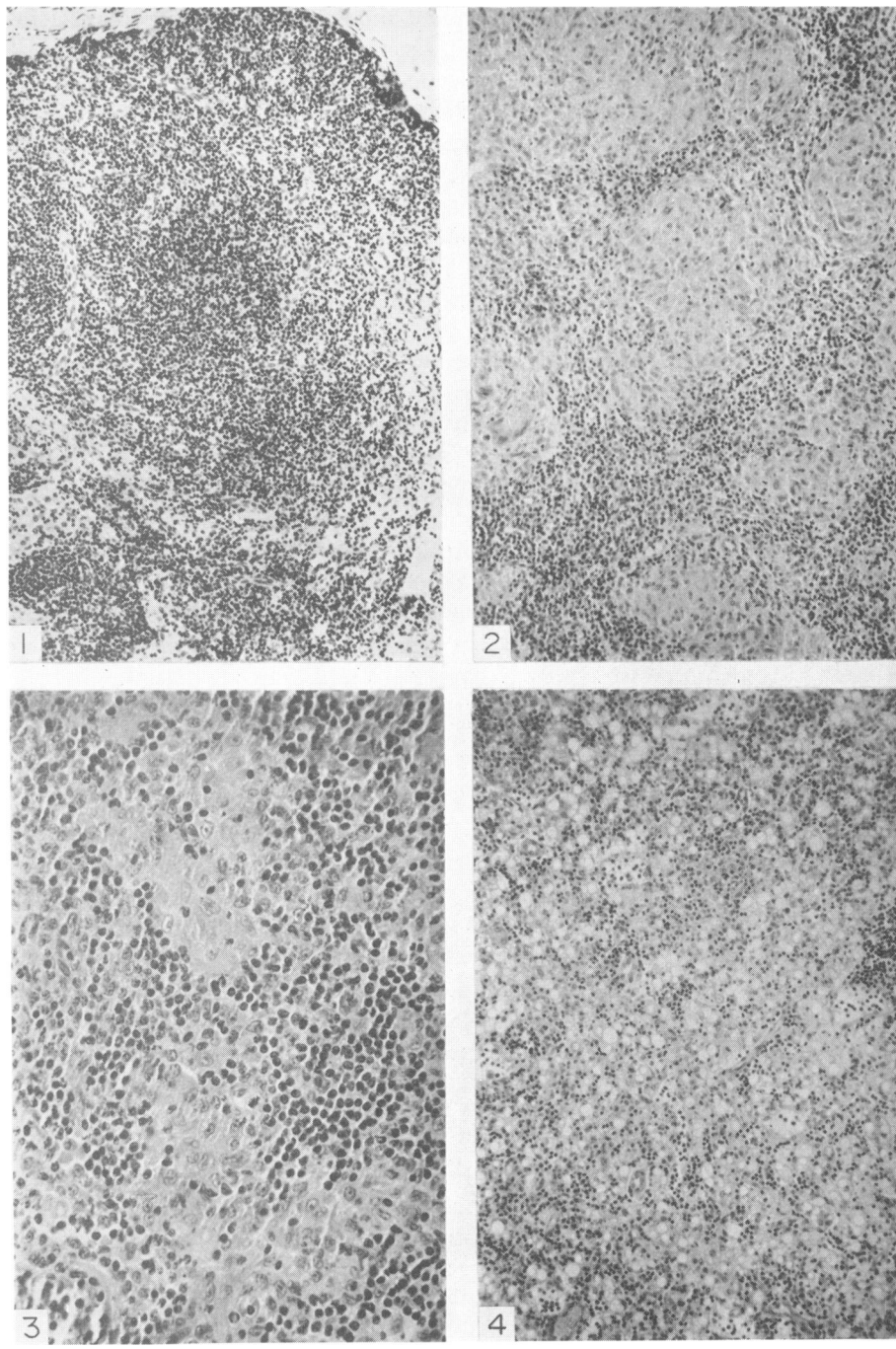
The infiltrate was remarkable in that it presented an appearance in many ways resembling that seen in sarcoidosis, although minor points of difference could usually be detected. The paracortical areas were invaded and in some nodes largely replaced by a multicentric infiltrate consisting of discrete whorls of epithelioid cells or near-epithelioid cells (Fig. 2). The whorls were well demarcated from the surrounding paracortical lymphocytes. In most lymph nodes, broad strands of lymphocytes separated the individual whorls, although in very heavily infiltrated nodes some coalescence was seen to occur. However, even in these, the multicentric origin of the infiltrate remained obvious. In some nodes the infiltrate consisted of typical epithelioid cells, and small numbers of typical Langhans' giant cells were also present. In other nodes, especially in those from patients closer to BB than BT, the cells were less typical; they appeared only slightly epithelioid, the nuclei being more oval, and less heavily staining, and the cytoplasm was less eosinophilic and less elongated. Similarly, the Langhans'-type giant cells were less typical, although the nuclei remained placed near the periphery of the cell. One lymph node showed fibrinoid necrosis of the collagen around the edges of the whorls. The overall impression in these nodes was that the degree of histiocytic infiltration paralleled that seen in the skin. Where the infiltration in the skin contained a large proportion of small lymphocytes, histiocytic infiltration in the nodes was localized and well defined. Where histiocytes formed a large proportion of the infiltrate in the skin, the infiltration in the nodes was diffuse and not so well defined.

3a. BL and BB/BL lymph nodes

Seven patients were studied who had typical BL leprosy. All were of the histiocytic type (Ridley & Jopling, 1966). Four were completely untreated, and none of the other three had received more than 2 months' treatment with dapsone. Two of the untreated patients subsequently went into reversal reaction and were rebiopsied at 5 months. Individual skin smears were very variable. Whereas ear lobes were frequently negative, thick BL papules and plaques were quite highly bacilliferous (4+ or 5+). Bacterial indices ranged from 2·7 to 3·8; and morphological indices from 6 to 46. Lepromin tests were 0–3 mm in diameter. Five of the seven patients were tuberculin negative, although this is probably accounted for by the fact that all were within the 11–21 years old age group. Despite this, four of the five tested could be sensitized to dinitrochlorobenzene (DNCB).

The lymph nodes varied considerably in size but the majority were moderately enlarged. Acid-fast bacilli were invariably present in the great majority of infiltrate cells, usually as groups of individual bacilli. Microglobi were seldom if ever detected. The cells situated in the subcapsular region appeared more heavily parasitized with bacilli that those situated deeper in the gland structure. Germinal centres were slightly or moderately more prominent than in normal nodes, and plasma cells were usually moderately increased in numbers.

Whereas the typical cell of the BT and BT-BB infiltrate was of the epithelioid cell type, in the BL infiltrate the histiocytes which predominated were neither epithelioid nor foamy (Fig. 3). These cells were usually situated in small groups scattered throughout the paracortical area, and did not appear to be well demarcated from the surrounding lymphocytes. In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these areas, lymphocytes were sometimes seen in variable numbers scattered among the histiocytes. In three nodes histiocytes were also present in larger groups or in small sheets. Although non-foamy, many of the histiocytes were seen to contain small, elongated, straight-edge vacuoles in their cytoplasm when they were stained by haematoxylin and eosin. These vacuoles could have corresponded to individual leprosy bacilli. They appeared 'harder' and more refractile than the foamy vacuoles present in the highly parasitized histiocytes of lepromatous (LL and LI) patients.

Four untreated patients were biopsied who were in the process of deteriorating from BT/BB or BB to BL; three had definite downgrading reactions and the fourth an incipient reaction. The bacterial index ranged from 2·7 to 4·2; the morphological index was even more variable ranging from 0 to 29. The lepromin test in three patients measured 4–5 mm. All four patients gave a long history (3–20 years) from the time of the appearance of their first lesions.

The individual infiltrate cells of these four patients were non-foamy histiocytes, similar to those seen in BL patients. In three cases these cells contained the refractile 'hard' small vacuoles described above. However, the arrangement of the infiltrate was reminiscent of the multicentric arrangement of the epithelioid cell infiltrate of the BT to BB part of the leprosy spectrum. It consisted of round or oval groups of cells, well demarcated from the surrounding paracortical lymphocytes, and which were relatively free from invasion by lymphocytes.

One patient underwent serial lymph node biopsy at 3 months when the downgrading reaction had just settled and when the simultaneous skin biopsy was graded 'BL, quiescent'. In this node, many of the groups of infiltrate cells were even less well demarcated from the surrounding paracortical lymphocytes, than those of the 'typical' BL nodes. Furthermore, a number of microglobi were present in the Ziehl-Neelsen stain, and in the haematoxylin and eosin stain, small foamy vacuoles could be detected in the corresponding areas (Fig. 4).

3b. Reversal reactions from BL

Two of the 'typical' BL patients developed mild reversal reactions while under treatment, although they only shifted slightly along the leprosy spectrum towards borderline. These patients underwent serial lymph node biopsy, both after 5 months' treatment with dapsone. The changes in the lymph nodes during the reaction were not striking.

One of the four patients who had moved from borderline to BL developed a severe reversal reaction after he had received 8 months' treatment. Serial biopsy was performed when the reaction had settled and when simultaneous skin biopsy was classified 'BT (late stage of reversal reaction)'; the bacterial index was then 0·7 compared with 2·7 before the start of treatment. The lymph node biopsy showed only small numbers of infiltrate cells, the majority of which were in the subcapsular region of the paracortical area. These cells

FIG. 1. Tuberculoid leprosy (TT) hyperplasia of lymphocytes in paracortical area. H. & E. ×80.

FIG. 2. Borderline tuberculoid (BT) paracortical area replaced by multicentric discrete whorls of epithelioid cells. H. & E. ×80.

FIG. 3. Borderline lepromatous (BL) histiocytes neither epithelioid nor foamy forming small groups scattered throughout paracortical area. H. & E. ×200.

FIG. 4. BL downgrading. Infiltrate cells less well demarcated from surrounding paracortical lymphocytes. Histiocytes more foamy. H. & E. ×80.

tended to be slightly separated from each other. Although the nucleus and cytoplasm remained oval or rounded, the nucleus stained much more deeply and its structure was much thicker and less delicate than in the pretreatment node. However, the cytoplasm of a few cells still contained one or two hard 'refractile' vacuoles, even though no acid-fast bacilli could be detected by the Ziehl-Neelsen stain. The appearance of the histiocytes in this case tended to approach that seen in the epithelioid cells found in the lymph nodes of BT patients.

4. *Lepromatous (LL and LI) lymph nodes*

Lymph nodes are often considerably enlarged in lepromatous leprosy. The series studied included thirty-two nodes (thirty supratrochlear, one inguinal and one mesenteric) obtained from twenty-six LI patients; five patients underwent simultaneous left and right supratrochlear node biopsy, and in one patient serial biopsy was performed after an interval of 2 weeks. Eight lymph nodes from five patients with polar lepromatous leprosy (LL) were studied, including two bilaterial biopsies, and one serial biopsy taken 1 year after the start of treatment. In addition, nodes obtained from two patients who were moving from BL to LI leprosy will also be described.

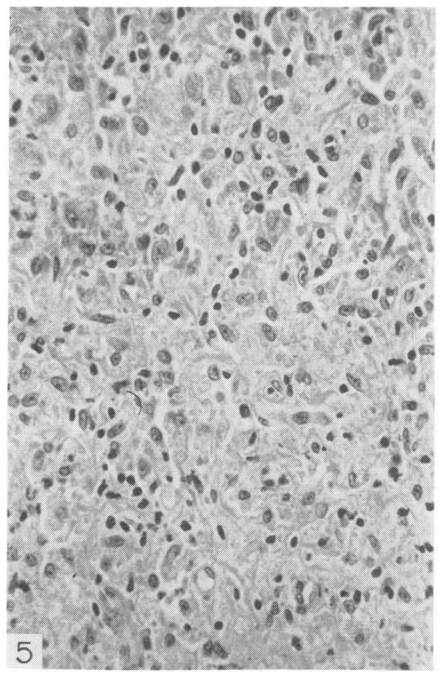
(*a*) *Untreated LI lymph nodes.* Twenty-one lymph nodes were biopsied from sixteen patients who were either untreated, or who had received not more than 3 months of effective treatment. Four patients had relapsed, three following premature stopping of treatment, and one because of possible sulphone resistance; the remaining twelve were newly diagnosed cases of LI leprosy. In all the morphological index was raised (range 6–48); the bacterial index was invariably high (range 4·3–5·0). The lepromin test was completely negative in nine, measured 2 mm in four and 3 mm in one. Nine patients were tuberculin positive and five negative, whereas only two of eleven patients tested could be sensitized to DNCB. One patient was suffering from ENL; no other patient was in reaction. In all except one lymph node the paracortical areas were largely depleted of lymphocytes, being infiltrated with huge sheets of histiocytes containing large numbers of mycobacteria. In patients with relatively early lepromatous leprosy the bacilli tended to lie singly or in small groups in the histiocytic cytoplasm, although occasional microglobi were seen. In advanced cases many bacilli were arranged in small and medium sized globi, and in one or two nodes a few large-sized globi were also visible. Similarly the appearance of the histiocytes varied somewhat. In early cases they remained as individually discrete, rounded or hexagonal-shaped cells containing small refractile vacuoles in their cytoplasm, which in some had coalesced (Fig. 5). In moderately advanced cases, not only were foamy macrophages common, but atypical giant cells were also present. In these cells the nuclei were scattered randomly in the pale cytoplasm, unless pushed to one side by foamy vacuoles surrounding one or more small globi. In very advanced cases, close to LL, the cell boundaries of the

FIG. 5. LI. Histiocytes rounded or hexagonal containing small refractive granules in their cytoplasm. Lymphocytes sparse. H. & E. ×300.

FIG. 6. LL. Paracortical areas virtually depleted of small lymphocytes and replaced by histiocytes. Germinal centres, with marginal cuff of small lymphocytes and medullary plasma cells, well developed. Pyronin-methyl green. ×52.

FIG. 7. LL. Foamy sometimes syncytial histocytes replacing paracortical area. H. & E. ×200.

FIG. 8. LI treated for 6 years. Foamy histiocytes in deeper part of paracortical area. H. & E. ×120.



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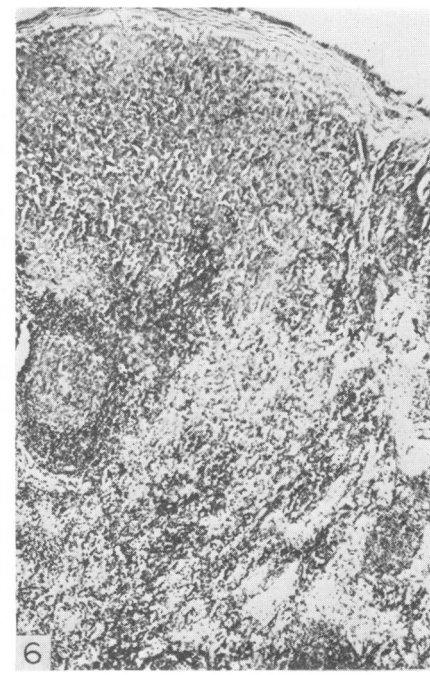

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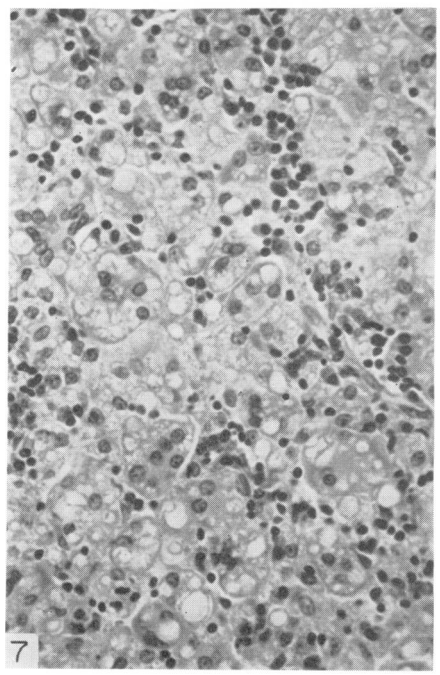

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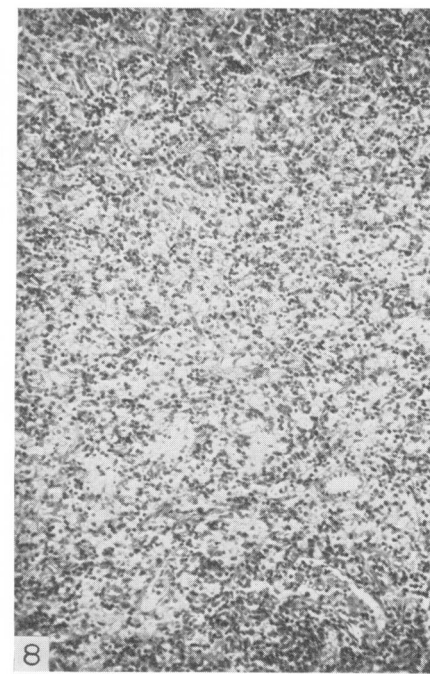

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individual histiocytes could appear almost invisible, so that the infiltrating cells resembled a syncytium.

Despite the extensive infiltrate in the paracortical areas, the germinal centres and their marginal cuff of small lymphocytes were invariably prominent; and they were considered to be moderately or markedly increased in numbers and size in at least seventeen of the twenty-one nodes. In all nodes there was excessive proliferation of plasma cells at the cortico-medullary junction and in the medullary cords.

(*b*) *LL (polar lepromatous) lymph nodes.* These nodes were similar to those of advanced LI leprosy. Their paracortical areas were virtually completely depleted of lymphocytes, being infiltrated with huge sheets of foamy, sometimes 'syncytial' histiocytes containing masses of globi and groups of bacilli (Figs 6 and 7). Giant cells were frequently present in considerable numbers. Germinal centres were invariably increased in size and numbers, standing out prominently in the infiltrate even to the naked eye, and plasma cells were very numerous.

All five LL patients were lepromin-negative. Four were tuberculin positive, although none of the three tested could be sensitized with DNCB. One patient had ENL following several months' treatment with dapsone; the mycobacteria in his node were very fragmented.

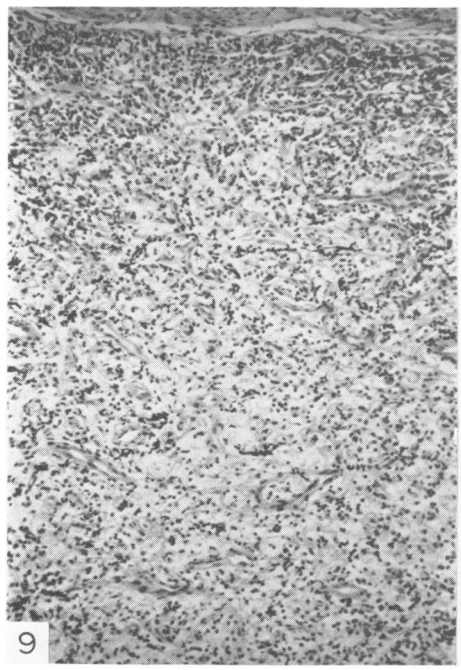
(*c*) *Lymph nodes from BL patients downgrading towards LI.* Two untreated patients were considered clinically to be in process of deteriorating from BL to LI leprosy, even though their skin biopsies were graded BL. Both were lepromin negative; one was tuberculin positive but could not be sensitized with DNCB, the other was tuberculin negative, and was not tested with DNCB. The bacterial indices were 4·3 and 4·0 respectively. Both lymph nodes resembled those from patients with early LI. The paracortical areas were widely infiltrated with sheets of histiocytes, and there were few residual lymphocytes. Bacilli were present singly, in groups and as occasional small globi. The histiocytes contained refractile vacuoles or were slightly foamy. No giant cells were seen.

(*d*) *Effect of treatment and of ENL in lepromatous lymph nodes.* Eleven lymph nodes were available for study from ten LI patients who had received 5 months' to 10 years' effective treatment. One patient developed ENL shortly after her first biopsy and a second lymph node was removed at a fortnight's interval. Six of the other nine patients were suffering from ENL of varying severity at the time of biopsy. Two patients, including one whose mesenteric lymph node was obtained at post-mortem and who died from secondary amyloidosis, suffered from ENL earlier in their course of treatment, and only one, who had been treated with clofazimine continuously for 6 years for dapsone-resistant leprosy, had never developed manifestations of ENL. In addition, one lymph node was available for study from a BL/LI patient treated for 20 months.

The majority of lymph nodes obtained from patients who had received up to 6 years' treatment remained considerably enlarged, with massive histiocytic infiltration, prominent germinal centres and marked plasma cell proliferation. The first sign of response to treatment was that all the acid-fast bacilli appeared fragmented, and no solid-staining, presumed viable, bacilli could be found. From about 12 months onwards single and small groups of intracellular bacilli progressively decreased in numbers, so that after 2 years' treatment the great majority of bacilli became more and more granular in appearance. In patients suffering from severe or moderately severe ENL the acid-fast debris developed a clumped or 'flocculated' appearance, which was particularly noticeable around the rim of the globus vacuole.

After approximately 2 years' treatment, two further changes were noted. Lymphocytes

began to reappear in the paracortical areas, sometimes scattered diffusely in small numbers throughout the infiltrate, and sometimes appearing in irregular bands, often mixed with considerable numbers of plasma cells, which tended to break up the infiltrate. In addition, the volume of infiltrate began to decrease in size, especially in the subcapsular and medullary areas. By 6 years only small islands of foamy histiocytes could be detected situated in the deeper parts of the paracortical areas (Fig. 8). In the single lymph node available from a patient who had received 10 years' treatment residual foamy histiocytes could still be detec-



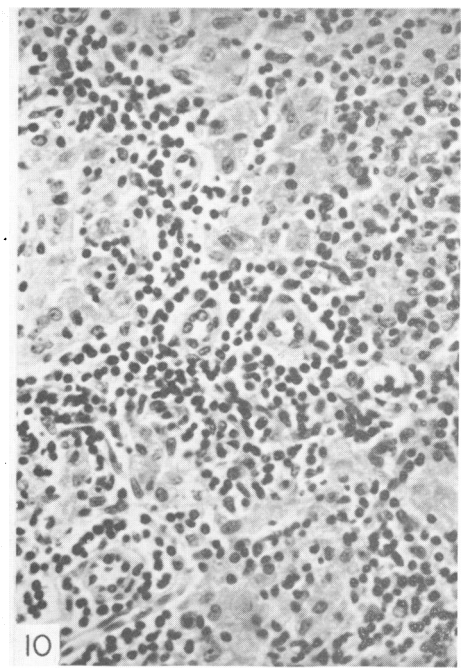


FIG. 9. LI treated for 10 years. Paracortical area still partly replaced by histiocytes. H. & E. ×120.

FIG. 10. Reversal reaction from LI to BT. Lymphocytes repopulating paracortical area round post-capillary venules. Histiocytes still have 'lepromatous' appearance. H. & E. ×300.

ted in the paracortical area, although free of acid-fast debris (Fig. 9). The node was, however, normal in size, germinal centres were not prominent, and plasma cells were present in normal numbers.

(*e*) *Reversal reactions from LI to borderline* (*BB or BT*). Two patients who were classified on admission as BL/LI, and histologically as LI, subsequently developed reversal reactions after 6 weeks' and 5 months' treatment respectively with dapsone. In the former patient a supratrochlear lymph node was biopsied at 10 months; at that time skin biopsy was graded 'BT, in reaction', his bacterial index had fallen from 3·5 (before treatment) to 0·8, and his lepromin reaction had increased from 3 mm (before treatment) to 5 mm. The latter patient underwent axillary lymph node biopsy at 7½ months, when he was definitely borderline and no longer lepromatous.

The lymph nodes obtained from these two patients showed similar features. In both, the paracortical infiltrate cells remained the vacuolated or foamy histiocytes of lepromatous leprosy. Groups of mycobacteria or microglobi could still be detected in the histiocytes, although the acid-fast material was extremely granular, appearing as acid-fast debris rather than as fragmented bacilli. Germinal centres remained prominent and plasma cells increased in numbers. But the most striking feature was the partial repopulation of the paracortical areas with lymphocytes. The infiltrate was broken up by broad bands of lymphocytes, in some areas lymphocytes were also scattered diffusely in the infiltrate, and in others small or large accumulations of lymphocytes were also present usually situated around post-capillary venules (Fig. 10).

DISCUSSION

Lymph nodes have been examined from sixty-two leprosy patients representing the whole range of the disease spectrum from the high resistance form (tuberculoid) to the specific immunity deficiency form (lepromatous). In lepromatous leprosy the paracortical areas are enlarged and replaced by undifferentiated histiocytes, similar to those seen in lymph nodes of experimental animals draining the site of intradermal injection of a non-antigenic colloidal material such as aluminium hydroxide or colloidal silica (Gaafar & Turk, 1970). Similar cells are seen in lymph nodes draining the site of intradermal injection of microganisms such as BCG or Leishmania in guinea-pigs treated with antilymphocyte serum (Bryceson & Turk, 1971). However, as the disease spectrum is crossed from the lepromatous to the tuberculoid pole increasing numbers of lymphocytes are present in this area. In individual patients who have had a 'reversal reaction' and have moved from the LI to the BT form of leprosy these lymphocytes can be seen to form collections around the postcapillary venules and also in broad bands breaking up the infiltrating mass of histiocytes. In patients established towards the tuberculoid end of the spectrum the histiocytes show more and more of an epithelioid appearance. Thus in borderline (BB) disease the histiocytes appear far less undifferentiated than in the BL form. In BT leprosy the infiltrate cells form very typical tuberculoid granulomata which may resemble those seen in sarcoidosis and may be associated with some degree of fibrinoid necrosis.

There is evidence from experimental studies that the epithelioid appearance of macrophages may be related to their participation in a cell-mediated immune reaction. Blanden (1968) has shown that macrophages from BCG-infected mice spread more rapidly and fully on glass and have a much more extensive cytoplasm with more numerous mitochondria than macrophages from normal animals. Moreover, Godal, Rees & Lamvik (1971) have found that supernatants from mixed lymphocyte cultures activate rabbit macrophages *in vitro* so that they proliferate, elongate and form intracellular cytoplasmic bridges and giant cells. They also found similar activation of blood-derived macrophages from patients with tuberculoid leprosy, in the presence of lymphocytes; no such activation of macrophages was observed in cultures from patients with lepromatous leprosy. A correlation appears to exist between the development of an epithelioid appearance in histiocytes and the ability of these cells to eliminate mycobacteria. Undifferentiated histiocytes, sometimes multinucleate or syncytial, occur in leprosy under conditions where the ability of these cells to eliminate the microorganisms is 'impaired' although the ability to phagocytose the microorganisms is normal. Under experimental conditions such undiffer-

entiated histiocytes are found in granulomata in lymph nodes draining the site of concentrations of 'irritant' non-antigenic material or microorganisms such as mycobacteria or Leishmania under conditions where a cell-mediated immune reaction has been inhibited, as by antilymphocytic serum. However it is probable that the epithelioid appearance of the cells develops independently of the immune elimination of microorganisms. This is indicated by the observation that in a reversal reaction in leprosy, ability to eliminate mycobacteria can develop without the histiocytes becoming epithelioid.

A further observation of interest is that histiocytic infiltration of the paracortical areas of lymph nodes persists in patients with lepromatous leprosy for at least 10 years after the beginning of anti-leprosy treatment, when little or no mycobacterial material can be detected in the tissues. It is likely that a high proportion of patients with lepromatous leprosy do not regain their ability to develop an immune reaction against *Myco. leprae* despite the reduction in antigenic load following treatment. This is associated with persistent lepromin negativity (Guinto, 1968) and if the disease relapses as a result of premature cessation of therapy, it always takes the typical lepromatous form. Such patients are probably in a state of persistent 'specific immunological tolerance'. Under such conditions viable organisms are not completely eliminated from the body for many years (Waters, 1967). Residual organisms can thus replicate and the patients maintain a sub-clinical infection, sufficient to cause histiocytic infiltration of the tissues. Under these conditions, if therapy is discontinued, the organisms will accumulate and the clinical disease will recur. Genetic inability to react to one antigen or group of antigens has been well documented (McDevitt & Benacerraf, 1969). It may therefore be that the inability of at least some patients in this group to respond with CMI to *Myco. leprae* is genetically determined. In this case, the mechanism of specific anergy to the organism might well not be related to the phenomenon of immunological tolerance. In such a case a reduction in bacterial load following therapy would not be expected to result in the patient developing immunity to the organism. Other patients with lepromatous leprosy, most of whom showed evidence of having passed through a borderline phase, have been found to regain a degree of immunity against the microorganism following a lowering of the antigenic load as a result of chemotherapy (Ridley & Waters, 1969). Under such conditions it could be said that they have 'broken tolerance'. The result of this will be the acute development of an immune state. There will then be a cellular immune reaction with the still relatively high level of mycobacterial antigens in the tissue. The result of such a process will be both a persistent elimination of the organisms and also allergic reactions causing local tissue damage. Thus the development of such a 'reversal reaction' would parallel the development of a state of immunity, so that the patient should not need such prolonged chemotherapy.

Patients at the tuberculoid end of the spectrum could be said to have a high degree of cell-mediated immunity. In TT tuberculoid leprosy the state of immunity is indicated by the well developed paracortical areas containing immunoblasts, some of which can be seen in mitosis. Under these conditions the infecting organism is limited to the affected nerves, muscle or skin and no histiocytic infiltration is seen in the lymph nodes. In BT tuberculoid leprosy, the ability to control the spread of the organism by cell-mediated immune processes is weaker. The presence of sarcoid-like granulomata in the lymph nodes could indicate that histiocytes containing mycobacteria drain from the peripheral tissues into the local lymph nodes. As lymphocytes capable of reacting in cell-mediated immune processes are present in these tissues a local reaction develops in the nodes causing the localized concentric

appearance of epithelioid cells and giant cells with associated fibrinoid necrosis which is particularly characteristic of this point of the spectrum. In borderline leprosy where the patient is nearer the lepromatous end of the spectrum the granulomata are far less localized and the histiocytes develop a progressively less epithelioid appearance.

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