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Mechanisms of Reactions in Leprosy

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The term "Reaction" has been given to those episodes of significant inflammation occurring in leprosy which are the direct result of infection with *Mycobacterium leprae*, and are not due to secondary infection, trauma, etc. Many different types of reaction have been described, and the subject remained extremely confused throughout the first half of this century. However, since 1958 ([3]) it has increasingly been agreed that the majority fall into one or other of two groups, even though terminology remains controversial ([4, 8, 14, 21]). The better defined group is commonly known as erythema nodosum leprosum (ENL) ([3, 7]), although the Panel of Reaction of the 8th International Congress of Leprology recommended the term "Lepromatous Lepra Reaction" ([4]). Briefly, it consists of episodes of crops of painful, tender, erythema nodosum-like papules, which in severe cases may pustulate or necrose, which are often accompanied by fever and malaise, and which may be complicated by neuritis, orchitis, lymphadenopathy, iridocyclitis, arthritis and proteinuria. ENL occurs only in lepromatous and small numbers of borderline-lepromatous patients (i.e., LL, LI and BL on the modified Ridley-Jopling spectrum classification ([15, 16])). Although well recognized before the introduction of sulfone treatment, it is particularly common in treated lepromatous leprosy, more than 50 per cent of such patients developing ENL by the end of the first year of treatment ([22]). Histologically, on a background usually of resolving lepromatous leprosy, the lesions consist of vasculitis, polymorphonuclear infiltrate, hyperemia and fragmented leprosy bacilli. The manifestations of ENL may be rapidly suppressed either by corticosteroids or by thalidomide. Reactions belonging to the second main group, usually known as "Lepra Reactions" [7th International Congress of Leprology, 1958 ([3])], may occur anywhere on the leprosy spectrum save at the two poles. Whereas each crop of ENL papules lasts only a comparatively few days, skin lesions in lepra reactions[2] remain inflamed for many weeks or months. Clinically and histologically, such lesions are consistent with the type of leprosy the patient is suffering from or developing; there is edema and hyperemia, but no extraneous inflammatory infiltrate (although patients becoming more tuberculoid will have an accumulation of lymphocytes in their lesions). Neuritis is a not uncommon complication. In general, the end result of such reactions is a shift in leprosy classification; a patient who develops a lepra reaction before commencing antileprosy treatment becomes more lepromatous, whereas one who reacts while receiving effective treatment becomes more tuberculoid. The former reaction subgroup has been named "Downgrading Reaction" by Ridley and the term "Reversal Reaction" has been used for the latter ([14]). Both subgroups are rapidly suppressed by corticosteroids, but not by thalidomide.

It has been widely assumed that the mechanisms underlying both these main groups of reactions have immunologic bases. There is now a great weight of evidence that the position of a patient on the leprosy spectrum is related to the degree of cell-mediated immunity (CMI) which he is able to develop to *M. leprae* ([18]). Thus patients with polar tuberculoid (TT) leprosy have a very high degree of CMI; their lymph nodes (Fig. 1) show some hyperplasia of the paracortical lym-

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[2] As the term "Lepra Reaction" has been applied to both main groups of reaction, solely to avoid confusion in this paper we use the term "ENL" for the first group and "lepra reaction" for the second group of reactions.

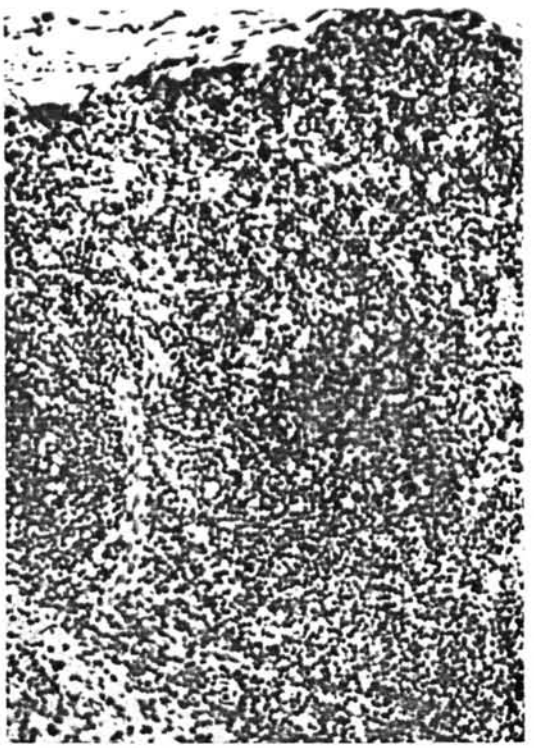

FIG. 1. Lymph node from patient with polar tuberculoid (TT) leprosy, showing some hyperplasia of the paracortical lymphocytes, normal lymph follicle and the absence of leprous infiltrate. (Hematoxylin-eosin, 100×).

phocytes with the presence of immunoblasts, and the absence of paracortical infiltrate and of mycobacteria ([19, 20]). On the other hand, lepromatous patients have gross depression of CMI against *M. leprae*; the paracortical areas of their lymph nodes are almost completely denuded of lymphocytes, being filled by foamy histiocytes full of acid-fast bacilli (Figs. 2 and 3). However, there is evidence of stimulation of humoral antibody production, with hyperplasia of germinal centers and excessive proliferation of plasma cells at the corticomedullary junction and in the medullary cords, in keeping with the known high serum immunoglobulin levels in lepromatous leprosy ([1, 17, 23]). Therefore ENL occurs in patients with depressed (and unchanging) CMI, whose bodies contain large quantities of mycobacterial antigen and who have high humoral antibody titers. Because of this and because of the various manifestations of the reaction, we have suggested ([19, 23]) that ENL is a clinical manifestation of the Arthus phenomenon. Lepra reactions, both downgrading and reversal reactions, are associated with changes in leprosy classification, and would appear to be related to changes in CMI against *M. leprae*. This paper summarizes and brings up to date work we are carrying out designed to substantiate these hypotheses.

1. Immunofluorescent Studies in ENL

MATERIALS AND METHODS

These have been described in detail elsewhere ([23]). In brief, biopsy specimens were taken from ENL lesions in the skin of 38 lepromatous patients; subsequently sev-

FIG. 2. Lymph node from patient with polar lepromatous (LL) leprosy, showing replacement of lymphocytes of paracortical area by pale staining histiocytes, numerous germinal centers with unaffected marginal zone of lymphocytes, and hyperplasia of plasma cells at the cortico-medullary junction. (Pyronin-methyl green, 40×).

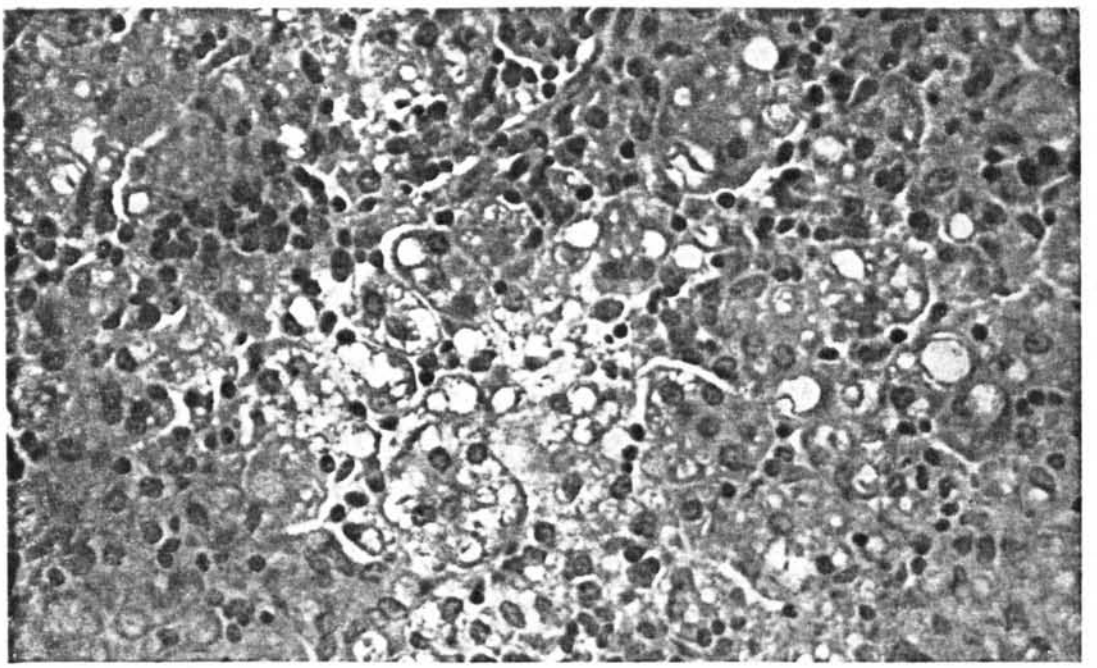

FIG. 3. Lymph node from patient with polar lepromatous (LL) leprosy, showing foamy histiocytes in the paracortical area (Hematoxylin-eosin, 250×).

en patients underwent second (serial) biopsy, and two of these were biopsied for a third time, making a total of 47 biopsies. The majority of papules biopsied were bright red and tender, but a number were dark purple and beginning to resolve, and at least one was necrotic. The specimens were quick-frozen immediately in dry tubes placed in a mixture of acetone and dry ice. In addition, as controls, biopsy specimens were similarly collected from lepromatous skin lesions from 13 patients who did not have ENL. Each specimen was flown in dry ice to London, where 5μ sections were cut in a cryostat at —20°C, and were examined within 72 hours of removal from the patient.

At the time of biopsy, serum also was taken from each patient for immunoglobulin and complement assay. The following reagents were prepared: Rabbit anti-human immunoglobulin (IgG), rabbit anti-human complement (β1C/β1A globulin), and goat anti-rabbit immunoglobulin, by two techniques, one using Freund's complete adjuvant (containing *Mycobacterium tuberculosis*, H37Ra), and the other Freund's incomplete adjuvant, thereby avoiding the use of mycobacteria in the immunization schedule. The D.E.A.E.-cellulose globulin fraction of each goat anti-rabbit immunoglobulin serum was conjugated with fluorescein isothiocyanate.

For fluorescence microscopy air-dried, fixed and washed cryostat sections were incubated with rabbit anti-human immunoglobulin, rabbit anti-human complement, or normal rabbit serum. After further washing, they were incubated with one or other of the fluorescent goat anti-rabbit immunoglobulin sera, washed again and mounted.

Parallel sections were also stained with hematoxylin-eosin and Ziehl-Neelsen stains.

Serum IgG, IgA, IgM and β1C/β1A globulins in each patient's serum were estimated using immunoplates (Hyland Laboratories, Los Angeles).

RESULTS

Immunoglobulin and complement were demonstrated by fluorescence (Figs. 4 and 5) in the areas of perivascular polymorph infiltration in the dermis of ENL lesions in 20 out of 38 patients (21 out of 47 biopsies). In general, lesions containing many polymorphs were positive for both IgG and

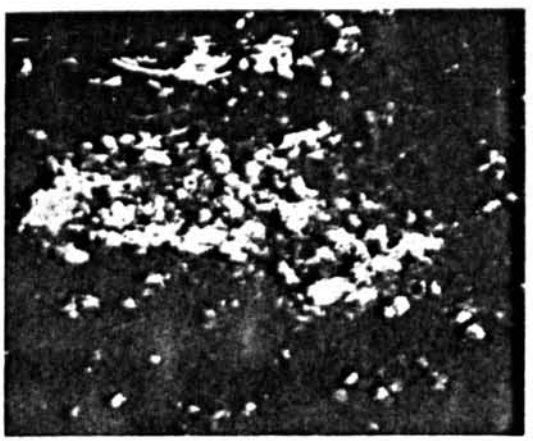

FIG. 4. Section of ENL lesion of the skin, stained to demonstrate immunoglobulin, showing granular fluorescent deposits in the dermis. (250×).

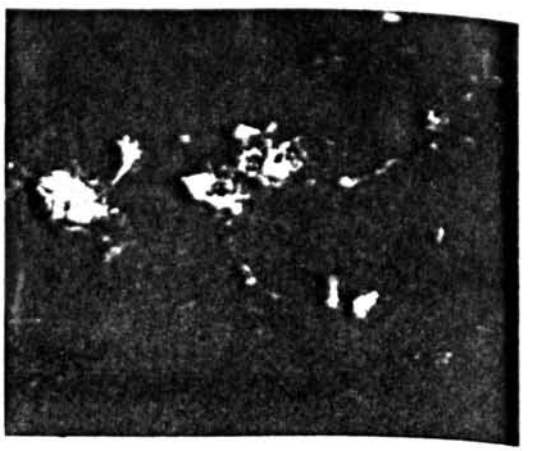

FIG. 5. Same lesion as in Fig. 4 stained to demonstrate complement (β1C/β1A globulin), showing granular fluorescent deposits in the dermis. (250×).

β1C/β1A globulin, whereas lesions containing few polymorphs or only disintegrated polymorphs were likely to be negative. No such deposits were found in lepromatous lesions from the 13 patients without ENL (see Table 1). The deposits were granular in form, and did not correspond to the areas of bacillary infiltration; they could sometimes be demonstrated within the walls of blood vessels (Fig. 6).

Groups or globi of *M. leprae* failed to stain with goat anti-rabbit fluorescein conjugate prepared with Freund's complete adjuvant (containing *M. tuberculosis*). However, in seven of the ENL lesions the deposits containing immunoglobulin and complement did stain with this conjugate alone, if used undiluted. This staining was taken to indicate the presence of mycobacterial antigen in the immune complexes, because no staining was found with the goat anti-rabbit fluorescein conjugate made from sera prepared without *M. tuberculosis*. Furthermore, no staining was detected when the former conjugate was diluted 1:2 or 1:4, and under these conditions it was possible to detect immunoglobulin and complement specifically by the sandwich technique. A similar pattern of staining with the conjugate alone was

TABLE 1. *Detection of human immunoglobulin and complement (β1C/β1A) by immunofluorescence in the skin of lepromatous patients with and without Erythema Nodosum Leprosum (ENL).*

Reactional state of lepromatous patients	Number of patients	Total number of skin biopsies	Number of patients with biopsies positive for immunoglobulin and complement	Total number of positive biopsies
Patients with ENL	38	47[a]	20	21
Patients with no ENL	13	13	0	0

[a] Biopsies taken from active ENL skin lesions.

FIG. 6. Section of ENL lesion of the skin, stained to demonstrate immunoglobulin, showing granular fluorescent deposits in a vessel wall. Autofluorescent collagen fibers are also visible as linear structures in the media of the vessel and in the lower part of the photograph. (250×).

found in lepromatous lesions in two control patients without ENL.

Serum protein levels (IgG, IgA, IgM and β1C/β1A globulin) are shown in Table 2. No significant differences were found in the mean and range of immunoglobulin levels in the lepromatous patients with and without ENL. Although there was no significant difference between the mean of the β1C/β1A globulin levels of patients with and without ENL, 10 out of the 46 patients with ENL had levels of β1C/β1A globulin which were in excess of that which formed the upper limit of the range found in the control group. The highest level (5.13 mgm/ml.) found in a patient with ENL was over twice that found in any patient without ENL (2.45 mgm/ml.).

2. Lymph Node Studies in Downgrading and Reversal Reactions

MATERIALS AND METHODS

Lymph node biopsy was performed on 15 patients in reaction (including Malays, Chinese, Southern Indians and Gurkhas) receiving inpatient treatment at Sungei Buloh Leprosarium. Five untreated patients were in downgrading reaction, and one was biopsied three months later when his reaction had settled. Ten patients who were under treatment with dapsone had reversal reactions; four of these had previously undergone lymph node biopsy before commencing antileprosy treatment. Therefore a total of 20 lymph nodes, including five serial lymph nodes, were available for study; 19 were supratrochlear and one axillary. The great majority of the nodes were fixed in Carnoy's solution (one early node was fixed in formol saline, but this method proved less satisfactory); they were embedded in paraffin, and sectioned at 5μ, triplicate sections being stained one each by the pyronin-methyl green, the hematoxylin and eosin, and the Ziehl-Neelsen methods.

Patients underwent full clinical and chest x-ray examination. The leprosy status of each was classified as precisely as was possible in the presence of the reaction, both clinically and by skin biopsy according to the modified Ridley-Jopling scale ([15, 16]). The type and severity of the reaction were carefully noted, and current and past antileprosy and reaction treatments were 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) and the morphologic index ([22]). All new patients (including all downgrading patients) were tested intradermally with lepromin (Wade-Mitsuda) and with tuberculin (RT23, 1 TU, and if negative, subsequently with 20 TU); some reversal patients were retested around the time of lymph node biopsy, and others when the reaction had eventually settled.

The 15 patients represented points on the leprosy spectrum from BT (with multi-

TABLE 2. *Comparison of serum protein levels (mgm. ml.) in lepromatous patients with and without ENL.*

Leprosy classification	Number of patients	Mean serum protein levels (range given in brackets)			
		IgG	IgA	IgM	β1C/β1A globulin
Lepromatous with ENL	38	23.5 (10.84 – 43.65)	5.00 (1.59 – 10.46)	2.19 (0.46 – 6.61)	2.07 (1.10 – 5.13)
Lepromatous without ENL	13	23.8 (13.18 – 38.9)	5.00 (2.48 – 8.41)	2.79 (1.25 – 6.61)	1.82 (1.20 – 2.45)

ple lesions) to BL/LI. They formed part of a larger series, to be reported elsewhere ([20]), of 77 lymph nodes obtained from 62 patients representing not only all parts of the leprosy spectrum, but including the effect of up to 10 years' antileprosy treatment on lepromatous leprosy.

RESULTS

The major series (of 77 lymph nodes) showed that in BT lymph nodes, the paracortical lymphocytes were infiltrated by discrete multicentric whorls of epithelioid cells, sometimes containing occasional Langhans' giant cells, with acid-fast bacilli either very scanty or else undetectable by routine procedures. As first pointed out by Desikan and Job ([6]), there was a considerable resemblance to sarcoidosis. As the spectrum was crossed toward lepromatous leprosy, the infiltrate cells became less epithelioid and more histiocytic, and the acid-fast bacilli increased in number. Thus in BL lymph nodes, the leprous infiltrate consisted predominantly of groups of nonfoamy histiocytes, not well demarcated from the surrounding lymphocytes, and which nearly all contained single or groups of individual acid-fast bacilli (very rarely were microglobi present). However it was not easy to assess over the BT to BL part of the spectrum changes in numbers of paracortical lymphocytes, their decrease in numbers being far more obvious and dramatic over the BL to LL range. The appearance of lepromatous nodes has already been described ([19]).

In 13 out of the 15 patients in reaction, there were no striking differences in their lymph nodes compared with lymph nodes from patients situated at the same points on the leprosy spectrum who were not in reaction. In some the infiltrate cells were slightly separated from each other, presumably as a result of edema and hyperemia. Ridley (personal communication) considers that the presence of Langhans' cells in BT to BB leprosy is usually associated with reaction.

The results from the five paired or serial biopsies were also no more than suggestive, perhaps because in at least three of the five patients the changes in classification associated with the reactions were only minor. The one patient who was in downgrading reaction on admission, was at that time graded BB/BL clinically, and "BT/BB in downgrading reaction" histologically. His lymph node (Fig. 7) showed infiltration of the paracortical areas with nonfoamy histiocytes, containing small refractile vacuoles, similar to those seen in BL patients, although the arrangement of the infiltrate was reminiscent of the multicentric arrangement of the epithelioid cell infiltrate of the BT to BB part of the spectrum; it consisted of round or oval groups of cells well demarcated from the surrounding paracortical lymphocytes, being relatively free from invasion by lymphocytes. Three months later, when his downgrading reaction had settled following treatment which included dapsone and prednisolone, and when he was histologically classified (on

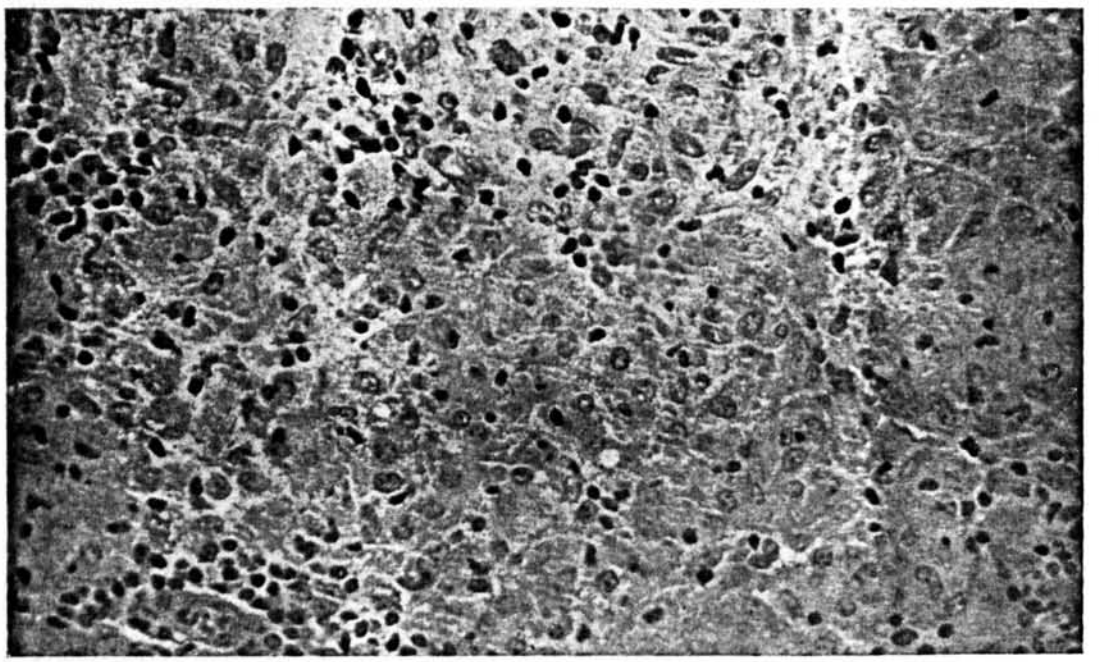

FIG. 7. Lymph node from untreated borderline (BT/BB) patient in downgrading reaction. The paracortical area is infiltrated by elongated, non-foamy histiocytes containing few tiny vacuoles, which are well demarcated from the surrounding paracortical lymphocytes. (Hematoxylin-eosin, 250×).

simultaneous skin biopsy) as "BL, quiescent," a second lymph node was biopsied. In this node (Fig. 8) the groups of infiltrate cells had become much less well demarcated from the surrounding paracortical lymphocytes, perhaps even less so than in typical BL nodes. Furthermore, a number of microglobi were present in the Ziehl-Neelsen stain, and in the hematoxylin-eosin stain small foamy vacuoles could be detected in the corresponding areas.

The second (serial) lymph nodes of the four patients with reversal reactions similarly showed minor changes in the opposite direction. Thus in the lymph nodes of two BL patients who underwent mild reversal reactions and who were rebiopsied after five months' treatment with dapsone, the nuclei of the histiocytic infiltrate stained more deeply, and appeared less delicate than in the pretreatment biopsy. One BB/BL patient (graded BL histologically), developed a severe reversal reaction at eight months, and underwent serial biopsy at 15 months, when the reaction had settled, and when simultaneous skin biopsy was classified "BT (late stage of reversal reaction)". This lymph node contained only small numbers of infiltrate cells, the majority being in the subcapsular region of the paracortical area. Although the nucleus and cytoplasm of each infiltrate cell remained oval or rounded, the nucleus stained more deeply and its structure was 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 fourth reversal reaction patient was graded BB before commencing treatment, when his node showed in some areas well demarcated multicentric infiltrate consisting of slightly whorled, atypical epithelioid cells, whereas in other areas the infiltrate consisted of groups of nonfoamy histiocytes, not well separated from, and diffusely invaded by lymphocytes. Two weeks after the start of dapsone treatment he developed a very severe reversal reaction, and the serial lymph node taken at that

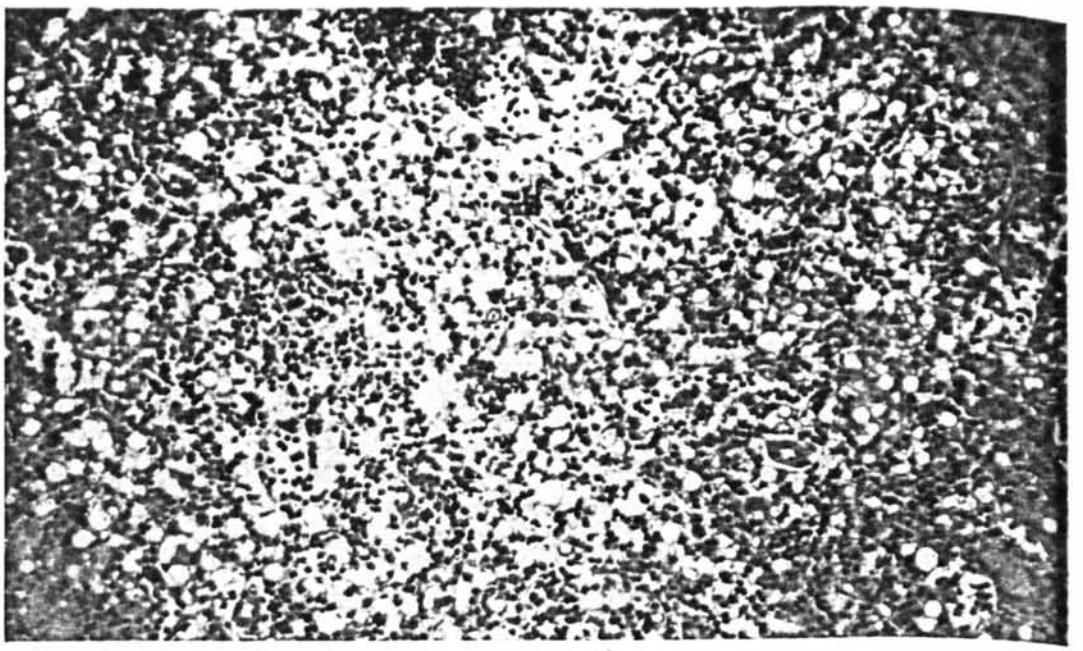

FIG. 8. Lymph node from same patient as Fig. 7, biopsied after three months, when his downgrading reaction had settled and he was classified borderline-lepromatous (BL). The groups of infiltrate cells are much less well demarcated from the surrounding paracortical lymphoctyes, and many of the histiocytes contain foamy vacuoles. (Hematoxylin-eosin, 100×).

time showed that the infiltrate consisted of uniformly multicentric whorls of atypical epithelioid cells.

Far more significant were the findings in two patients who were classified on admission as BL/LI clinically and LI histologically, and who subsequently underwent very marked reversal reactions, shifting to BB or BT on skin biopsy, and showing dramatic falls in their bacterial indices and some increase in lepromin positivity. In both patients, lymph node biopsy during reaction revealed that the paracortical infiltrate cells remained the vacuolated or foamy histiocytes of lepromatous leprosy. Groups of mycobacteria or microglobi were still present in the histiocytes, although the acid-fast material appeared as extremely granular, acid-fast debris rather than as fragmented bacilli. Germinal centers were still prominent, and plasma cells increased in number. But the most striking feature was the partial repopulation of the paracortical areas with lymphocytes. The infiltrate was broken up by broad bands of these cells; 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 (Figs. 9 and 10).

DISCUSSION

The finding of granular deposits of immunoglobulin and complement in a perivascular distribution in relation to the polymorph infiltrate in ENL lesions from 20 of 38 patients would appear to be highly significant. The appearance was similar to that found by Cochrane and Ward ([2]) in Arthus reactions in the skin of laboratory animals. A similar appearance has been found by Miescher *et al.* ([9]) in the skin of patients with acute necrotizing vasculitis. Failure to find deposits in 26 skin biopsies is consistent with the observation that such deposits may not be found in Arthus reactions examined 24 hours after their induc-

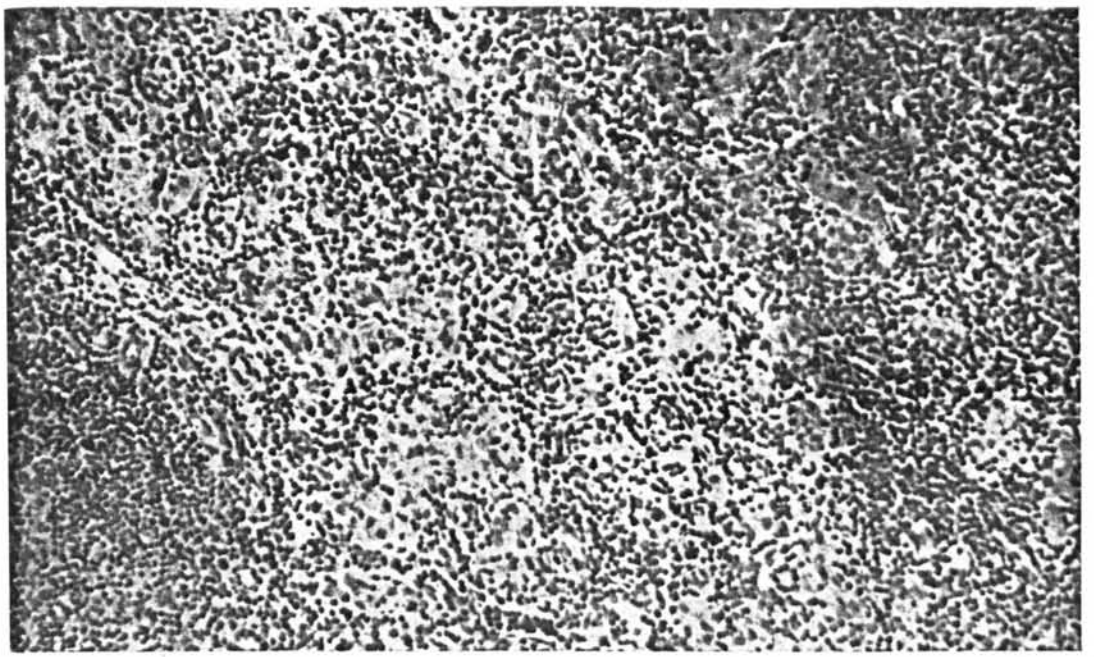

FIG. 9. Lymph node from patient who had undergone a reversal reaction from near the lepromatous end of the spectrum (BL/LI) to borderline-tuberculoid (BT) leprosy. The paracortical infiltrate is broken up by broad bands of lymphocytes, which are also scattered diffusely among the histiocytes. (Hematoxylin-eosin, 100×).

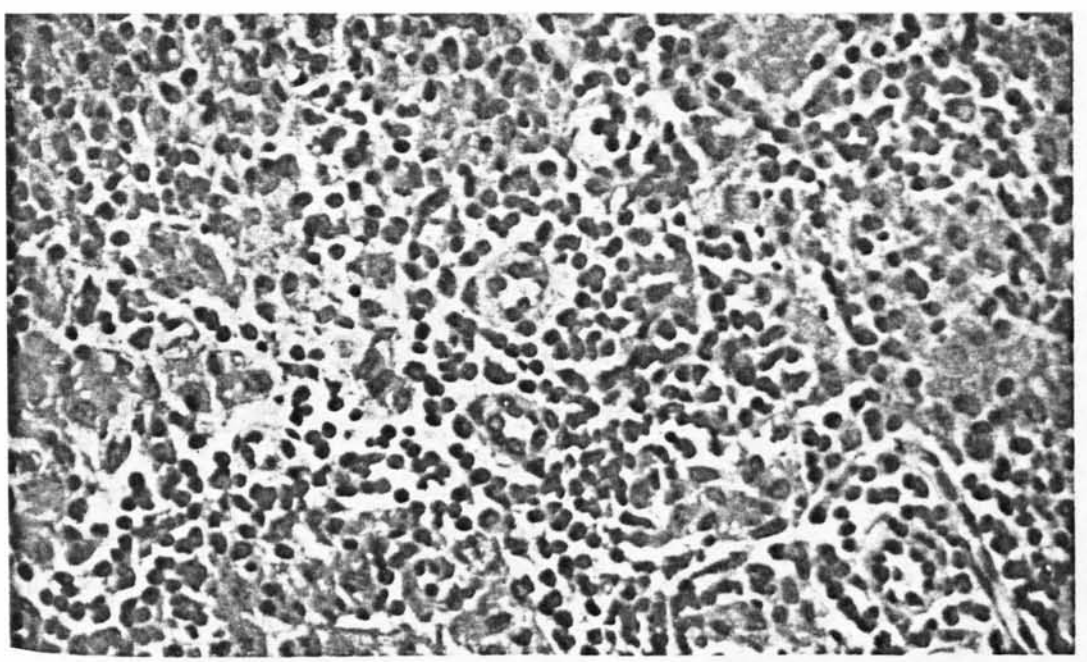

FIG. 10. Same lymph node as Fig. 9 showing accumulations of lymphocytes around post-capillary venules. The infiltrate cells remain as vacuolated histiocytes. (Hematoxylin-eosin. 250×).

tion in laboratory animals (5). For most of the duration of this immunofluorescent study of ENL skin lesions, dry ice could easily be obtained only by advance order; therefore not infrequently biopsies were perforce taken from ENL lesions already changing color, and beginning to subside. Positive results were obtained in most lesions containing very numerous polymorphs; whereas lesions in which polymorphs were either relatively few in number and replaced by lymphocytes or else were necrotic were usually negative for immune deposits.

Throughout the ENL study, serum prepared with *M. tuberculosis* failed to stain *M. leprae*. Therefore the antigen detected by that serum in the immune complexes was probably a soluble antigen which was released from dead organisms into the tissues, and which was not exposed on the surface of the organisms directly displayed in the lesions. It is noteworthy that this antigen was also detected in control biopsies from two lepromatous patients not suffering from ENL. Both this presumed mycobacterial antigen, and the human antimycobacterial antibody require further investigation, so that they may be more precisely defined. Nevertheless, there would appear little doubt that ENL is an immune complex disease. We have not as yet determined whether the immune complexes are formed locally, as in the Arthus phenomenon, or are present in the circulation, but we incline to the former view. This would appear more in keeping with the clinical distribution of the ENL lesions, especially in BL patients.

Studies of lymph nodes obtained from patients suffering from ENL (20) have confirmed that humoral antibody production remains stimulated in this condition, and that no change in leprosy classification occurs during the course of the reaction. It is well known clinically that ENL eventually fades away, perhaps after a number of years, even in patients with severe ENL reactions, provided that antileprosy treatment is continued. Therefore it is noteworthy that the single node obtained from a lepromatous patient treated continuously with dapsone for 10 years, and who had earlier suffered from ENL which had completely resolved, showed no evidence of excess humoral antibody production (no hypertrophy of germinal centers or hyperplasia of plasma cells), although histiocytes could still be detected in the paracortical area.

The findings in lymph nodes obtained from patients undergoing "downgrading" and "reversal" reactions support the view that such reactions are associated with changes in CMI, which increases in reversal reactions, and decreases in downgrading reactions. Changes in the infiltrate cells, which belong to the histiocyte-macrophage series, were relatively minor, although they tended to become more histiocytic in downgrading reactions, and more epithelioid in reversal reactions. However, the partial repopulation by lymphocytes of the paracortical areas in the nodes obtained from two patients undergoing marked reversal reactions from BL/LI to BB or BT, was considered highly significant. The concept is further strengthened by the experimental work of Rees and Weddell (11, 12, 13) who have obtained "reversal reactions" in lepromatous inbred mice subjected to thymectomy and x-irradiation before being inoculated with *M. leprae*, by means of syngeneic lymphoid tissue replacement. However, why these changes occur in human patients remains obscure.

Newell (10) has suggested that the development of lepromatous leprosy is genetically determined. If this is so, then patients with borderline and lepromatous leprosy probably have a gentically-determined impaired ability to respond with CMI to stimulation with antigens of *M. leprae*. Therefore it is possible that in untreated borderline (BT, BB and BL) patients, factors (e.g., intercurrent infection or pregnancy) which lower nonspecific resistance may allow the leprosy bacilli to multiply, and induce a state of immunologic tolerance. This would result in a downgrading reaction, and a change of classification toward lepromatous. Conversely, the killing of leprosy bacilli by effective treatment

may allow tolerance to be broken, resulting in a reversal reaction, and a shift in the disease toward the tuberculoid side of the spectrum. Ridley and Waters ([16]) found that one-third of all BL patients and 10 per cent of LI patients (i.e., lepromatous patients who had passed through an earlier borderline phase) developed reversal reactions by the end of the first year of effective antileprosy treatment. Patients who develop primary, polar (LL) lepromatous leprosy probably have a more severe genetic impairment of response to antigens of *M. leprae*. As a result, they develop tolerance very easily and therefore do not pass through a borderline phase. Moreover, the degree of tolerance which they develop is so great that they are not able to regain immunity when the antigenic load is reduced following the killing of leprosy bacilli by effective antileprosy treatment. In this way, the generally accepted stability of polar lepromatous (LL) leprosy may be explained.

SUMMARY

Although terminology remains controversial, it is becoming increasingly agreed that most reactions in leprosy fall into one or other of two groups. The first is commonly known as Erythema Nodosum Leprosum (7th International Congress of Leprology) or Lepromatous Lepra Reaction (8th International Congress). Because of similarities between ENL and the experimental Arthus reaction, biopsies of ENL skin lesions were studied for immune complexes using immunofluorescent techniques. Biopsies taken from 20 of 38 ENL patients were found to contain both immunoglobulin and complement (β1C/β1A globulin), and sometimes also soluble mycobacterial antigen, whereas control biopsies taken from 13 lepromatous patients not suffering from ENL were uniformly negative for immunoglobulin and complement. It is concluded that ENL is an immune complex disease.

Reactions belonging to the second main group are usually known as Lepra Reactions (7th International Congress of Leprology) subdivided according to the form of leprosy from which the individual patient is suffering. They may occur anywhere on the leprosy spectrum save at the two extreme poles. Their end result is usually a shift in leprosy classification; a patient who develops such a reaction before commencing antileprosy treatment becomes more lepromatous ("Downgrading Reaction"), whereas one who reacts while receiving effective treatment becomes more tuberculoid ("Reversal Reaction"). A study was made of 20 lymph node biopsies obtained from 15 patients in reaction (five downgrading and ten reversal), part of a larger series of 77 lymph nodes from 62 patients representative of the whole leprosy spectrum. In all 20 reaction lymph nodes the paracortical areas were infiltrated by cells of the macrophage-histiocyte series. Particular note was made of the morphologic characteristics of these infiltrate cells, including the changes in their appearance which occurred on serial biopsy, and of the number and distribution of the paracortical lymphocytes and of leprosy bacilli. The results presented suggest that this group of reactions is associated with changes (increase or decrease) in cell mediated immunity.

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REFERENCES

1. Bullock, W. E. and Ho Min Fu and Chen Mei Jan. Studies of immune mechanisms in leprosy. II. Quantitative relationships of IgG, IgA and IgM immunoglobulins. J. Lab. and Clin. Med. **75** (1970) 863-870.

2. COCHRANE, C. G. and WARD, P. A. The role of complement in lesions induced by immunologic reactions. *In* Immunopathology, IVth International Symposium. P. GRABER and P. A. MIESCHER, Eds. Basel, Schwabe, 1966, pp. 433-445.
3. [CONGRESS, TOKYO] Technical Resolutions. Bacteriology and Pathology. VIIth International Congress of Leprology, Tokyo, November 1958. Internat. J. Leprosy **26** (1958) 380-385.
4. [CONGRESS, RIO DE JANEIRO] Report of the Panel on Lepra Reaction. VIIIth International Congress of Leprology, Rio de Janeiro, September 1963. Internat. J. Leprosy **31** (1963) 480-482.
5. CREAM, J. J., BRYCESON, A. D. M. and RYDER, G. The disappearance of immunoglobulin and complement from the Arthus reaction and its relevance to studies of vasculitis in man. British J. Dermatol. (in press).
6. DESIKAN, K. V. and JOB, C. K. Leprous lymphadenitis. Demonstration of tuberculoid lesions. Internat. J. Leprosy **34** (1966) 147-154.
7. JOPLING, W. H. On Erythema Nodosum Leprosum. Leprosy Rev. **29** (1958) 116-118. (Correspondence).
8. JOPLING, W. H. Reactional leprosy or leprosy in reaction. Leprosy Rev. **30** (1959) 194-196 (Correspondence).
9. MIESCHER, P. A., PARONETTO, F. and KOFFLER, D. Immunofluorescent studies in human vasculitis. *In* Immunopathology, IVth International Symposium. P. GRABER and P. A. MIESCHER, Eds. Basel, Schwabe, 1966, pp. 446-456.
10. NEWELL, K. W. An epidemiologist's view of leprosy. Bull. Wld. Hlth. Org. **34** (1966) 827-857.
11. REES, R. J. W. Immunological aspects of experimental leprosy in the mouse. Proc. Roy. Soc. Med. **63** (1970), (in press).
12. REES, R. J. W. and WEDDELL, A. G. M. Experimental models for studying leprosy. Ann. N.Y. Acad. Sci. **154** (1968) 214-236.
13. REES, R. J. W. and WEDDELL, A. G. M. An experimental model in mice for studying the reversal reaction. Internat. J. Leprosy **36** (1968) 629-630.
14. RIDLEY, D. S. Reactions in leprosy. Leprosy Rev. **40** (1969) 77-81.
15. RIDLEY, D. S. and JOPLING, W. H. Classification of leprosy according to immunity. A five-group system. Internat. J. Leprosy **34** (1966) 255-273.
16. RIDLEY, D. S. and WATERS, M. F. R. Significance of variations within the lepromatous group. Leprosy Rev. **40** (1969) 143-152.
17. SHEAGREN, J. N., BLOCK, J. B., TRAUTMAN, J. R. and WOLFF, S. M. Immunologic reactivity in patients with leprosy. Ann. Int. Med. **70** (1969) 295-302.
18. TURK, J. L. Cell-mediated immunological processes in leprosy. Bull. Wld. Hlth. Org. **41** (1969) 779-792.
19. TURK, J. L. and WATERS, M. F. R. Immunological basis for depression of cellular immunity and the delayed allergic response in patients with lepromatous leprosy. Lancet **2** (1968) 436-438.
20. TURK, J. L. and WATERS, M. F. R. Immunological significance of changes in lymph nodes across the leprosy spectrum. Clin. Exp. Immunol. (in press).
21. WADE, H. W. The Rio Congress reports. Internat. J. Leprosy **32** (1964) 427-428. (Editorial).
22. WATERS, M. F. R., REES, R. J. W. and SUTHERLAND, I. Chemotherapeutic trials in leprosy. 5. A study of methods used in clinical trials in lepromatous leprosy. Internat. J. Leprosy **35** (1967) 311-335.
23. WEMAMBU, S. C. N., TURK, J. L., WATERS, M. F. R. and REES, R. J. W. Erythema nodosum leprosum: a clinical manifestation of the Arthus phenomenon. Lancet **2** (1969) 933-935.