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Exacerbation Reactions in Hyperactive Lepromatous Leprosy[1]

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Lepromatous leprosy is marked by periods of activity which may be intense, often followed by a spontaneous decline of activity not necessarily due to chemotherapy. This is apparent clinically ([10]), and more so histologically ([22]), and the rate of proliferation of the granuloma macrophages usually proceeds in parallel with bacterial multiplication. Although most workers have regarded histoid lesions as a clinicopathological entity, their features are inconstant ([3]) and many of them are shared with non-histoid lesions that are hyperactive both bacteriologically and cytologically ([21]). Hyperactivity is the essential feature of histoid lesions ([9, 19, 24]) which are its ultimate expression.

In describing histoid lesions, Wade ([30]) referred to "local reactional areas," and Ridley ([20]) noted that any highly active lepromatous lesion might show similar reactional changes consisting of infiltration of neutrophil polymorphs and cellular disintegration. These reactions can be severe histologically but they are not accompanied by any systemic disturbance, and their nature is not so far understood. Here we give a full account of these "exacerbation reactions" (ER) and their evolution, and we differentiate them histologically from erythema nodosum leprosum (ENL) with which they have points in common. We also compare the two reactions using immunocytochemical procedures.

MATERIAL AND METHODS

Patients. From our collection of hyperactive lepromatous lesions, we obtained 13 biopsies from 12 patients which exhibited reactions of the type hereafter referred to as exacerbation reactions (ER). One other biopsy from one of these patients was a non-reacting histoid. Six of the patients came from the Medical Research Unit at Addis Ababa, Ethiopia; four came from the Medical Research Council Unit at Sungei Buloh, Malaysia, and one each came from Malawi and Nigeria. All 12 of the patients were said to be active clinically, 5 untreated and 7 in relapse. Most of the lesions were inflamed and three patients had ulcerated lesions, although these were not all biopsied. None of the patients was ill and none had systemic symptoms. Four biopsies were studied by immunohistology.

The 13 ERs were compared particularly with two biopsies of ENL lesions occurring in patients with unusually active leprosy, one being Case 4 of Waters and Ridley ([31]). In addition, reference was made to the 20 cases of ENL which were the subject of a previous study ([25]).

Five nonreacting histoid lepromas were included for comparison, especially of immunohistological features.

Method. The biopsies were fixed in formal-mercuric chloride-acetic acid (FMA) for 2 hr and transferred to 70% alcohol before processing. They were examined by hematoxylin-eosin (H&E) and for acid-fast bacilli (AFB) by the modification of Fite's stain of the Armed Forces Institute of Pathology, Washington, D.C., U.S.A. ([21]). Bacilli were also stained by methenamine silver impregnation for bacterial cell-wall components, using oxidized and unoxidized sections, and by immunoperoxidase techniques using anti-BCG anit-serum for soluble *Mycobacterium leprae* antigen. Other stains used were MSB for fibrin, Verhoeff's elastic, toluidine blue for mast cells, periodic acid-Schiff (PAS), and reticulin.

Immunocytochemistry. The PAP immunoperoxidase technique (IPX) used here, and the analysis of results, has been described in detail ([23]). As in previous studies ([25, 27]), antisera against a variety of immunological

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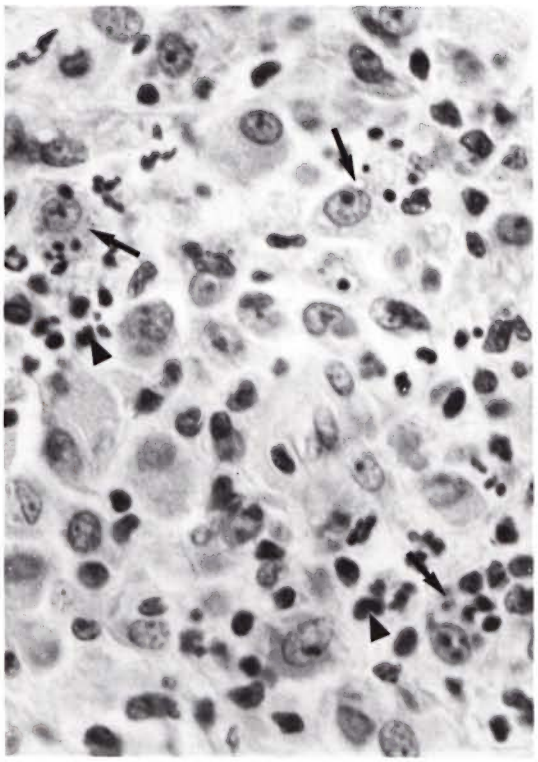

FIG. 1. Hyperactive ER showing early degeneration of individual macrophages containing pyknotic nuclear material (↑). Mild polymorph infiltration (▲) also occurs (H&E ×500).

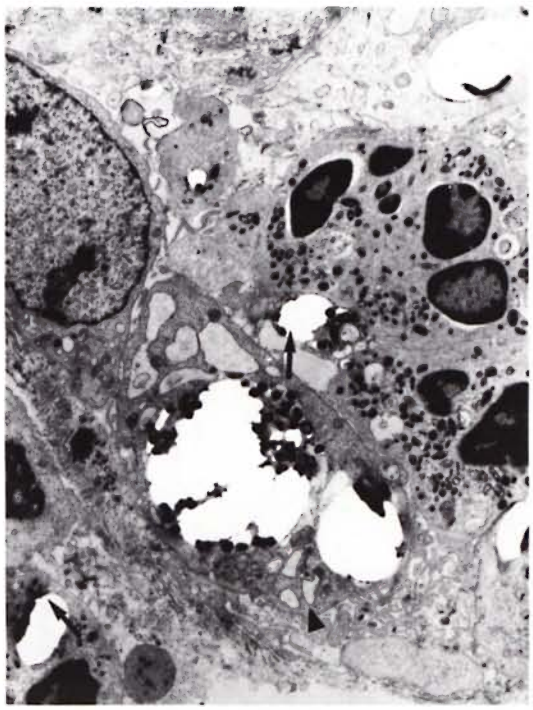

FIG. 2. Ultrastructure of extracellular bacilli ingested by polymorphs (↑) in close association with bacteria-laden macrophage (▲) (×7000).

and inflammatory factors were employed as follows: BCG (to locate *M. leprae* antigen); immunoglobulins IgA, IgG, IgM, and IgE; complement components C3, C1q, C3d, and C4; the acute phase reactants C-reactive protein (CRP) and apoB containing lipoprotein (LDL); α_1-antitrypsin; α_2-macroglobulin (to locate protease inhibitors); lysozyme and factor VIII (to distinguish macrophages and endothelial cells, respectively); fibronectin; serum amyloid P factor (SAP); and the coagulation protein, plasminogen. The antisera came from DAKO-PATTS (U.K.) with the exception of CRP, SAP, fibronectin (Dr. M. B. Pepys, London) and LDL (Miles-Yeda).

Controls. Endogenous peroxidase was demonstrated by DAB + peroxide. Other controls included normal rabbit serum in place of the first antibody or absorption of the antibody by purified antigen prior to staining.

RESULTS

Exacerbation reactions. All of the ER lesions were in highly active lepromas (LL), the granulomas being composed of almost uniformly active macrophages with fairly copious homogenous cytoplasm and minimum foamy change. In such a state it was difficult to say with confidence whether the lesions were subpolar lepromatous (LLs) or polar lepromatous (LLp), but the majority of cases appeared to be LLs. Of the 13 lesions, 5 showed infiltrative spread at the periphery and 8 were expansile nodules with a pseudocapsule (histoid). In all cases the bacterial index (BI) within the granuloma was a heavy 6+, the majority of organisms being solid-staining or fragmented with few granular forms.

Histopathology. Mild, possibly early, reactions consisted of an infiltration of polymorphonuclear neutrophils which was associated with small clusters of degenerate macrophages, some of which contained small vacuoles filled with AFB (Fig. 1). Similar cells in smaller numbers could be found

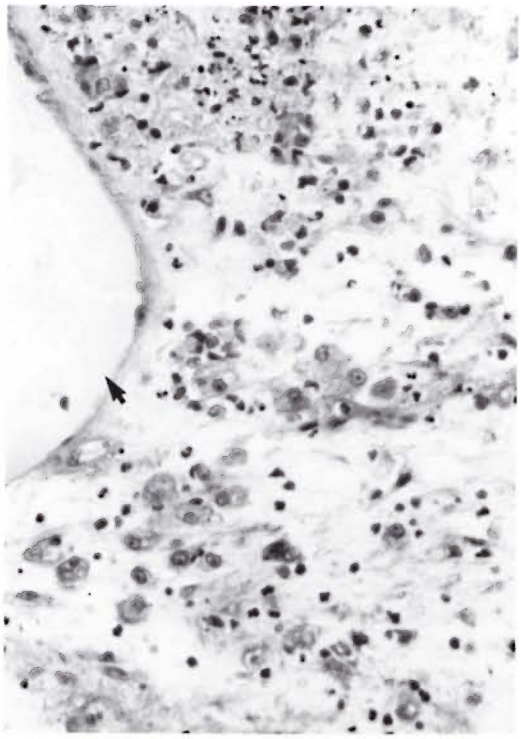

FIG. 3. Acute stage ER showing intense edema and dilatation of lymphatic (↑). Macrophages are filled with bacilli (H&E ×300).

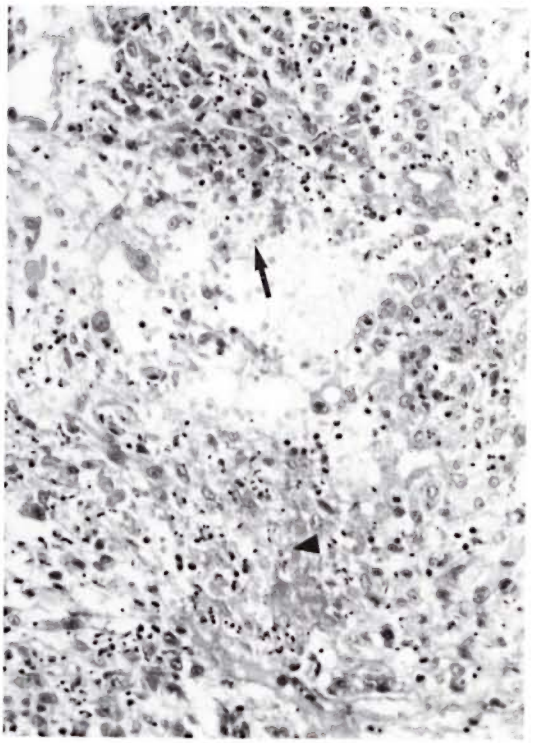

FIG. 4. Necrosis with extravasated red blood cells (↑) and eosinophilic exudate (▲) (H&E ×200).

even in hyperactive but nonreacting lesions, and the reaction thus appeared to be an exacerbation of the hyperactive state. The polymorphs were all intact, and were ingesting extracellular bacilli released from the macrophages (Fig. 2). The cellular infiltrate was relatively compact, as were the more advanced lesions, and was not scattered diffusely throughout the granuloma. Its situation was either central or superficial under the epidermis; it was never peripheral. Edema at this stage was slight, with minimal interstitial space in the area of reaction, and blood vessels were normal.

Severe or advanced reactions were more extensive but still compact, and they were quite distinct from nonreacting lesions. They were associated with a number of features which progressed in parallel with each other, according to the degree of severity of the reaction, which were as follows:

1) Marked interstitial edema separated the macrophages in the reaction center, and some of these cells assumed a rounded form isolated in a sea of fluid (Fig. 3); the superficial lymphatics were grossly dilated with fibrinoid change of the endothelium.

2) An eosinophilic exudate with aggregated PAS-positive material appeared to be composed of a mixture of extravasated or lysed red blood cells, degenerate macrophage cytoplasm, and fragments of swollen elastic fibrils (Fig. 4); there was no fibrinoid in this exudate.

3) The capillaries at the center of the reaction showed hyaline swelling of the muscle layer or a frank necrotizing vasculitis with flecks of fibrinoid (Fig. 5). Towards the periphery, polymorphs were seen emigrating out of the small blood vessels which were otherwise normal.

4) There was much karyorrhexis and nuclear debris at the reaction center, with few intact polymorphs to be seen in the more advanced reactions (Fig. 6). Macrophage degeneration was more marked.

When the reaction was superficial there was usually some damage to the basal lamina of the epidermis due to edema (Fig. 6)

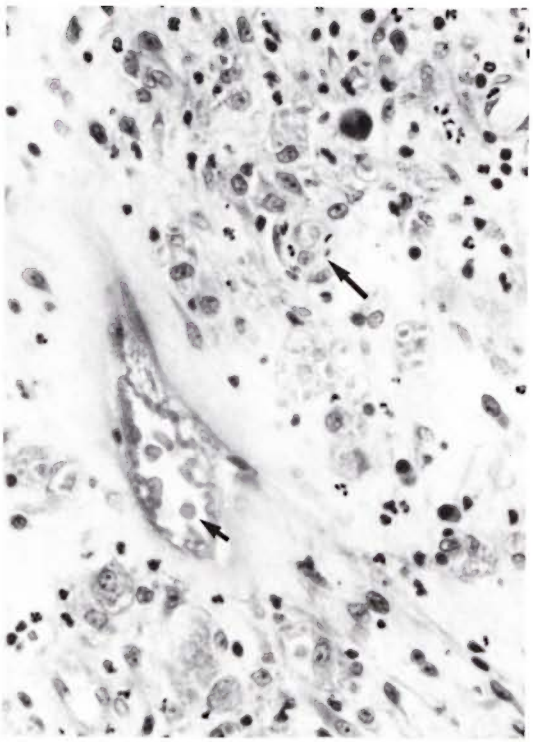

FIG. 5. Vasculitis involving a venule (↑) and a small capillary (⇑) (H&E ×300).

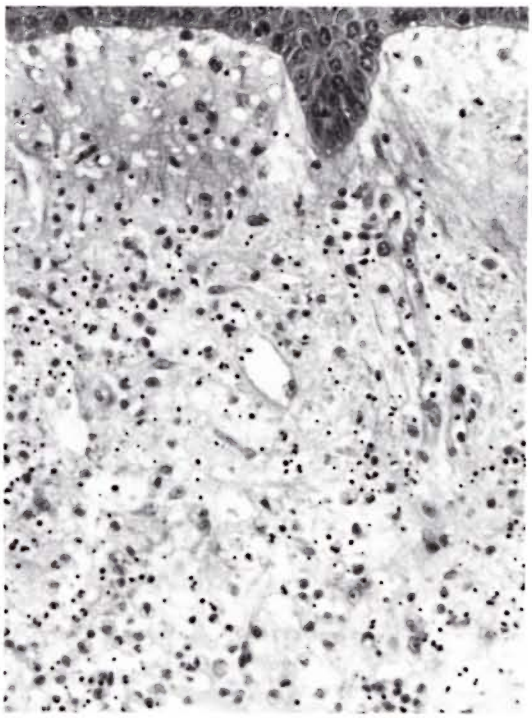

FIG. 6. Advanced ER showing cellular degeneration, karryorhexis, edema, and disruption of basal lamina (H&E ×300).

and perhaps thinning of the squamous layer. In one case there was bulla formation, and in another there was an incipient ulcer with considerable fibrinoid necrosis at the base. Reticulin fibrils were well defined throughout the lesion and intercalated with dermal collagen but, except for some collagenation of basal lamina, there was no marked fibrosis. Fibrinoid degeneration was seen in the stroma of lymphatic vessels. Elastica was normally detectable as fine fibrils except in the areas of degradation.

Lymphocytes were always present and diffusely sited but not numerous and not definitely increased by comparison with non-reacting lesions. Plasma cells were variable in number, sometimes moderate, sometimes scanty. Mast cells were increased in number and relatively numerous around the reaction site; at the center they were all degranulated. Eosinophils were seldom present and at the most scanty.

For the purpose of analysis the reacting lesions were categorized in five grades:

I. Polymorph infiltrate and macrophage degeneration only, with no significant edema.

II. Polymorph infiltration and macrophage degeneration, with edema but little or no other exudate.

III. Same as II but with eosinophilic exudate although few if any extravasated red blood cells.

IV. Same as II but with extravasated red cells.

V. Same as II including capillary necrosis and extensive exudate.

When the 13 lesions were graded in this way it was found that there were either two or three lesions in each grade. The three lesions of grade V were all of the expansile type but otherwise there was no correlation with the type of lesion. There was no correlation between grade of reaction or type of lesion and relapse as opposed to untreated infection.

M. leprae. Bacilli at the reaction center were exceedingly numerous, more so than in other parts of the hyperactive granuloma, and the majority were solid staining with few granular forms. By methenamine silver

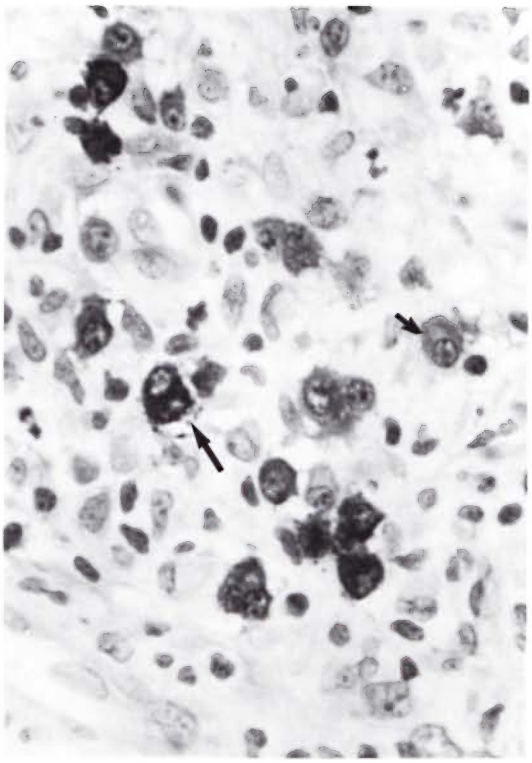

FIG. 7. ER showing IgE-positive plasma cells (↑) and mast cells, one degranulating (⇑) (anti-IgE ×500).

staining, they were all solid and the reaction was the same after oxidation or non-oxidation. In the more severe reactions, the acid-fast bacilli were dispersed extracellularly, in the polymorphs and in the reaction center, as a result of the rupture of some of the host macrophages. In 6 of the 13 reacting lesions, AFB were quite numerous in the epidermis, and in 4 they had penetrated as far as the keratin layer. AFB were present in some endothelial cells of blood vessels or of dilated lymphatics, and in nerves they were very numerous. *M. leprae* antigen revealed by anti-BCG was enormously increased and was mostly intracellular and granular, but also bound to connective tissue fibrils in the exudate. It was marked in the area of polymorph infiltration and necrosis where bacilli could be demonstrated also by acid-fast stains. This was in contrast to most ENL lesions where polymorphs did not contain acid-fast components but only BCG-positive material and Ig.

Immunohistology. In reacting lesions, immunoglobulin IgG was at a low level, IgM was moderate, and IgE was markedly raised (Fig. 7). Immunoglobulin was seen in the plasma cells throughout the lesion in relatively mild reactions, and at the periphery in severe reactions. In the center of severe reactions, extracellular IgE was prominent in the exudate and necrosis. IgM was also seen at these sites. Mast cells were strongly positive for IgE, and they were aggregated and degranulated. In addition, immunoglobulins were present in the basal lamina bound to connective tissue supporting fibrils, especially in early infiltrative lesions. Bacilli contained in rounded, vesiculated macrophages in areas of edema or necrosis had bound IgG. No Ig was seen in the polymorphs.

Complement components were weak or not detected except for C1q which was strongly positive, bound to extracellular bacilli in the interstitial space, in the basal lamina, and around blood vessels and distended lymphatics of the dermis. It appeared as dense aggregates in the necrotic debris. It was not removed by 0.2 M NaCl solution and no more immunoglobulins were detected after this procedure.

Bacilli throughout the lesion were strongly positive for CRP, which was seen also in the exudate and connective tissue around reaction sites. SAP appeared as a dark, granular deposit or as "whorled" structures in the majority of the macrophages, and it bound some but not all the elastic fibrils. It was strongly positive in the basal lamina. The "whorled" structures corresponded to fragments of elastica, stained by special methods. Fibronectin was increased in the basal lamina and in the epidermis of some lesions, and it was clearly visible in the interstitial space and between dermal collagen in most lesions, especially in edematous exudate. Distended lymphatics were marked by granular deposits. The distribution of fibronectin in some ways resembled that seen by reticulin staining and was associated in part with C1q.

By contrast with nonreacting lepromas, ERs had numerous intact lysozyme-positive polymorphs throughout the lesion. Extracellular lysozyme was striking in areas of karyorrhexis. Lysozyme-positive monocytes were fewer than in histoid lepromas, and other macrophages containing bacilli had varying quantities. The scanty foam cells

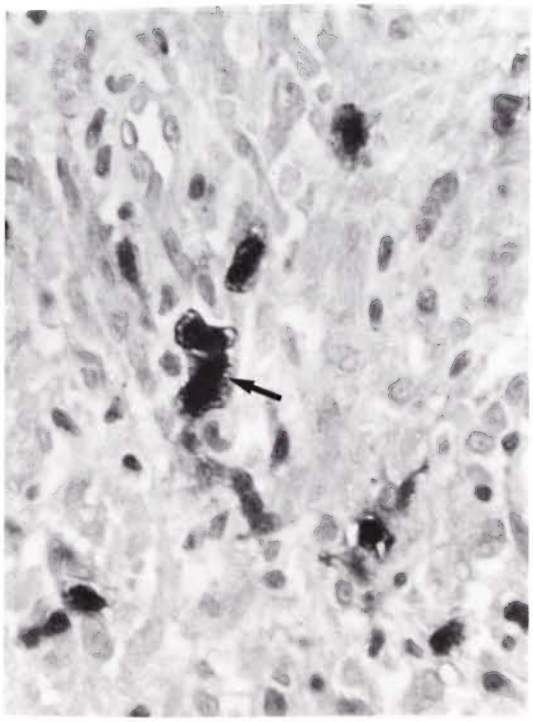

FIG. 8. Nonreacting histoid lesion showing increased numbers of freshly recruited lysozyme-positive monocytes (↑) among highly activated macrophages (anti-lysozyme ×500).

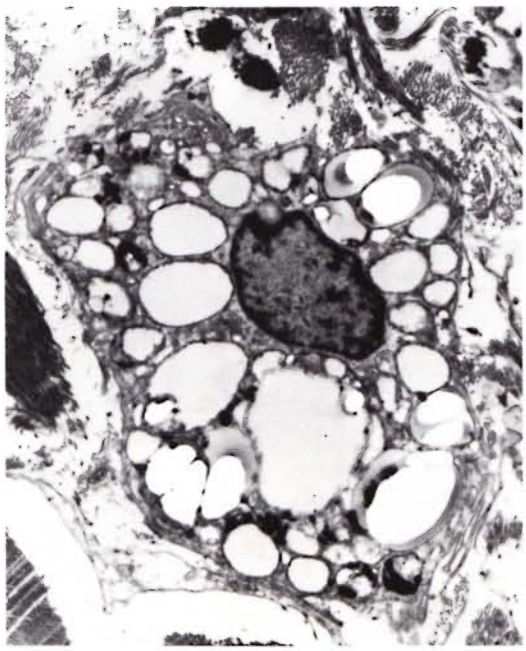

FIG. 9. Erythema nodosum leprosum. Degenerate macrophage with ingested bacterial debris for comparison with macrophage in ER in Figure 2 (×7000).

retained this enzyme in vacuoles containing bacilli, but the vesiculated macrophages in the edematous fluid were only weakly positive.

Plasminogen and α_2-macroglobulin were moderate or low, both intracellularly and extracellularly, in the exudate.

Endogenous peroxidase was demonstrated in most polymorphs and in areas of their degradation. No staining was observed when normal rabbit serum was used in place of the anti-serum.

Nonreacting histoid lesions. By contrast with ER, all histoid lesions had increased levels of IgG and IgM, intracellular in plasma cells and B lymphocytes, and extracellular in the granuloma and basement membrane of the subepidermal zone. Antibody was marked along the supporting fibrils of this zone. Antibody-coated bacilli were seen in a few macrophages in micro-reactive areas of the lesion. IgE and IgA were not demonstrated. Moderate amounts of complement C3 and C1q were present, and C3 appeared as dense granules in macrophages with few or no bacilli. Extracellular C3d was markedly increased, especially in the basal lamina. This C3d was found to persist after immersing sections in 0.2 M NaCl for 5 min, but immunoglobulins were not increased afterwards. Lysozyme, α_1-antitrypsin and α_2-macroglobulin reached peak values. Lysozyme was conspicuous, dark and granular in small monocyte/macrophages which were especially dense in the superficial dermis around the subepidermal zone (Fig. 8). These cells were difficult to identify in the H&E sections. Smaller numbers infiltrated the granuloma, between the dermal collagen. Polymorphs, positive for lysozyme, were also distinguished among the monocytes. Macrophages containing bacilli had varying amounts of pale, diffusely stained lysozyme and clusters of foam cells were conspicuous by lysozyme-positive, phagocytic vacuoles.

Acute-phase reactants CRP, SAP, and LDL were weakly demonstrated in cells with bacilli. These plasma proteins together with fibronectin were heavily deposited in the basal lamina associated with connective tissue supporting fibrils.

THE TABLE. *Approximate concentration of immunological factors in nonreacting histoid lesions and in reactional states of lepromatous leprosy.*

	Antigens	Ig	C3	C3d	C1q	CRP	SAP	Fibronectin	α_2-macroglobulin	Lysozyme	Monocytes	Polymorph neutrophils
Histoid	AFB[a] +++ BCG[b] +++ (mø)	IgM +++ IgG +++ IgE −	+	+++	+ −	+++	+++	++	+++ (exc)[c]	++++ (monos)[d]	+++	+ (small foci)
ER Grades I, II	AFB +++ (mø) BCG +++++ (mø, exc)	IgM + IgG ± IgE +	−	−	+++	+++	+++	+++	++++ (mø, exc)	+++ (pmn)[f]	+++ (act. mø)[g]	++
ER Grades III, IV, V	AFB ++++ BCG +++++ (møs, exc, ct[c])	IgM + IgG ± IgE +++	−	−	++++	+++	+++	+++	++++ (mø, exc, ct)	++++ (pmn)	+++ (act. møs)	+++
ENL	AFB + foam (mø) BCG ++ (mø, pmn, ct) GMS[h] +++ (møs, pmn, ct)	IgM +++ IgG +++ IgE −	+++	+++	+++	+++	++	+	++	+++	++	++++ acute focal necrosis

[a] AFB = acid-fast bacilli.
[b] BCG = positive with anti-BCG anti-serum.
[c] exc = extracellular.
[d] monos = monocytes.
[c] ct = bound to connective tissue.
[f] pmn = polymorph neutrophil.
[g] act. mø = activated macrophage.
[h] GMS = Gomori's methenamine silver stain.

The amount of *M. leprae* antigen as revealed by anti-BCG was related to the mass of AFB. Some BCG-positive material was found in polymorphs which did not stain for immunoglobulins.

Comparison with ENL. The two cases of ENL in exceptionally active lepromas were histologically similar to the more usual ENL in regressing lepromas (Fig. 9). There was more nuclear debris than usual. Bacteriologically the most active of the ENL lesions were less active than the ER, with fewer AFB, and more granular forms in spite of the high morphological index (MI). In the reaction centers bacilli were solid in ER, granular in ENL.

Comparing exacerbation reactions with the ENL group, the following differences were noted. Exacerbation reactions, although extensive in severe cases, were compact and localized; the more severe ENL lesions were dispersed. In severe cases of ER, there was more edema and notable lymphatic distention; more eosinophilic exudate; more necrotizing vasculitis, especially of the capillaries, and more nuclear debris than in most ENL lesions. There were more mast cells and more mast cell degranulation than in ENL. IgE was the predominant immunoglobin in ER, IgG in ENL. C3 was lacking in ER.

DISCUSSION

Exacerbation reactions have been differentiated from ENL, histopathologically, bacteriologically and immunologically. Most obviously, the difference is that ER occurs in hyperactive lepromas, ENL in regressing granulomas. In common, both ER and ENL commence with polymorph infiltration in areas of macrophage cell death. The macrophages in ER are large and cytoplasmically active, containing increased numbers of solid organisms, while those in ENL lesions are effete, with poorly detectable degraded bacterial debris. Rarely, ENL can occur in regressing foci of otherwise bacteriologically active lesions, but in this case foam cells are abundant. The localized, compact, although sometimes extensive, distribution of ER contrasts with the more diffuse spread of severe ENL and suggests that each ER is a particular event. It can be attributed to the fact that hyperactive lesions are few and, if large, nodular; and it explains the lack of systemic consequences. But it is not clear why ER is not more general in hyperactive lepromas. Their precise incidence is not known, but they are not uncommon.

Nearly all the hyperactive lepromatous lesions in which ER originates show occasional polymorphs and dead macrophages. This is insufficient to constitute a reaction although it might indicate a reactional tendency, and it suggests that the ER develops out of a pre-existing situation. Hyperactive lesions are characterized by a high cell turnover ([29]), the extreme example of which is the histoid lesion, the site of the majority of exacerbations. This is indicated by the large influx of granular, darkly stained, lysozyme-positive monocytes in the histoid granuloma. However, in reacting lesions these cells are fewer and more dispersed, but granuloma macrophages are larger and show even stronger evidence of metabolic stimulation. Such cells may be likened to the stimulated macrophages of experimentally infected nude mice which are attributed to a lack of suppressor T cells ([12, 16]). Stimulation of this sort is distinct from microbicidal activation ([2]), and in leprosy the cells in ER support the highest possible number of viable *M. leprae,* suggesting that the organism does not impede protein synthesis ([5, 28]).

We suggest that in the early stages of histoid or other hyperactive lesions the influx of new cells exceeds the death rate, but that in due course the influx declines, the macrophages begin to age and the cell death rate increases. It appears that these events take place before the multiplication rate of the bacilli falls. Consequently at the reaction site the macrophages are large, cytoplasmically active cells, swollen with bacilli and probably ingested edema fluid, and there is little or no foam.

Although maturation of macrophages with an exceptional bacterial load may be a predisposing factor, the initiation of the lytic process is not fully explained. The histological features point to increased capillary permeability associated with damage to some vessels in the central reaction area where mast cell degranulation is marked. Although there are no eosinophils present, IgE is raised, both in plasma cells at the periphery and in extracellular situations bound to connective tissue fibrils, or aggregated in

the area of necrosis. Mycobacterial antigens in the form of acid-fast or soluble BCG-positive components are found in the same situations, so that immune complexes involving IgE could occur. C3 was not demonstrated. This seems to us important, since cytophilic IgE, and immune complexes, in the absence of complement, can be the main cause of lysis, triggering macrophages in antibody-mediated cytotoxic killing ([6]). Furthermore, IgE can bind to and inhibit some T lymphocyte functions ([8]), which could account for the perpetuation of the lesion and the lack of microbicidal capacity of the activated macrophages, analogous to the situation in nude mice. Serum IgE also is raised in lepromatous leprosy ([17]). IgE and *M. leprae* antigen were found at the same sites in reacting lesions, but the fact that similar IgE complexes were not observed in active lepromatous leprosy or histoid lesions, leaves open the question of the antigen involved in ER. It could be native or altered immunoglobulin or other proteins ([4]). The role of IgE in LL needs further elucidation ([13]).

Once the degradation of mature metabolically stimulated macrophages had been initiated, it could be further perpetuated by the release of lysosomal hydrolases, elastase, and proteolytic enzymes secreted by polymorphs and stimulated macrophages which degrade connective tissue ([32]). In support of this hypothesis, we observed fragments of elastic fibrils in macrophages close to the areas of connective tissue degradation, and SAP which binds to elastin ([18]) was prominent in granuloma cells and in pericellular or extracellular situations. Such a situation does not arise in ENL which involves effete macrophages, and polymorphs primarily engaged in the disposal of immune complexes, which are of direct pathological significance ([25]).

Another possible mechanism is that polymorphs can themselves cause lysis by their proteolytic enzymes and myeloperoxidase ([7]), and activated macrophages in antibody-dependent lysis can also be effector cells in this mechanism ([14, 15]).

The question of reaction to dapsone ([1]) does not arise in ER since, in the first place, many of the patients studied were untreated, and secondly, as far as we are aware, all of the patients responded successfully to antileprosy treatment. Hyperactivity in relapse was no different histologically from that in primary disease.

Recent studies on T cell subsets and interleukin in leprosy leave open the possible role that lymphocytes might play in ER. Lymphocyte function may be abrogated in a situation involving IgE immune complexes, but this appears to be a local event. With regard to antibody, local lesional levels vary in individual patients ([11]) but, in general, higher levels obtain in active as opposed to regressing lepromas which decline sharply despite raised serum levels ([27]). The generally low levels of antibody, and the different classes, in the severe reactional states of hyperactive lepromatous leprosy raise interesting questions whose further study may be of value in characterizing some important immunological features of leprosy.

SUMMARY

Exacerbation reactions (ER) are acute reactions occurring locally in histoid or other highly active lepromatous lesions with an exceptionally heavy bacterial load. Clinically, they are almost silent although they may cause ulceration and the release of viable bacilli. Histologically, the influx of polymorph neutrophils and coincident macrophage degeneration mimic erythema nodosum leprosum (ENL). Later, the signs of increased permeability or necrosis of small blood vessels and mast cell degranulation are differential features. The predominant immunoglobulin is IgE, and the main complement component is C1q, C3 being mostly undetectable. The reactions appear to be mediated in part by reagins (although eosinophils are not seen). Immune complexes probably form at antigen excess. Of equal importance may be the release from highly activated macrophages and neutrophils of hydrolases and proteases, which are capable of degrading connective tissue and other cell surfaces.

This report is based on a histopathological and an immunocytological study of 13 exacerbation reactions in comparison with nonreacting hyperactive lesions and with ENL. The results support the view that the essential feature of histoid lesions is their hyperactivity.

RESUMEN

Las reacciones de exacerbación (RE) son reacciones agudas que se presentan localmente en la lepra lepromatosa histioide o en otras lesiones lepromatosas activas con una exagerada carga bacteriana. Clínicamente son lesiones casi silentes, aunque pueden causar ulceración y liberación de bacilos viables. Histológicamente, el influjo de neutrófilos y la coincidente degeneración de macrófagos, recuerda al eritema nodoso leproso (ENL). Más tarde las características diferenciales son, los signos de permeabilidad aumentada o la necrosis de los pequeños vasos sanguíneos y la desgranulación de las células cebadas. La inmunoglobulina predominante es la IgE y el componente principal del complemento es C1q, siendo C3 casi indetectable. Las reacciones parecen estar mediadas al menos parcialmente por reaginas (aún cuando no se observan eosinófilos). Probablemente se forman complejos inmunes en exceso de antígeno. De igual importancia puede ser la liberación de hidrolasas y proteasas por los macrófagos activados y por los neutrófilos. Estas enzimas pueden degradar el tejido conectivo y otras superficies celulares. Los hallazgos histopatológicos e inmunocitoquímicos en 13 reacciones de exacerbación y su comparación con los hallazgos en lesiones hiperactivas no reaccionales y en ENL, constituyen la base de la presente comunicación. Los resultados apoyan el concepto de que la característica esencial de las lesiones histioides, es su hiperactividad.

RÉSUMÉ

Les réactions d'exacerbation (ER) sont des réactions aiguës qui surviennent localement dans les lésions histoïdes, ou dans d'autres lésions lépromateuses fort actives présentant une charge bactérienne exceptionnellement lourde. Cliniquement, ces exacerbations sont presque silencieuses, encore qu'elles puissent causer des ulcérations et la libération de bacilles viables. Histologiquement, la mobilisation de neutrophiles polymorphes, et la dégénération concommittante des macrophages, miment l'érythème noueux lépreux (ENL). Plus tard, les signes d'une perméabilité accrue, ou la nécrose des petits vaisseaux sanguins et la granulation des mastocytes, constituent des caractéristiques différentielles. L'immunoglobuline prédominante est l'IgE, et le constituant principal du complément est C1q, C3 étant le plus généralement non décelable. Les réactions semblent dépendre en partie de l'intervention de réagines (quoiqu'on n'observe pas d'éosinophiles). Les complexes immuns représentent probablement l'excès d'antigènes. Egalement important à noter est la libération d'hydrolases et de protéases par des macrophages fortement activés et par des neutrophiles; ces enzymes sont capables d'entraîner la dégénérescence du tissu conjonctif et d'autres surfaces cellulaires.

Ce rapport est basé sur l'étude histopathologique et immunocytologique de 13 réactions d'exacerbation, que l'on a comparées avec des lésions hyperactives mais non réactionnelles et avec l'ENL. Les résultats renforcent l'hypothèse qu'une caractéristique essentielle des lésions histoïdes est leur hyperactivité.

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