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Events Surrounding the Recognition of *Mycobacterium leprae* in Nerves[1]

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Peripheral nerve involvement is generally recognized to be fundamental to the establishment of infections with *Mycobacterium leprae* in man. The bacillus usually attains a higher density in the nerves than in the skin ([1, 25, 30]), which is not entirely explained by an affinity between nerve tissue and *M. leprae* since the preferential involvement of nerves is limited to the incipient infections, or to those in which some immunity survives ([23, 25]). Probably more important is the role of the nerve as an immunologically protected site ([2, 4, 5, 21]) in which antigen is not readily detected. Recently, we noted that the classification of nerves could be modified by events associated with the delayed recognition of *M. leprae* antigen in neural tissue ([25]). In many such cases, episodes of acute inflammation detected histologically in nerves were accompanied by a diminution locally of the bacterial load, and although such inflammation was taken to signify a leprosy reaction, there was no clinical evidence of reaction in nerve or in the generalized histological response, particularly in the skin ([25]).

The order of events surrounding the recognition of antigen in protected sites is highly important to the pathogenesis of leprosy, but poorly understood. This applies particularly to peripheral nerves which are also anatomically structured for the preservation of their internal integrity ([33]). The recognition of antigen screened by the basement membrane of Schwann cells must depend on its level, its immunogenic potential, and the integrity of the cell and local tissue.

In the present paper we are concerned with a) the significance of local, histologically apparent reactional episodes, and the probable sequence of events that follow them; and b) the inter-relationships between antigen load, inflammatory response, and the patho-physiological properties of nerves.

PATIENTS AND METHODS

Patients

All 42 patients supplying the main group of biopsies had active, untreated leprosy which had been assessed clinically by the late Dr. J. C. Pedley at the United Mission Hospital, Tansen, Palpa, Nepal ([22]). Clinically visible or palpable nerves were chosen for biopsy. The material selected by us for this and previous investigations ([25]) represented the whole spectrum of the disease.

Tissues

Forty-two nerve biopsies had been classified on a slightly modified schedule in the previous study. The granuloma fraction was irrelevant, and acid-fast bacilli (AFB) were estimated over the whole area of nerves as in smears ([25]). The 3-mm or 4-mm longitudinal nerve specimens contained 1 large or 1 to 3 smaller fascicles. They had been fixed overnight in FMA (a mixture of Formalin, mercuric chloride, and acetic acid, 10:2:3, in 100 ml distilled water) before transfer to 70% ethanol (Dr. D. J. Harman's method). Serial paraffin sections were stained by hematoxylin and eosin (H&E) and for AFB by a modified Wade-Fite stain (Armed Forces Institute of Pathology, Washington, D.C., U.S.A.) ([24]). AFB were also stained by methenamine silver impregnation to reveal cell walls ([26]).

Additional nerves from six untreated patients were received at the Hospital for Tropical Diseases, London. They were classified as: TT = 1, BT = 2, BL = 2, LL = 1,

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and were fixed in buffered Formalin. They were used mainly to demonstrate myelin by Weil's method and axons by Bielschowsky's technique. Staining by TRIFF ([24]) after fixation in FMA demonstrated neural structure and cells clearly. Other methods used on selected samples were periodic acid-Schiff (PAS) for polysaccharide substances; Martius scarlet blue (MSB) for fibrinoid, collagen, and basement membrane; iron hematoxylin for basement membrane; and Verhoeff's stain for elastic fibers.

Immunocytochemistry

Pretreatment of sections with trypsin or pepsin did not enhance the sensitivity of the peroxidase–anti-peroxidase (PAP) technique, and was omitted. Following deparaffinization in xylene, sections were brought to water, treated with iodine followed by sodium thiosulfate to remove the mercury, and then with 1% hydrogen peroxide in methanol to quench endogenous peroxidase activity. After washing in Tris-buffered saline (0.05 M, pH 7.4), the following reagents were applied sequentially: normal swine serum 1/10 for 30 min to reduce nonspecific binding; optimally diluted rabbit antiserum, 30 min; Tris saline to wash; swine anti-rabbit immunoglobulin 1/20 for 30 min; Tris buffer to wash. Finally, the PAP reagent was applied diluted 1/50 for 30 min. Staining was performed in a moist chamber at room temperature. The reaction product was visualized after exposure to freshly prepared 0.05% 3,3'diaminobenzidine tetrahydrochloride (DAB; Sigma) in 0.01% hydrogen peroxide diluted with Tris-saline buffer for 2–5 min. The sections were washed in tap water and counterstained in Mayer's hemalum.

Anti-serum and controls. Anti-BCG antibody was used at 1/250, the optimal dilution obtained by a checkerboard titration using sections of active lepromatous leprosy. Anti-human S-100 IgG antibody was diluted 1/200, anti-human Factor VIII IgG 1/50, and anti-human lysozyme IgG 1/100. All reagents and antisera, unless otherwise stated, were obtained commercially from Dakopatts, High Wycombe, U.K. They were raised in rabbits without Freund's complete adjuvant.

Controls for the immunoreaction were performed as follows: a) The primary antiserum was replaced with normal rabbit serum. b) Absorbed anti-BCG IgG and anti-lysozyme IgG were substituted for the antibody: for absorption 50 μl BCG antiserum was mixed with 100 μg BCG (Glaxo), and 50 μl lysozyme antiserum was mixed with 100 μg lysozyme (Sigma); the mixtures incubated for 24 hr at 4°C centrifuged, filtered, and used. c) Sections were stained in DAB-peroxide after quenching endogenous peroxidase activity. The absence of positive staining in each case confirmed the specificity of the result.

Identification of cells. Schwann cells are reactive to S-100 protein antiserum ([8, 31]), as are also melanocytes and interdigitating reticulum cells, but the number of the latter type of cells in nerves must be small. The use of polyclonal or monoclonal antiserum makes no difference ([17]). Schwann cell morphology was characteristic. The cells were elongated with a smooth contour and a large nucleus encased in cytoplasm. The axons were clearly visible as slightly hyalinized fibers which stained specifically. The basal lamina was better seen after staining with PAS or Martius scarlet blue (MSB), iron hematoxylin, or TRIFF. Macrophages were recognized by the use of anti-lysozyme antiserum ([13, 28]). Other cells positive for lysozyme are mast cells and neutrophil polymorphs (PMNs), but perineurial cells and fibroblasts are negative ([13]). Factor VIII antibody identified vascular endothelial cells.

Quantitative estimate of *M. leprae* antigen

M. leprae is known to cross react with BCG antibody, which was used to identify the organism and its degradation products ([26]). The amount of BCG-positive antigen deposited in macrophages and Schwann cells was assessed separately using the following scale: ++++ = large amount widely distributed over a large area of the nerve; +++ = large amount deposited in localized areas; ++ = moderate amount in localized areas; + = little, scattered over the whole nerve section. The bacterial index (BI) calculated on a log scale from 1+ to 6+ was used to estimate AFB ([24]).

RESULTS

The 48 nerve biopsies revealed complex lesions that were essentially similar

TABLE 1. *Estimation of acid-fast bacilli and their location in nerve lesions.*

Nerve	Location	Type of leprosy							
		TTp	TTs	TT-BT	BT	BB	BL	LLs	LLp
Severe reacting[a]	Schwann cells		0.5		1.5	3.0	4.5	5	
	Macrophages		—		—	1.5	2.5	5.5	
Post-reaction	Schwann cells	—	—	1.0	3.0	4.5	5.0	6	5
	Macrophages	—	—	—	—	2.0	2.0	5	5

[a] Reacting lesions = microreaction in large part of fascicle.

throughout the spectrum except in LL (10 cases). The remaining 38 lesions could be analyzed as a whole, and typically they had three constituent parts: a) There were AFB in Schwann cells which excited no inflammation; b) there were small clusters of Schwann cells and macrophages undergoing destruction associated with subacute inflammation which we call microreactions; and c) there were small foci of granuloma which appeared to follow the microreactions. We concluded that these three constituent parts of the lesion represented three phases of the same process, but because the lesions were multifocal and nonsynchronous the different phases could each be identified in most nerve lesions. Only the largest and most severe reactions were synchronized.

***M. leprae* antigen.** Acid-fast bacilli, silver-impregnated cell-wall products, and BCG-positive antigen were distinguished. Anti-BCG antibody identified whole *M. leprae* and also a diffuse soluble degradation product, whose density and location are summarized together with those of AFB in Tables 1 and 2. AFB, especially solid forms, were more numerous in the Schwann cells than in macrophages in all types of lesions except active LL. Only very occasionally were solid AFB seen in perineurial cells or in vascular endothelial cells. Myelinated cells had lower numbers of AFB, often only a single granular organism, compared to unmyelinated cells in which there were higher numbers of AFB present, including solid and granular forms. Surface BCG-reactive antigen present on some macrophages was absent on Schwann cells. Soluble antigen adhered to components of myelin, producing laminated or globular BCG-positive inclusions which were internalized in the Schwann cells and, occasionally, in macrophages. When the BI was high all forms of antigen, solid and granular AFB, soluble BCG-reactive substances, cell wall products, and BCG-positive antigen–myelin complexes were detected (Fig. 1).

Microreaction in nerves

The majority of lesions showed sporadic, microscopic areas of subacute inflammation which occupied part of one or more fascicles. They were the most striking feature, involving the entire fascicle in 7 out of 38 cases. They were associated with diminished amounts of *M. leprae* antigen. Heavy edema caused a widening of inter-

TABLE 2. *Estimation of BCG-reactive* M. leprae *antigen and its location.*

Nerve	Location	Type of leprosy							
		TTp	TTs	TT-BT	BT	BB	BL	LLs	LLp
Severe reacting	Schwann cells		+		+	+++	+++	++++	
	Macrophages		−		++	++	+++	++++	
	Ag-myelin[a]		−		++	+++	++++	+	
Post-reaction	Schwann cells	−	+	+	+++	+++	++++	++++	++++
	Macrophages	+	++	+++	+++	++	++	++	++
	Extracellular	−	−	−	+	++	++++	++	−
	Ag-myelin	−	−	−	++	+++	+++	++	++

[a] Ag-myelin = antigen-associated myelin.

FIG. 1. BL. BCG-positive soluble components (⬟) and antigen–myelin products (⬟ ⬟) are increased (immunoperoxidase anti-BCG ×900).

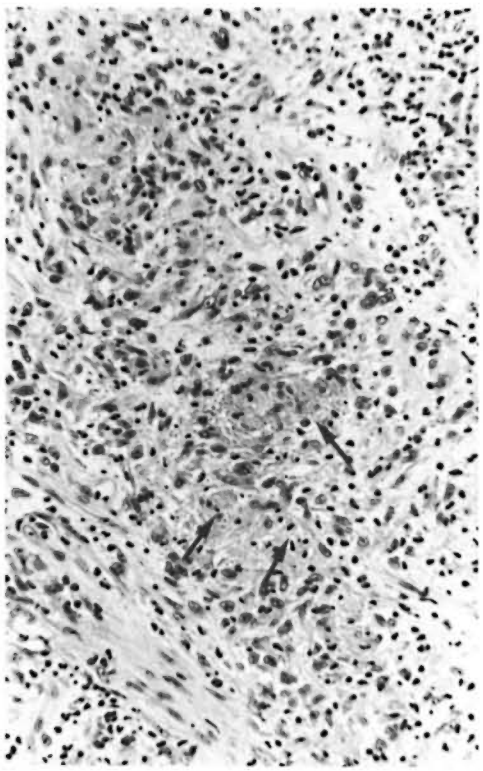

FIG. 2. TTsR. Microreaction showing edema, hypercellularity, and necrosis (⬟) of Schwann cells and macrophages (H&E ×250).

stitial spaces and inflammatory cells of all types, except PMN, dominated the scene (Fig. 2). The infiltrate included mast cells and active fibroblasts. Derangement of neural parenchyma was severe. There was coalescence of the endoneurial and perineurial regions of the nerve, and when disorganization of the main fascicle was heavy, smaller adjacent fascicles might be indistinctly demarcated by a thin perineurial lining. Reduplicated layers of swollen epineurial connective tissue, intercalated with mononuclear cells, were observed in all groups although not only in reacting lesions.

Necrosis. Small, poorly delineated foci of necrosis were found scattered over the microreactional areas, in which isolated Schwann cells or groups of Schwann and granuloma cells lost their cell membranes (Fig. 3). The form of this microscopic necrosis varied across the spectrum, depending largely on the nature of the granuloma cell or intrafascicular tissue involved. In TT, there was fibrinoid change; in BT, karyorrhexis was common; in BL, necrotic areas were formed of acidic granular, PAS-positive material deposited subperineurially. There was wide dispersal of antigen which varied in form and amount. There was no necrosis in LL, and necrosis or abscess formation was never the main feature of any lesion in the series. Although blood vessels were severely damaged, there was nothing to suggest ischemia as the cause of the necrosis in any of the groups. Capillary proliferation was intense.

Schwann cells. There was little difference between cells harboring intact *M. leprae* and those without ingested bacilli. Their destruction was preceded by the adherence of monocytes, mast cells, lymphocytes, and plasma cells to their surfaces. This was especially true of myelinated cells. Degenerative changes in infected and noninfected Schwann cells alike affected myelin, causing swelling, condensation, and, finally, pyknosis or destruction by inflammatory cells. In LL, it was common to see greatly swollen,

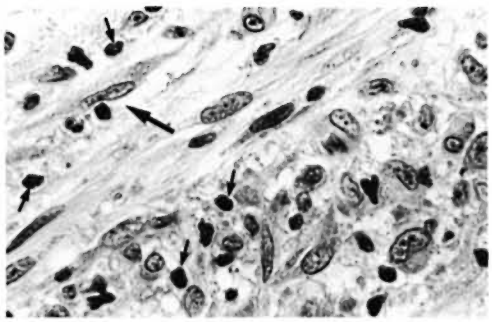

FIG. 3. BT. Microreactional area shows disintegration of Schwann cells (⬆) and pyknosis (⬆) of immature epithelioid cells (H&E ×600).

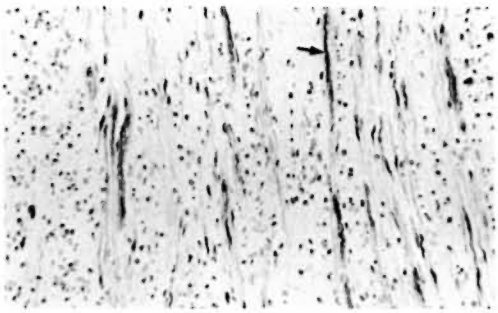

FIG. 5. BB. Increased survival of Schwann cells (⬆) (immunoperoxidase anti-S-100 ×150).

irregular, and contorted Schwann cells that resembled foamy macrophages. Not all had ingested AFB. Infected myelinated cells had few AFB, and when degraded AFB were present, the cell invariably showed signs of degeneration. BCG-positive antigen adhered to myelin (Fig. 4), sometimes delineating the cell below the basal lamina. The number of Schwann cells surviving the inflammatory process increased across the spectrum from BT to LL (Fig. 5); it was minimal in TT (Fig. 6). Regeneration of Schwann cells proceeded simultaneously with destruction, although not necessarily at the same site. Newly formed cells were observed in discrete groups of 3 or 4 cells, except in BL where rapid proliferation resulted in groups of about 10 poorly differentiated cells. Many of the newly formed cells were in mitosis, and all reacted to S-100 antibody.

Post-reactional granuloma

Small granulomatous foci of epithelioid cells or macrophages were noted in the 38 lesions. They were associated locally with a diminution of edema and cellular infiltrate. The granulomas were situated in the endoneurial and perineurial regions, the differentiation of the cell type being in accordance with the position in the spectrum. Mature epithelioid cells filled large spaces between the Schwann cells, in tuberculoid lesions (Fig. 7), and soluble antigen was detected in some of the immature epithelioid cells, mainly in TT and BT lesions (Fig. 4). Small clusters of similar cells were seen occasionally in BB and BL lesions; more commonly, macrophages in BL had a foamy appearance (Fig. 8) and around them all forms of antigen were distinguished (Fig. 1). Schwann cells became elongated and occupied the remainder of the lesion in all groups. Bacilli were unevenly distributed in the fascicle but were always more dispersed and degraded in the granulomatous foci than in Schwann cells.

Resolution. Wherever cellular activity declined the stages of regression and clearance

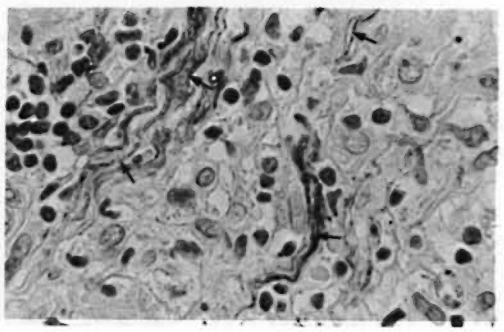

FIG. 4. TT-BT. BCG-reactive antigen associated with myelin (⬆) (immunoperoxidase anti-BCG ×750).

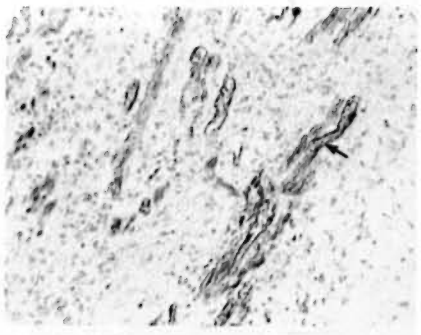

FIG. 6. TT-BT. Fewer fragmented and swollen Schwann cells (⬆) (immunoperoxidase anti-S-100 ×150).

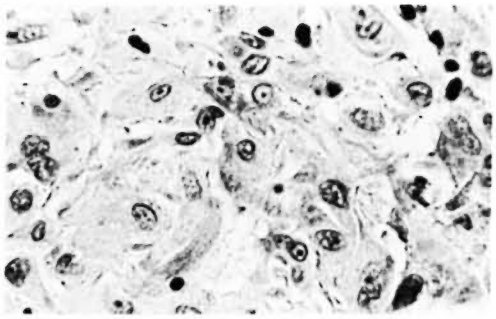

FIG. 7. TTS. Mature epithelioid cell in post-reaction granuloma (H&E ×600). (Compare with immature epithelioid cell, Fig. 3.)

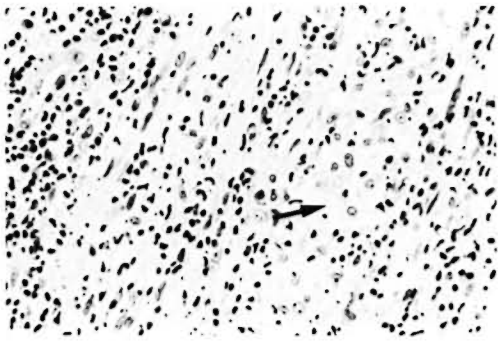

FIG. 9. BT. Resolution is by reduction of granuloma (⬟) and increased scattered lymphocytes (H&E ×150).

of granuloma became apparent. Macrophage cell death occurred in one of two ways: by degeneration of the cell membrane or by cytoplasmic vacuolation. Sometimes this was associated with surface adherence of lymphocytes. In BL and LL, macrophages in an advanced state of decay persisted in perivascular areas of the endoneurium and perineurium. In all groups except LL the granuloma appeared to resolve by the infiltration of lymphocytes (Figs. 9 and 10) and plasma cells in sequence. Clearance of the necrotic residue was patchy; solid AFB remained in fibrous areas (BT), and sometimes pockets of externalized antigen (BL) were visible. There was no erythema nodosum leprosum (ENL).

DISCUSSION

The results of this study draw attention to the occurrence of three types of histological responses in the nerves of patients with tuberculoid or borderline leprosy. a) There are areas of relatively normal nerve in which AFB are moderately numerous (TT excepted). b) There are areas of subacute inflammation, often involving a whole fascicle, in which the architecture is destroyed by edema, inflammatory cells, and necrosis; AFB are fewer and more granular. c) In areas in which the inflammation has subsided, there are small foci of granuloma in which AFB are scanty or absent but BCG-reactive products are more profuse. The relationships among these three types of responses, one to another, and to the progressive degradation of their antigen content, suggest that they represent three phases of a sequence in which *M. leprae* masked in nerve becomes recognized, induces a local reaction as a result of which the bacilli are destroyed, and, finally, the antigenic products become ingested in a post-reactional granuloma. The observations receive some support from those of other workers ([4, 12, 14, 15, 19, 21, 22]) re-

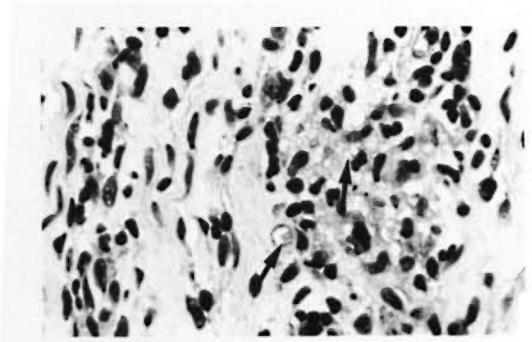

FIG. 8. BL. Post-reactional granuloma showing macrophages (⬟) among lymphocytes (H&E ×600).

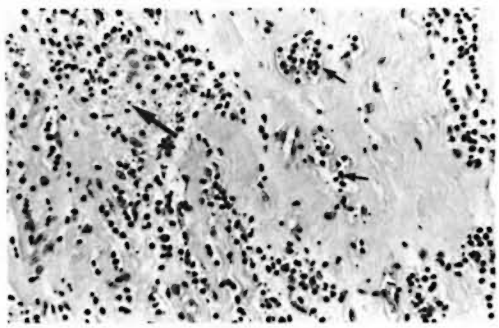

FIG. 10. BT (same case as Fig. 9). Later stage in resolution shows that lymphocytes collect around capillaries and disappear (⬟); macrophages die *in situ* (⬟) (H&E ×150).

viewed by Dastur ([9]). This histological sequence has not previously been described, but our interpretation that reaction associated with antigen recognition is often a local event is consistent with the observation of others of markedly abnormal nerve lesions in clinically nonreacting patients ([12, 21]). None of our 48 cases was in clinical reaction, and there was no neuritis despite nerve thickening.

The key to the evolution of these lesions is the role of nerve as a barrier to the immunological detection of *M. leprae* and its antigens, the evidence for which is well attested ([25]). The present results suggest that the barrier needs to be viewed at two levels: a) the Schwann cell, and b) the nerve fascicle within the perineurium. Considering the first, the Schwann-cell barrier is adequately explained by the basement lamina of these long-lived cells ([4, 21]). Furthermore, the absence of BCG-reactive antigen at the cell surface and in the neighborhood of intact Schwann cells means that antigen is unlikely to be presented by them or to leak from them. It will not be detected so long as the cell remains intact. Even in TT or BT, solid AFB in Schwann cells may excite no inflammation ([19, 34]). To be recognized, bacterial antigen has first to be externalized by Schwann cell destruction. Our data pointed to differences in the handling of *M. leprae* by the two types of Schwann cells; unmyelinated cells showed markedly higher numbers of bacilli ([29]), but the lower numbers of bacilli in myelinated cells, observed also by experiment ([6]), appeared to be degraded more quickly, and their products became associated with myelin. Myelin is constantly degraded and renewed in Schwann cells, which are particularly vulnerable at the time of synthesis ([18]). Only after intracellular AFB were degraded did degenerative change become apparent in the cell. On this evidence, it seems likely that antigen-associated myelin, probably in the form of a complex, is more toxic than whole undegraded *M. leprae*. It may also be difficult to clear from the tissues. Antigen–myelin complexes were externalized following cellular disintegration. Myelin loss is reported to occur in all types of leprosy and in the absence of AFB ([4, 11, 16]), which our study confirmed. It could possibly be attributed to the ingestion of undetectable degraded antigen by other Schwann cells ([20]). We suggest that in infected nerves there is continuous low-grade damage, due to the destruction of Schwann cells, which is largely independent of immunological mechanisms.

These events set the stage for immunological recognition of released antigen, and for a more general involvement of neural tissue. If there is a critical level at which antigen becomes immunologically detectable ([21]), it is not the level in Schwann cells, and the form of this antigen is as important as the amount, as already noted ([2]). There are intact and granular AFB, cell walls, and soluble and degraded products that may be complexed with myelin. The accumulations of antigen-myelin products ([10]), and of large amounts of extracellular mycobacterial antigen, were the focus of inflammatory changes. That the development of the inflammatory process is impeded by the anatomy of nerves ([32]) and by the constraint of intraneural pressure ([33]) was evident from the multifocal nonsynchronous response of most cases. At first, only small mononuclear cells infiltrated the compact neural tissue, but increased edema and disintegration of neural structure allowed the influx of larger cells, especially macrophages which facilitated the recognition of the abundant antigen released by the destruction of unmyelinated cells. Later, with the partial restoration of neural architecture, the egress of macrophages was restricted. Resolution was often incomplete, resulting in micronecrotic areas, with deposited residual antigen. In BL lesions, it was the mass of antigen that made clearance difficult. In tuberculoid lesions, degradation of antigen was effective but the large size of the epithelioid cells impeded clearance. Resolution is probably achieved by repetition of the processes of recognition, inflammation, and clearance, which is apparent from the patchy and multifocal type of granulomatous response that is characteristic of infection in nerves ([11, 21]). The collection of mononuclear cells around newly formed capillaries and in the perineurium suggested that these might be escape routes. The commonly observed fibrinoid necrosis of intrafascicular connective tissue in TTs lesions could reasonably be attributed to delayed hypersensitivity (DH), and so also could the karyorrhexis of BT lesions. Lower down the

leprosy spectrum, the etiology of the acidic granular necrosis was obscure. The increasing levels of antigen might be expected to inhibit a DH response, and this was the impression in our previous study ([25]). The amounts of antigen and plasma cells suggested that conditions were present for immune complex formation at antigen excess which could be a factor in the Schwann cell necrosis. Although antigen–antibody complexes at equivalence can produce a different form of necrosis ([27]), the absence of neutrophil polymorphs argues against it. There was no ENL.

Despite previous observations ([7, 12, 21]), the prevalence of localized microreactions in clinically nonreacting nerves was a surprise. By analogy with the response in skin, mild histological reactions are frequent in the skin of borderline patients and are associated with a small rise in the lymphocyte transformation test values ([3]), which in overt, clinically apparent reactions is much greater. The mild and overt reactions in skin are histologically similar, indicating that the underlying mechanism is the same. The situation in nerves differs mainly in that the subacute reactions, which are mild and clinically inapparent, are more localized but more severe than those in the skin, connected no doubt with the irregular patchy distribution of antigen recognition. The relationship between mild histological reactions and those in overt reaction is presumably a matter of degree in nerves as in the skin. This needs further study. Since immunological granulomas develop only after the recognition of antigen, tuberculoid granulomas in nerve are similarly more localized and patchy. In the skin, outside protected sites, there is no barrier to antigen recognition and granulomas form without delay over the whole area of antigen distribution. In LL leprosy, the uptake of the very numerous bacilli by macrophages is a nonimmunological process, and the response in nerves is much the same as in the skin.

SUMMARY

Histological examination and immunocytochemistry of Schwann cells, macrophages, and mycobacterial antigen were used to study 48 nerves of untreated patients with leprosy. None of the patients was in reaction clinically, but microreactions, involving small clusters of Schwann cells and macrophages in all cases except LL, were marked by progressive degradation of acid-fast bacilli (AFB). This was thought to be the response to the recognition of mycobacterial antigen. In the first phase, the disintegration of one or more Schwann cells caused the release of AFB, accompanied by subacute inflammation. In the second phase, as edema and cellular infiltration subsided, the necrosis of Schwann cells was replaced by granuloma formation, mycobacterial antigen being in a soluble form. Myelinated cells harbored few degraded AFB, and there was evidence that antigen-associated myelin hastened the death of Schwann cells. Only then did antigen become immunologically detectable to induce an inflammatory response whose clearance and resolution was impeded by the restraint on cellular movement due to the structure of neural tissue.

These developments were sporadic but continuous. AFB and antigen released by disintegrating Schwann cells were ingested by regenerating Schwann cells and by macrophages, producing a self-perpetuating cycle which might involve either small areas or the greater part of a fascicle, and could conceivably progress to a generalized reaction.

RESUMEN

Se hizo el examen histopatológico y el examen histoquímico de las células de Schwann, de los macrófagos, y de los antígenos micobacterianos en 48 nervios de pacientes con lepra no tratada. Aunque ninguno de los pacientes estuvo clínicamente en reacción, se encontraron microreacciones involucrando a pequeños agregados de células de Schwann y de macrófagos en todos los casos excepto en los LL. Se pensó que estas microreacciones, caracterizadas por la degradación progresiva de bacilos ácido resistentes (BAR), representaban la respuesta al reconocimiento de los antígenos micobacterianos. En la primer fase, la desintegración de una o más células de Schwann causaría la liberación de BAR, y una inflamación sub-aguda. En la segunda fase, cuando el edema y la infiltración celular hubieran cedido, la necrosis de las células de Schwann sería reemplazada por la formación de granuloma, encontrándose el antígeno micobacteriano en forma soluble. En este estudio, las células mielinizadas contuvieron pocos bacilos degradados y hubieron evidencias de que la mielina asociada al antígeno retardó la muerte de la células de Schwann; sólo entonces el antígeno llegó a ser inmunológicamente detectable y capaz de inducir una respuesta inflamatoria cuya re-

solución fue estorbada por el dificultoso movimiento celular en la estructura del tejido neural.

Estos eventos fueron esporádicos pero continuos. Los BAR y el antígeno liberado por desintegración de las células de Schwann fueron ingeridos por nuevas células de Schwann y por macrófagos produciendo un ciclo autoperpetuante capaz de afectar a pequeñas áreas o a la mayor parte de un fascículo, o de progresar hasta una reacción generalizada.

RÉSUMÉ

On a procédé à des examens histologiques et immunocytochimiques des cellules de Schwann, des macrophages, et de l'antigène mycobactérien, pour étudier 48 nerfs prélevés chez des malades de la lèpre non traités. Aucun des malades ne présentait une réaction clinique; mais, dans tous les cas, excepté dans les cas LL, des microréactions entraînant de petits amoncellements de cellules de Schwann et de macrophages, étaient caractérisées par une dégradation progressive des bacilles acido-résistants. On considère que ces manifestations constituent une réponse à la reconnaissance de l'antigène mycobactérien. Dans une première phase, la désintégration d'une ou de plusieurs cellules de Schwann entraîne la libération des bacilles acido-résistants, qui s'accompagne d'une inflammation subaiguë. Dans une seconde phase, lorsque l'oedème et l'infiltration cellulaire diminuent la nécrose des cellules de Schwann est remplacée par la formation de granulomes, l'antigène mycobactérien étant alors sous forme soluble. Les cellules myélinisées abritaient quelques bacilles acido-résistants; on notait également des signes qui indiquaient que la myéline associée à l'antigène accélérait la mort des cellules de Schwann. C'est alors seulement que l'antigène peut être décelé immunologiquement, car il entraîne une réponse inflammatoire, dont la résolution est empêchée pas les contraintes imposées sur la migration des cellules par la structure particulière du tissu nerveux.

Ces développements étaient sporadiques, mais continus. Les bacilles acido-résistants et l'antigène libéré par les cellules de Schwann désintégrées étaient ingérés par les cellules de Schwann en régénération et par les macrophages. Ceci produit un cycle qui se renouvelle perpétuellement, pouvant atteindre, soit de petites zones d'un fascicule, soit la plus grande partie de celui-ci, ce qui peut en fin de compte aboutir, comme on peut le concevoir, à une réaction généralisée.

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