Histological classification and the immunological spectrum of leprosy

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The clinical and histological manifestations of leprosy are known to be closely correlated with the immunological state of the patient, which determines prognosis and constitutes the natural basis for the classification of this disease. A classification based on this correlation has come to be widely used but needs to be brought up to date and expanded in the light of more recent experience. The author of the present paper presents a much fuller account of the histological side of the classification, taking into account the results of recent experience. This histological classification has been found to provide a workable and widely applicable system, different histologists achieving remarkably good agreement with one another.

The classification of leprosy has proved to be a contentious matter, and it is perhaps fair to say that no international committee on the subject has yet produced a satisfactory concord. The official classification of leprosy today is that of the Madrid Congress (1), which raises problems that are discussed by Cochrane & Smyly (2). Our scientific understanding of leprosy, however, has altered greatly in the last 21 years, whereas leprosy itself has become a subject of interest in other branches of medicine, especially immunology. As a result, there are many people for whom the Madrid classification—which is primarily clinical—is an inconvenient means of communication.

The classification of Ridley & Jopling (3, 4) was originally proposed for the convenience of research workers. It has proved to be widely comprehensible and to give a good clinical–histological correlation, as well as having the advantage of objectivity. The object was a classification defined in clinical and histological terms that was neither more nor less than a reflection of the immunological spectrum of the disease. The outcome was quite close to the classification of Madrid and the immunological validity of the scheme has gained support from the correlation recently obtained with the results of lymphocyte function tests by Myrvang et al. (5). The immunopathology committee of the Bergen Congress (6) accordingly recommended that the classification should be used generally,[a] which makes it desirable that the scheme should be made as simple as possible.

A point that has received very little attention is the bearing on classification of the state of activity or regression of the disease, which acts as a cross-current on the histological spectrum in the lepromatous region. Due account is here taken of this and other sources of confusion that have come to light since the initial description of the Ridley and Jopling classification.

The opportunity has been taken to re-evaluate the criteria of classification in relation to immunological data. The results indicate that the presence of numerous lymphocytes in leprosy lesions reflect immunological stability or potential for enhancement, but that they have little bearing on antibacterial action. The definitions of some of the histological groups have been revised in small ways to take account of this finding. It is assumed throughout that the patient has evidence of leprosy and, unless otherwise stated, that he is untreated and not in reaction.

MATERIAL AND METHOD

This paper presents an account of a system of classification whose development and results, described below, are for the most part based on pre-

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[a] Although the subject of this paper is histological classification, it should be remembered that histology is only one component of a system the other component of which is clinical observation. Ideally both should be considered. It is quite accepted that there are many situations in which biopsy is not feasible, and clinical classification alone must then suffice. But, if it is available, histology is nearly always helpful and for research almost essential.

vious publications, as stated in the text. Results have accumulated with experience, but since the original descriptions of the Ridley and Jopling classification (3, 4) there has been only one set of results that was thought to justify some modification of the classification, and that was a recent analysis of lymphocyte transformation test results. The histological slides used in the study of Myrvang et al. (5) were re-examined in the light of these results and certain conclusions were drawn, which are incorporated in the present paper. However, it remains to be seen whether the lymphocyte transformation test will provide a valid and clinically significant basis for classification.

Although the accumulated results and experience have not otherwise called for any modification of the classification, they have necessitated some revision of the previously published figures for the immunological performance of the various groups. In particular it was noticed that the introduction (unpublished) of 6½+ instead of 6+ as the maximum bacterial density in a granuloma in a histological section, used for the evaluation of the histological index or logarithmic index of biopsies (7), led to an appreciable increase in the estimated rate of decline of the histological index of patients on chemotherapy, i.e., of bacterial lysis by immunity. The recent multicentre trial of clofazimine *versus* dapsone (8, 9), which was based on material from 17 widely separated centres, provided a good opportunity for the re-evaluation of the rate of fall of the histological index in the lepromatous groups. Unfortunately, borderline patients were insufficiently represented for that purpose, and the multicentre cases had to be supplemented with borderline cases from a previously published series (3); these sections were re-evaluated for the histological index using 6½+ as the maximum bacterial density. It was stipulated that the initial granuloma should occupy at least 0.25 of the dermis, and this itself caused the exclusion of some multicentre patients. These results form the basis of Table 1.

To assess the maximum nerve diameter found in the dermis in each group, not previously recorded, sections of biopsies from the series of Myrvang et al. (5) and the multicentre trial were supplemented by biopsies currently being received from Sungei Buloh (Malaysia) and Addis Ababa.

Reactions

The classification used in this paper is that of Ridley (10). Reactions in borderline patients for the most part are associated with some shift in immunity, which is commonly upgrading (or reversal) and less often downgrading; occasionally there is no effective shift.

Table 1. Effect of reversal reactions on the rate of elimination of bacilli during the first 6 months of treatment (63 patients treated with dapsone)

Fall in histological index (%)	BL	LLs	LLp
all cases	23	14	5.5
without reaction	14	12	5.5
reaction only	42	32	...
No. of cases in reaction (%)	33	7.5	0

Taking a biopsy

The biopsy must extend down to the subcutis so as to include the nerves of the deep dermis. Zenker's fluid or a modified Zenker–formol fixative is to be preferred to formalin, which somewhat spoils the characteristics of a granuloma and makes it difficult to detect oedema. The author uses the following solution: 40% formaldehyde solution (formalin) 10 ml, mercuric chloride 2 g, glacial acetic acid 3 ml, distilled water to 100 ml; after 2–2½ h transfer without washing to 70% ethanol for as long as convenient before processing. Otherwise Zenker's fluid is very satisfactory.

Sections must be cut to a standard thickness, usually 5 μm. This is important as it is impossible to assess the number of lymphocytes and compare sections unless the latter are uniform. It is also necessary that sections should not be much more than one cell thick so that cellular morphology may be studied.

Routine stains of good quality are required: haematoxylin–eosin, Fite-Faraco or similar stains for acid-fast bacilli, or "Triff" stain. Special stains have not so far found a place in classification.

One biopsy is normally sufficient for classification, as lesions show a fairly uniform picture. This applies not only to skin lesions; biopsies of lymph nodes (11) and other tissues give an essentially similar histological classification, though skin provides more clues than any other tissue on account of its multiple components. However, during reversal reactions, which often affect some lesions more than others, a single skin biopsy may not be representative.

THE 5-GROUP OR 6-GROUP SPECTRUM

The immunological spectrum of leprosy is an infinitely graded continuum. The number of groups or positions in the spectrum that are defined is a matter of convenience. For ordinary purposes 5 groups have proved adequate and suitable. Evenly spaced, from tuberculoid to lepromatous, they are designated TT, BT, BB, BL, and LL.

On the other hand research may require the identification of patients in the sub-polar lepromatous region, that is intermediate between BL and the extreme polar form of LL. Although clinically the sub-polar form belongs to LL, from the point of view of immunological performance it is distinct from the polar form. In this paper, therefore, LL is redefined so as to cover the whole of the sub-polar region. At the same time it is subdivided (optionally) into polar and sub-polar components designated by the suffixes p and s.[a] The reason for making the alteration is that the old LL had two meanings, depending on whether it was used with a 5-group or a 6-group system. The new LL (LLp+LLs) equals the old LL+LI. LLs is identical to the old LI (13). Thus the 5 and 6 groups are integrated.

PRINCIPLES OF HISTOLOGICAL CLASSIFICATION

Most of the histological characteristics of tuberculoid and lepromatous leprosy were well known to leprologists long before the present work was contemplated. These and a number of other features that might have a bearing on immune relationships, notably the presence of lymphocytes in lesions, were tested independently by reference to various immunoprognostic factors: (*a*) the rate of clearance of *Mycobacterium leprae* from skin lesions under chemotherapy, and (*b*) the lepromin reaction (3). To these were soon added (*c*) the immunological stability of lepromatous patients on treatment and of tuberculoid patients without treatment (in so far as it was possible to observe them) and (*d*) susceptibility to reactions, and the effect of these two factors on the course of the infection. Some of these criteria were re-evaluated by Ridley (12) and by Ridley & Waters (13). However, although they produced a fairly conclusive definition of the middle and lower end of the spectrum, their application to the tuberculoid end was less successful and left a gap, which has now been filled by (*e*) lymphocyte function tests. Although the results of Myrvang et al. (5) were broadly in line with the original classification, a more detailed study of their lymphocyte transformation results has been used here as the basis for a slight modification of the histological definition of TT. The first and last of these 5 criteria carry the most weight as they give a numerical value. As a result of this correlative study, 5 histological features have been found to have a bearing on immunity and to be of use in classification. It is convenient first to discuss them in general terms.

(1) *Granuloma cell type.* The term " granuloma " is here applied to a proliferative lesion involving any of the cell types derived from mononuclear cells, which are the host cells of *M. leprae.*

In the upper half of the spectrum, from TT to BB, the granuloma is composed of epithelioid cells whose morphology does not vary (compare Fig. 1 and 6). In sections, these cells produce a characteristic mosaic pattern, which is best observed under the $\times 10$ objective. In addition, giant cells may be present in the tuberculoid region. Large differentiated cells of Langhans type (Fig. 3) are of greater immunological significance than nondescript or foreign-body giant cells are (Fig. 4). In BB, the epithelioid cells are often separated by oedema that makes them less readily identifiable; this signifies a mild reactional state due to rapid down-grading. Below BB, the epithelioid cells give place to macrophages (Fig. 17) whose cytoplasm becomes more and more fleshy, foamy, and fatty as the LL pole is approached. The appearance of the nucleus is unchanged throughout.

The sensitive variation in the cytology of the granuloma makes this a feature of prime importance in grading a patient within the lower half of the spectrum (BB–LL). Unfortunately, the cytology of nonepithelioid granulomas is influenced by regression, usually owing to treatment, in much the same way as it is by anergy. This is discussed in a separate section below.

(2) *Bacterial load.* For a given cell form, the denser the bacilli, the worse the immunological performance. This is one of the most valuable criteria for placing an untreated patient within the BT–BL region, but is of little value near either of the poles.

(3) *Lymphocytes.* These are important in classification, but the number seen in lesions does not bear a linear relationship to immunity. This is not altogether surprising because the lymphocytes belong

[a] The terms polar-LL and sub-polar-LL (or sub-L) are more explicit and euphonious in spoken English than LLp and LLs. But for the written notation the single letter suffix is more convenient.

to two populations (T and B) that cannot be distinguished histologically, though it is doubtful whether this fully explains the discrepancies. There are several comments to be made.

(*a*) Numerically, lymphocytes produce two peaks: in the TT–BT region and at BL, and two troughs: at BB and LL.

(*b*) Lymphocytes densely packed around the periphery of a granulomatous mass (Fig. 21) appear to be of greater immunological significance than a diffuse infiltrate (Fig. 8), and dense infiltration throughout a whole segment of granuloma is more significant than a clump of lymphocytes within a segment of granuloma (Fig. 12). Peripheral zoning occurs more often in the deep than in the superficial layer of the dermis, and may occur in TT or BT.

(*c*) It is impossible to state why immunity in one patient should be expressed histologically by an epithelioid differentiation of the host cells but no lymphocytes (e.g., BB), and in another patient by a lymphocytic infiltrate but no epithelioid cells (e.g., BL). However, the former has currently a greater measure of immunity as judged by the capacity to dispose of *M. leprae* while on chemotherapy, but he is in more imminent danger of losing his immunity unless treatment is promptly given. This is discussed further below.

(*d*) The number of lymphocytes in patients in the BL–LL range tends to increase after treatment (cf. Fig. 14, 15, and 16), though this does not always happen, and at the LL pole lymphocytes are never a significant feature except in erythema nodosum leprosum lesions.

(4) *Nerves.* The nerves of the dermis are important to an understanding of the histoimmunological relationship but the severity of their involvement is not readily predictable. Some tuberculoid and borderline infections are predominantly neural, others less so, irrespective of their exact position in the spectrum, though this is truer of early infections than it is of advanced infections. Especially in the former there may also be some variation in the histological response from one nerve site to another. In TT lesions there is the possibility that nerves may have been destroyed beyond recognition, but no certainty that they were ever present within the area of the section. Thus severe nerve involvement, relative to other aspects of histology, is significant for classification, whereas less severe nerve involvement (or an absence of nerve bundles) is not so significant.

Considering the cases that show relatively heavy nerve involvement, the degree of damage by granuloma formation in the nerve bundle (Fig. 5), of which the diameter of the bundle is an approximate measure, is maximal in TT and decreases progressively down the spectum to LLp. Perineurial damage, however, occurs mainly in the BB to LLs range (Fig. 7, 11, and 13), and is often the greatest in BL. Infiltration by lymphocytes, plasma cells, or bacteria-laden macrophages (Fig. 11) causes a lamination of the perineurium, which has been aptly likened to onion skin. This infiltrate is reduced in LLs, leaving empty slits (Fig. 13).

(5) *Epidermis and subepidermal zone.* In the BB–LL range the granuloma stops short of the epidermis, leaving a clear subepidermal zone about 30–75 μm deep. From BT upwards the granuloma extends nearer to the epidermis and finally may erode it with destruction of the basal layer and part of the stratum malpighii (Fig. 1). This is explained by two observations: The epidermal region is to some extent a preferential site for *M. leprae* when immunity is high, though otherwise it is unfavourable. And tissue reactivity here is either very high or very low (14). Unless immunity is high there are either no bacilli in this region or no reactivity to them. It is assumed that there is some granuloma present in the superficial dermis; otherwise the subepidermal zone is of no significance. Any very large granuloma may compress the subepidermal zone.

OTHER ASPECTS OF PATHOLOGY RELEVANT TO CLASSIFICATION

High and low cell turnover

Granulomas are characterized by either a high or a low rate of cell turnover—i.e., entry or proliferation and emigration, mitosis, or death of the component cells (15). Giant cells (of which the Langhans type is the best-differentiated and most mature) and, to a less extent, epithelioid cells, arise under conditions of high turnover, while at the other extreme long-lived macrophages are a response to inert and indigestible particles, which is the situation in lepromatous leprosy. Thus there is a general correlation between a high cell turnover due to a short life span and hypersensitivity, which has been confirmed in the case of mycobacterial infections by Ando et al. (16) and Dannenberg et al. (17). However, cell turnover is also higher in active lesions than it is in healing lesions (18). Thus the state of activity or

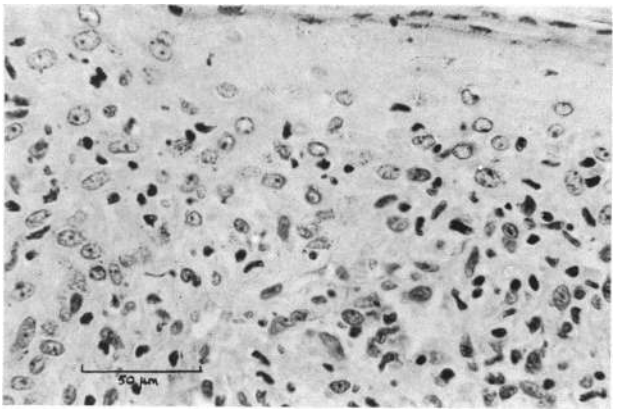

Fig. 1. TT. Erosion of epidermis by granuloma. (No acid-fast bacilli found.)

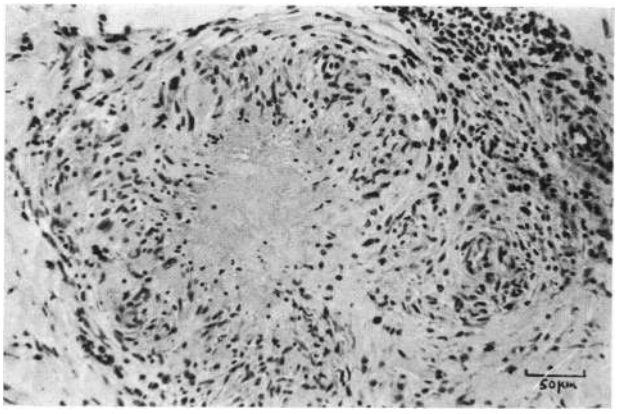

Fig. 2. TT. Caseation in a nerve centre in the dermis. An uncommon but significant finding. (No acid-fast bacilli found.)

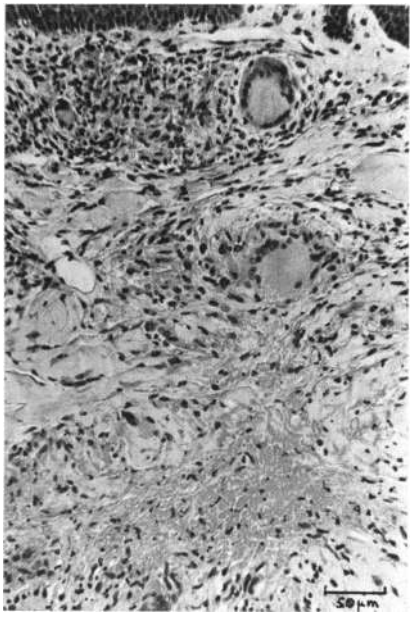

Fig. 3. TT. Granuloma with large differentiated giant cells. Note also the patch of fibrinoid necrosis in a reaction centre. This is a clear case of upgrading from BT, which may explain why there is a narrow clear subepidermal zone. (No acid-fast bacilli found.)

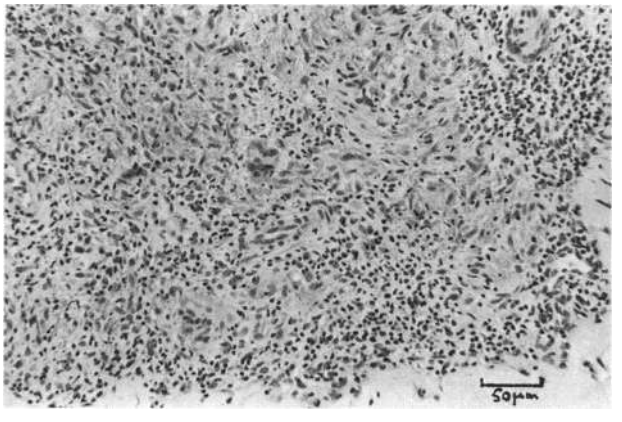

Fig. 4. BT or TT. Epithelioid cell granuloma with a significant number of lymphocytes forming clumps, and several giant cells. If there were no clear subepidermal zone this would be TT, but the form of the giant cells is more suggestive of BT and there was a clear zone. Therefore BT. (AFB 1+.)

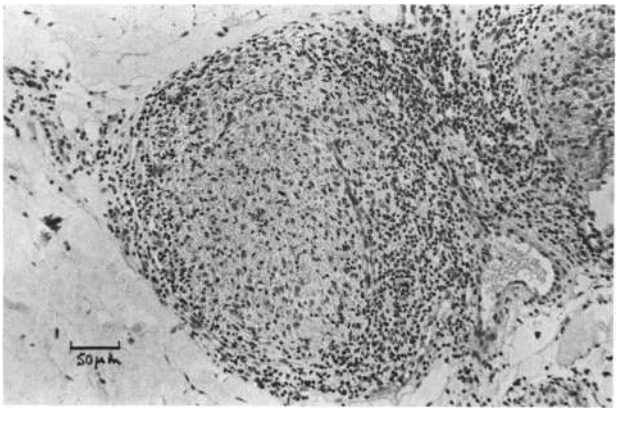

Fig. 5. BT or TT. Nerve destroyed by epithelioid cell granuloma with a zone of lymphocytes, fairly typical of BT. However, it could possibly be TT; if it were larger it would have to be TT. (No acid-fast bacilli found.)

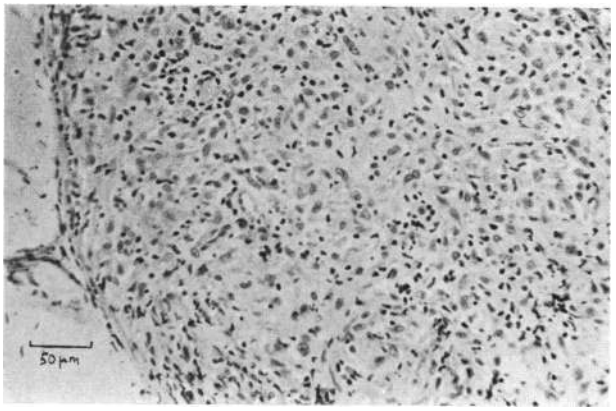

Fig. 6. BB. Epithelioid cell granuloma without giant cells or lymphocytes. There is unusually little oedema (AFB 4+.)

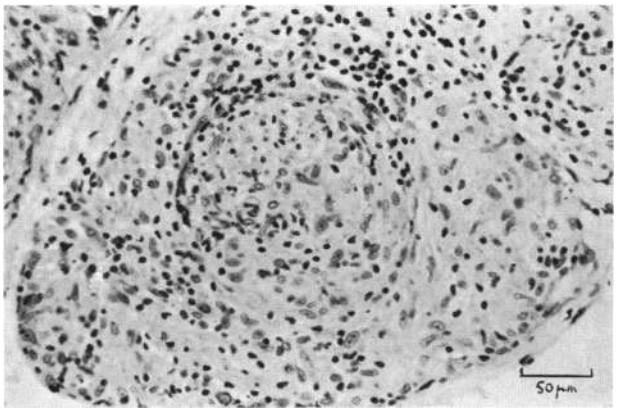

Fig. 7. BB. Nerve with epithelioid cells in one half only. These cells have broken through the perineurium, which is somewhat laminated. Nerves in BB may be less damaged than this. (AFB 4+.)

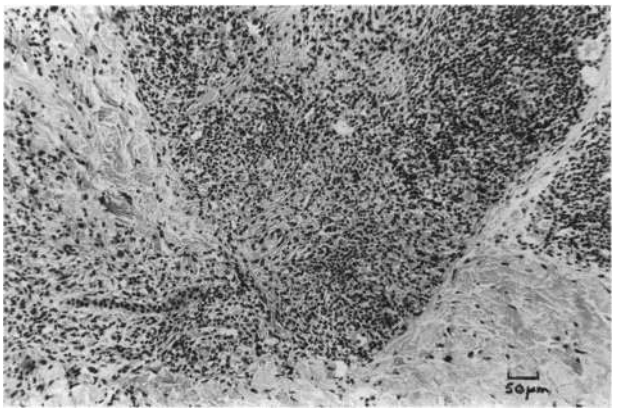

Fig. 8. BL. Granuloma heavily infiltrated by lymphocytes that extend to the periphery in some parts though not in others.

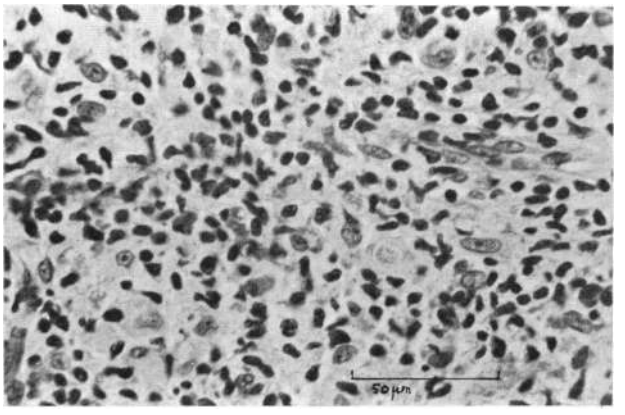

Fig. 9. BL. High-power view of section shown in Fig. 8. Note the foaminess and small vesicles. (AFB 5+.)

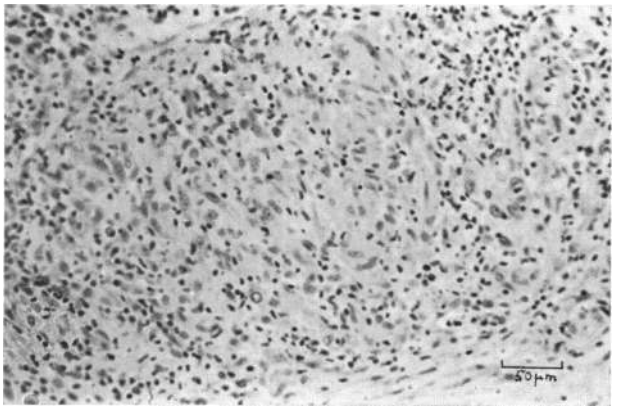

Fig. 10. BL. Epithelioid cell pocket in an otherwise foamy granuloma. None other in the section. (AFB 5+.)

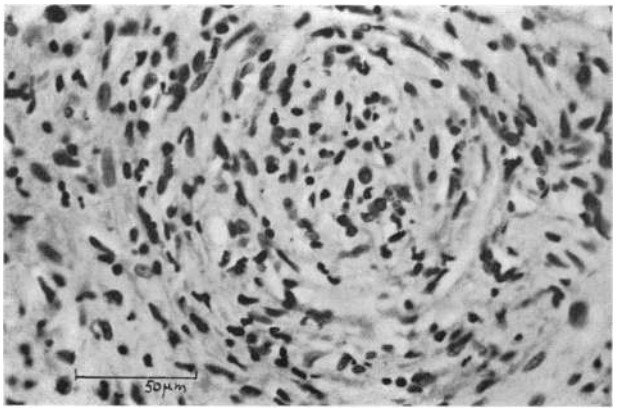

Fig. 11. BL. " Onion-skin " perineurium partly obscured by some cellular infiltration of nerve. (AFB 4½.)

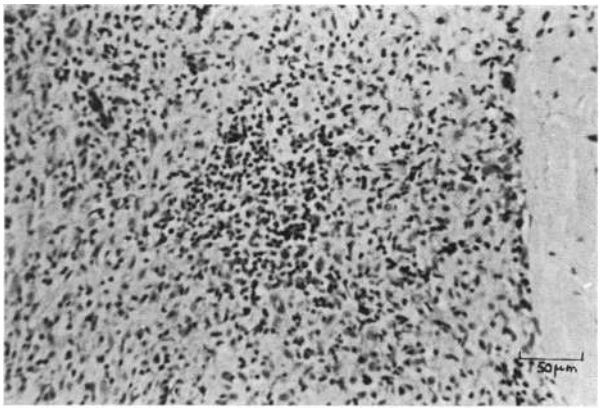

Fig. 12. LLs. A small clump of lymphocytes within a granuloma is not of great significance and is quite consistent with LLs. The lesion is mildly active. (AFB 5½+.)

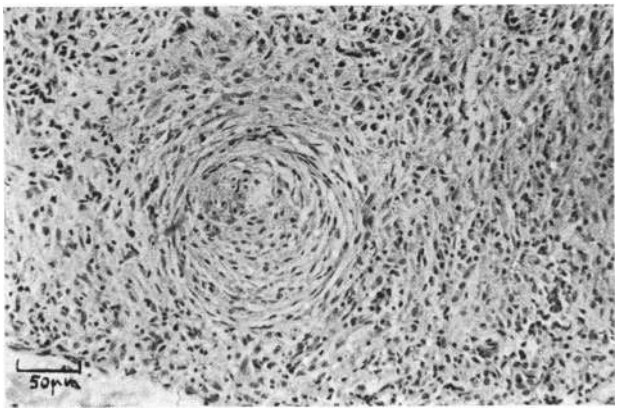

Fig. 13. LLs. A rather formless granuloma typical of active LLs. The closely packed macrophages mingle with some infiltrating cells. Note the nerve with onion-skin perineurium, which is less infiltrated than in BL.

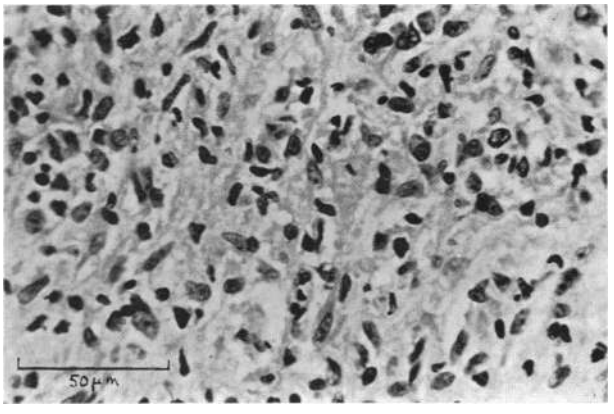

Fig. 14. LLs. High-power view of section shown in Fig. 13. Note the diffuse foaminess, lymphocytes, and plasma cells. (AFB 5½+.)

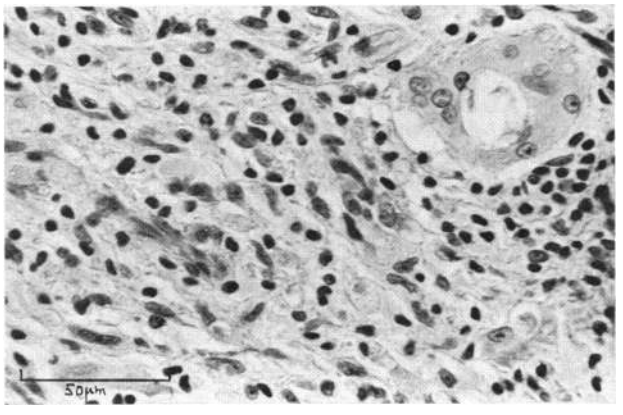

Fig. 15. LLs. Regressing. Same case as in Fig. 13 & 14 after 6 months' treatment. Note vacuole in giant cell and some increase of lymphocytes. (AFB 5½+.)

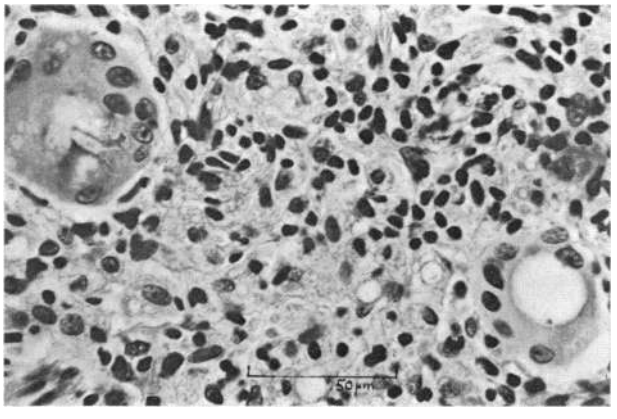

Fig. 16. LLs. Prelude to reversal reaction. Same case as in Fig. 14 & 15 after 18 months' treatment. The number of lymphocytes is much more than normal for LLs but the large vacuole is incompatible with BL. Reaction followed 3 months later. (AFB 4+.)

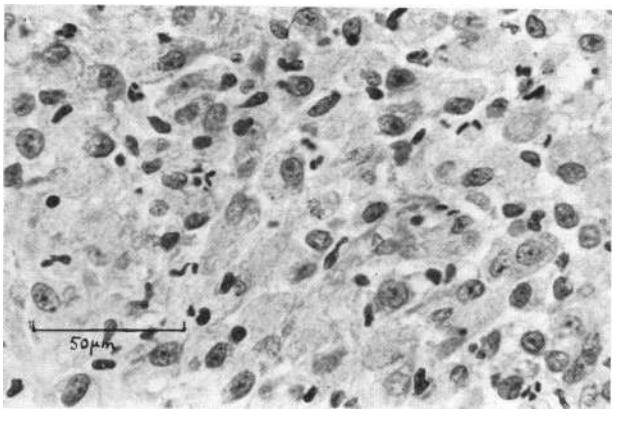

Fig. 17. LLp. Active. Macrophage granuloma with finely dispersed fat in the abundant cytoplasm. (AFB 6+.)

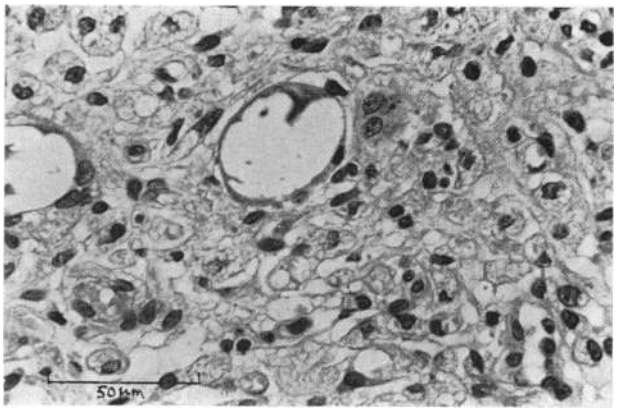

Fig. 18. LLp. Regressing after 2½ years' treatment. The vesicles and thinly membranated giant vacuoles are typical. Still very few lymphocytes. (AFB 5+.)

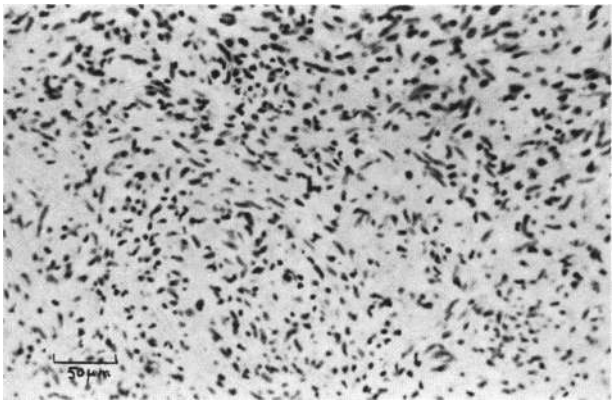

Fig. 19. Example of problem. See text.

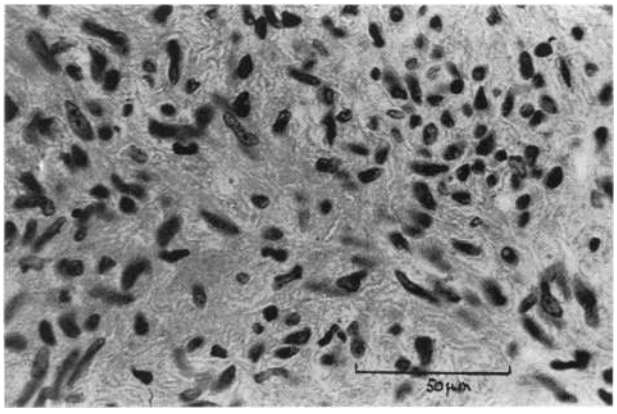

Fig. 20. High-power view of section shown in Fig. 19.

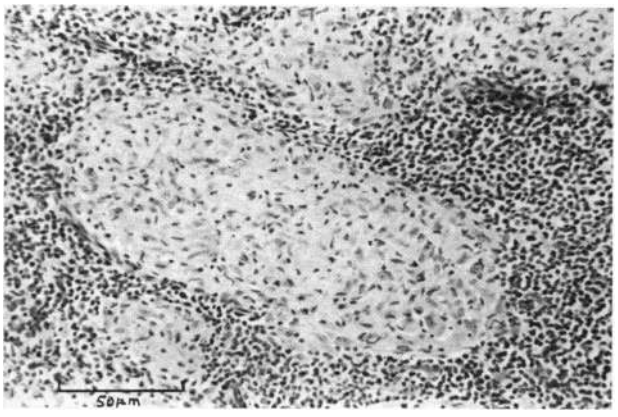

Fig. 21. Dense infiltration of lymphocytes with peripheral zoning is often associated with a relatively low lymphocyte transformation result and is no longer regarded as being of great significance in the classification of a tuberculoid case.

regression of leprosy has a bearing on the cytological features that are used in classification.

Activity and regression

The cytology of epithelioid cell granulomas, for some reason, is not affected by regression. But in a lepromatous granuloma regression is associated with an increase of fat that is unrelated to immunity (Fig. 14 & 15). Thus a regressing BL lesion may have as high a fat content as an active LL lesion, whereas a regressing LL lesion will have more fat than either. Thus regression influences fat accumulation in the same direction as anergy whereas, as has already been pointed out, it affects the bacterial load and possibly the number of lymphocytes in the direction opposite to anergy. It is likely that the similarity of the histological responses to the two causal influences has been responsible for some confusion over classification and for the assertion that different lesions belong to different groups. Except during reversal reactions, lesions are nearly always uniform as regards immunity, though often diverse in respect of activity.

It may be necessary, therefore, to make allowance for the state of activity or regression of a lesion before considering classification. This can be done in three ways: (1) The morphological index is the quickest and most obvious index of activity, though occasionally, as in relapse, bacterial activity may not be equated with histological activity. (2) In active LL granulomas the fat is finely dispersed in the cytoplasm (Fig. 14 & 17), whereas, in regression, the fat coalesces to produce small or large vacuoles (Fig. 15 & 18); this is only partly due to the increase in volume of the fat. (3) In activity the spread of the lesion usually produces spurs around the periphery of a granuloma as it infiltrates into the dermal collagen (19); this applies mainly to the superficial zone of the dermis; in the deep zone, spread seems to be more expansile than infiltrative.

Relapse

There is one exception to the correlation of cell turnover and immunity in leprosy. In relapse the granuloma though still fully lepromatous is often highly proliferative with many of the features of Wade's histoid lesions (20). This does not always coincide with high bacterial activity. It suggests, perhaps, that in second infections there may quite often be an ineffective form of macrophage activation. The same appearance may be seen less often in severe first infections, but in such cases there is always a high bacterial activity. The immaturity of the cells and their lack of differentiation makes classification a little difficult, though the principles are the same as for other active lepromas.

Reactions

Any sort of reaction is a complicating factor in classification. In the late stage of erythema nodosum leprosum (ENL) lesions there may be an increase of lymphocytes (21, 22). Plasma cells also may be increased in ENL, but these do not have much association with classification except that they are almost absent in the upper half of the spectrum.

In borderline reactions an increase of lymphocytes is more likely to occur if the patient's immunity is upgrading. In any sort of severe borderline reaction the granuloma is apt to be disrupted by oedema and foreign-body giant cells, which complicates classification. At a later stage there may be a widespread upheaval in the dermis that may mimic the process of infiltrative spread (19).

CLASSIFICATION: DEFINITION AND PRACTICE

Definition of groups

The groups are defined as follows, and summarized in Table 2. Reproducibility of results should be about 95%.

The index for acid-fast bacilli (AFB) is the 6+ scale used in the bacterial index (23), which in biopsies is applied to the granuloma alone. In biopsies, however, bacilli are sometimes so densely packed that 6½+ is required. This number of bacilli is uncountable.

TT. Epithelioid cell granuloma with a significant number of lymphocytes (Fig. 4) and evidence of a hyperactive tissue response: (*a*) deep and fairly extensive erosion of the epidermis (Fig. 1); or (*b*) central caseation of a nerve bundle in the dermis (Fig. 2); or (*c*) massive enlargement of a nerve bundle (over 400 μm in diameter) surrounded by a zone of lymphocytes; or (*d*) giant cells of any sort combined with the absence of a clear subepidermal zone. AFB 0–1+.

BT. Epithelioid cell granuloma with either giant cells or a moderate number of lymphocytes or both (but not both in addition to the absence of a clear subepidermal zone); (Fig. 4). There is no hyperactive tissue response (see TT). The giant cells are typically rather nondescript (Fig. 4), more foreign-body than Langhans type. Nerves may be moderately swollen by granuloma (Fig. 5) or show only Schwann cell proliferation. AFB 0–2½+.

Table 2. Guide to the histology and performance of the classification groups

	TT	BT	BB	BL	LLs	LLp
epithelioid cells	++	++	++	±/–	–	–
non-vacuolated giant cells	++/–	+/–	–	–	–	–
histiocytes/foamy macrophages	–	–	–	++	++	++
small vesicles	–	–	–	++/–	++/–	++/–
vacuolated giant cells	–	–	–	–	++/–	±/–
giant vacuoles	–	–	–	–	+/–	++/–
lymphocytes	+±/+	+±/±	±	++/+	+/±	±/–
dermal nerve, maximum diameter in μm	1000	400	250	200	200	80
onion-skin perineurium	–	±/–	+/–	++/±	++/–	–
clear subepidermal zone	±/–	++/–	++	++	++	++
erosion of epidermis	++/–	±/–	–	–	–	–
acid-fast bacilli in granuloma (BI)	0/1	0/2½	3/4½	4/5½	5/6½	5½/6½
acid-fast bacilli in nose	–	–	–	±	++	++
lepromin (Mitsuda) reaction	3+	2/1+	–	–	–	–
lymphocyte transformation test (% transformation)	15	6.0	2.8	0.9	0.6	0.4
leucocyte migration index	0.76	0.83	0.88	0.92	0.92	0.95
fall in histological index in 6 months (%)	...	100	78	23	14	5.5
immunological stability	++	±	–	±	+	++
borderline reactions	–	+	++	+	±	–
erythema nodosum leprosum	–	–	–	±	++	++
protection by BCG (?)	–	+	–	–	–	–
approximate distribution of cases (%)	9	24	8	10	31	18

BB. Epithelioid cell granuloma without any giant cells and only scanty diffusely spread lymphocytes (Fig. 6). The subepidermal zone is clear. The nerves are not greatly swollen by granuloma and may be fairly normal; they may show lamination of the perineurium, with epithelioid cell infiltration. AFB 3–4½+.

BL. Macrophage granuloma with (*a*) numerous lymphocytes densely packed over the whole of at least one segment of the granuloma (Fig. 8); and/or (*b*) an occasional small clump of a few epithelioid cells (less common; Fig. 10). There is some foamy change but no large vacuoles (Fig. 9). The subepidermal zone is clear. The nerves commonly show onion-skin perineurium with some cellular infiltration (Fig. 11). AFB 4–5½+.

LL. Macrophage granuloma with no epithelioid cells and not very many lymphocytes. Foamy change variable. The subepidermal zone is clear. Nerves show union-skin perineurium without much infiltration, or are fairly normal. AFB 5–6½+.

LLs. Active: rather closely packed macrophages with not much foamy change (Fig. 13 & 14); a small or moderate number of lymphocytes is usually present (Fig. 12 & 13). Regressive: foamy change with vacuolation; large vacuoles if present typically in multinucleate giant cell (Fig. 15); some lymphocytes are present. The nerves may have onion-skin perineurium (Fig. 13).

LLp. Active: macrophages with bulky cytoplasm and much diffuse foam. Lymphocytes are scanty (Fig. 17). Regressive: foamy change with vacuolation as in LLs, except that large vacuoles if present are typically enclosed in a thin multinucleate membrane (Fig. 18). Lymphocytes are few (except in ENL). The nerves are relatively normal, perhaps hyaline or

fibrosed, with thickening of the perineurium but no lamination.

Idt. The histology of indeterminate leprosy is the histology of the early lesion (24). If the evidence is sufficient for diagnosis but not for classification on the basis here described, the patient is assigned to the indeterminate group. This happens usually because there is no granuloma. The subject is discussed further by Ridley (25).

Key to classification

The following guide is intended to indicate the priorities in classification. The choice between the alternatives of each pair—e.g., B or I for A, and so on to the end—should take into account the group definitions given above.

A_1 There is a granuloma present . . . . . B

A_2 No granuloma has been found anywhere in the section I

B_1 The granuloma is composed predominantly of epithelioid cells (Fig. 6) C

B_2 The granuloma is composed predominantly of macrophages (Fig. 14 & 17) . . . . G

C_1 There is deep and fairly extensive erosion of the epidermis (Fig. 1) . . . . . J

C_2 The epidermis is not involved, or there is only a spike of erosion, or only the basal layer is destroyed, or there is only cellular infiltration D

D_1 There is central caseation of a dermal nerve (Fig. 2) or massive swelling (over 400 μm) with a zone of lymphocytes around the nerve . J

D_2 Less severe nerve enlargement and no caseation . . . . . E

E_1 (1) Giant cells are present: (2) moderate numbers of lymphocytes are present, with some clumping (Fig. 4); and (3) there is no clear subepidermal zone . . . . . J

E_2 One or more of these three features is lacking . . . . . F

F_1 There are either giant cells or a moderate number of lymphocytes present, or both (Fig. 4) K

F_2 There are neither giant cells nor lymphocytes (Fig. 6) L

G_1 Granuloma shows one or two small clumps of epithelioid cells (Fig. 10) . . . . . M

G_2 Epithelioid cells are absent . . . . . H

H_1 Lymphocytes are numerous, covering the whole of one or more segments of granuloma (Fig. 8) . . . . . M

H_2 Lymphocytes are only moderate in number, in small clumps (Fig. 12), or scanty . . . N

I Classification INDETERMINATE

J Classification TT

K Classification BT

L Classification BB

M Classification BL

N Classification LL. For subdivisions of LL O

O_1 The lesion is histologically active . . . P

O_2 The lesion is histologically regressive . . Q

P_1 The macrophages have abundant cytoplasm with diffuse foam or small vesicles; lymphocytes are scanty (Fig. 17) . . . . . R

P_2 The macrophages are more closely packed, with less foam; often a few lymphocytes and plasma cells are present (Fig. 14) . . S

Q_1 Lymphocytes are scanty (excluding ENL lesions), giant vacuoles, if present, are thinly membranated (Fig. 18) . . . . . R

Q_2 There is an appreciable number of lymphocytes (excluding ENL). Any giant vacuoles are mostly in multinucleate cells (Fig. 15) . . S

R Subgroup LLp.

S Subgroup LLs.

Example of a problem

Fig. 19 and 20 show a leproma with remarkably little foamy change. On the evidence of the figures it looks like a very active LLs, in which case bacilli in the granuloma should be about 6+; unless it was a relapse case—of which there was no evidence—the bacilli should be mainly solid. In fact, the bacilli proved to be no more than 4+ and were all non-solid. Furthermore, it was known that the patient had received 4½ months of treatment. This would not have diminished the number of bacilli sufficiently to account for the low BI, whereas it would have produced regressive changes and at least some fat accumulation; there was a little elsewhere in the section but not much. The classification therefore was given as a slightly atypical BL. The patient was downgrading from BB to LLs when treatment was started (cf. Fig. 10), and was arrested in the transitional BL position. Treatment has caused the disappearance of the reactional oedema that is a usual characteristic of such cases, but as yet there has been no reversal reaction.

This case illustrates the need to take account of the degree of activity or regression, the complication of treatment, about which reliable information is

often lacking, and the results of bacteriology, especially in borderline cases.

Modifications to the definition of groups

The most important innovation that has been introduced as a result of the study of lymphocyte function has been the disregard of the number of lymphocytes in tuberculoid lesions (over and above a certain minimum). This is discussed elsewhere in this paper. The outcome is that, under the new definition, there is some redistribution of cases between TT and BT, and some patients who appear to have upgraded from BT (though still clinically BT) are now classified as TT. The net effect on the numbers in each group is insignificant.

At the lepromatous end of the spectrum the change in the subgroups of LL is no more than a matter of nomenclature except in one respect—i.e., that the types of BL lesion previously described as histiocytic are now included under LLs unless there are epithelioid cells present. Further experience has shown that their immunological performance is indistinguishable from that of LLs cases, which simplifies the problem of their histological classification. As a result, the number of cases allocated to the BL group is reduced by about 30%.

EVOLUTION OF THE INFECTION AND IMMUNOLOGICAL PERFORMANCE

The figures for the distribution of the various groups when the infection is fully established (Table 2) refer to a mixed population of leprosy patients (9, 13), but there is appreciable variation among the various ethnic groups and these figures can be taken only as an approximate indication of group distribution. It must also be remembered that borderline patients are unstable. BT patients may upgrade to TT (26), though advanced cases are more likely to downgrade. BB patients always downgrade to LLs without treatment. LLp patients probably always originate as such. However, although the static nature of some groups and the range of movement of others appear to be distinctive, it is not asserted that histological distinctions between adjacent groups are absolute. The spectrum is continuous. The observation that only those patients who would have developed BT leprosy are protected by BCG was a preliminary finding of the Karimui BCG trial (27). However, according to Ridley (14), over half of all leprosy cases originate in the BT position. If it is confirmed, therefore, the Karimui result might be of greater significance than would at first appear.

The immunological performance of patients at different parts of the spectrum is summarized in Table 2. The figures for the bacteriological response to treatment are based on a revised assessment using the 6½+ scale, in consequence of which the rates of fall of the histological index [a] for LL are higher than previously published figures. As the index is logarithmic, the differences shown between the various groups are substantial. Furthermore, the difference between the two subgroups of LL is as great as that between the main groups. Table 1 shows the effect of reversal reactions in enhancing the rate of elimination of *M. leprae* from skin lesions. This is most pronounced in BL cases, which are too unpredictable for use in therapeutic trials. LLs patients are relatively stable, but their potential for upgrading is an important consideration in the planning of immunotherapy experiments, such as transfer factor studies.

The performance of the lymphocyte function tests is based on a study of the results of Myrvang et al. (5), who, however, used a 7-group system. Analysis of their results does not appear to warrant the subdivision of the TT group, because the performance of patients who upgrade from BT is variable and may probably equal or exceed that of patients who originate as TT. Their results are here recast on the basis of the 6 groups as now defined (Table 2). The revised mean figures for the lymphocyte transformation test for the TT and BT groups (the only groups to have been adjusted) happen to be exactly the same as the previously published results, but the figures for individual cases now show rather less deviation. However, the main difference between the two groups is found to be in the percentage of responders (transformation of over 2%) in each group. These figures are now 91% for TT patients against 36% for BT patients. The lymphocyte transformation rate among responders is not significantly different for the two groups: TT, 16.2%; BT, 14.8%. The explanation is not clear. It may be that the BT patients with a high lymphocyte transformation rate (see above) are in incipient reaction. Godal et al. (26) found that such patients may sometimes have a high rate even though they subsequently downgrade after, or as a result of, the reaction. No patient in the BB, BL, or LL group gave a test result higher than 8%. The results of the leucocyte migration index have not been reassessed.

[a] This was originally described as the logarithmic index of bacilli in biopsies.

Lymphocytes in lesions

It had previously been observed that tuberculoid patients with many lymphocytes zoned around epithelioid granulomata (Fig. 21) usually appeared to be free of histological signs of reaction or downgrading, and as they were often strongly tuberculoid clinically this type of lesion was considered to be TT. However, it could also be observed that, although these patients appeared to be immune against downgrading, they were by no means self-healing and the lesions were frequently of large size. It is now found that such patients have a low lymphocyte transformation test (8.4%) and, if there is no other histological evidence of a hypersensitivity response (as defined for TT), the mean value obtained in the test is only 5.3%.[a] Such patients therefore are now classed as BT unless there is other histological evidence of hypersensitivity.

There is an analogous situation in the other group of patients with numerous lymphocytes, BL. This would appear to be a distinct group that usually originates as such. BB patients downgrade directly to LLs; in the transient intermediate stage, in which there are surviving clumps of epithelioid cells, patients are graded BL, but under these circumstances lymphocytes are not very numerous. Patients with macrophage granulomas and numerous lymphocytes were originally graded as BL because they were intermediate between BB and LL in respect of their bacterial response to treatment and of the probability of their undergoing upgrading (reversal) reactions. This view now proves to be too simple. The bacterial response to treatment is not significantly different from that of LLs patients unless a reversal reaction supervenes: the fall in the histological index was 14% against 12% in the first 6 months of treatment if there was no reaction (Table 1). The leucocyte migration index is the same in BL as in LLs and the maximum diameter of dermal nerves is the same in the two groups (Table 2). Finally, there were no responders in the lymphocyte transformation test among the 7 patients of the lymphocytic type of BL who were tested, although there were among those of the epithelioid cell type. The immunological performance of lymphocytic BL patients, therefore, is superior to that of LLs patients only in respect of their potential for upgrading. The immunological performance of lymphocytic BL patients is inferior to that of BB patients (who have epithelioid cells but scanty lymphocytes) in respect of the bacterial response to treatment, but superior in respect of their tendency to downgrade without treatment.

The presence of numerous lymphocytes in leprosy lesions, therefore, appears to provide a good immunological prognosis, but not to represent enhanced antibacterial performance; that is the prerogative of epithelioid cells. The evidence suggests that, whereas a limited number of sensitive lymphocytes is sufficient to activate the macrophages in a lesion, an additional supply of lymphocytes with the same blastogenic potential prevents bacteria from gaining the ascendancy over the immune mechanism.

It is the number of lymphocytes relative to the size of the granuloma that is significant. This suggests that immunotherapy might have a better chance of success in early infections or in long-treated patients than in those with advanced, though possibly inactive, disease.

CONCLUSION

This paper is presented as a record of the system used by the author in previous studies, slightly modified as a result of a re-evaluation of immunological criteria. The system described has been found to be applicable to all the ethnic groups studied so far, as well as to experimental leprosy in mice (28). Histologists who have used it have been found to reach very good agreement. Histological classification provides a convenient means of standardization between patients at widely distant centres. It has the advantage over clinical classification, which it supplements, that it gives a better indication of any recent shifts in a patient's position in the spectrum. There are a few gaps, such as the exact position in the spectrum of the Indian maculoanaesthetic patients. It remains for the international study group at present being conducted by WHO through its collaborating centre at Caracas to decide whether to recommend some such system, to decide how much more investigation is required, and to produce a definitive histological classification. In spite of the length of experience gained with the TT–LL scale, the number of unselected patients on whom serial biopsies or immunological evaluation have been available is disappointingly small, at least as regards the smaller groups. It is on such cases that the evidence rests. It is desirable, in particular, that further correlative studies with lymphocyte function tests should be carried out in regard to reactions. The ultimate role of such tests in the classification of leprosy remains to be determined.

[a] The corresponding mean values for the histological features defined as signifying TT are: erosion of epidermis, 10%; nerve involvement, 18%; and the triad of giant cells, lymphocytes, and no subepidermal zone, 16%.

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RÉSUMÉ

CLASSIFICATION HISTOLOGIQUE ET SPECTRE IMMUNOLOGIQUE DE LA LÈPRE

On a montré précédemment que les manifestations cliniques et histologiques de la lèpre sont étroitement liées à l'état immunologique du malade, qui détermine le pronostic et fournit les éléments de la classification de l'affection. C'est sur la base de cette corrélation que Ridley & Jopling (1962, 1966) ont élaboré une classification, mais l'expérience a prouvé qu'il convenait de tenir davantage compte des aspects histologiques. C'est l'objet du présent article.

Un certain nombre de critères immuno-pronostiques ont été utilisés: *a*) la réponse au traitement du point de vue bactériologique; *b*) la réaction à la lépromine; *c*) la stabilité immunologique des malades lépromateux en traitement et des malades tuberculoïdes en l'absence de traitement (dans la mesure où elle a pu être évaluée); *d*) la tendance aux réactions et l'issue de celles-ci. Ces critères, qui ont été partiellement réévalués, se sont révélés moins concluants pour les formes tuberculoïdes que pour les formes lépromateuses. Cette lacune a maintenant été comblée par *e*) l'étude des fonctions lymphocytaires. Sur la base de ces cinq critères, on a reconnu l'importance de cinq aspects histologiques qu'on a mis à profit pour définir cinq groupes ou positions dans le spectre immunologique de la lèpre. Ces aspects histologiques sont: 1) la cytologie du granulome; 2) la charge en bacilles du granulome; 3) le nombre de lymphocytes dans les lésions; 4) les lésions nerveuses et 5) l'atteinte de la couche épidermique. Cependant, la régression histologique (par opposition à l'activité) d'un granulome à macrophages modifie la cytologie dans la même mesure que l'anergie, mais, dans certains cas, le nombre des lymphocytes subit des changements en sens opposé. On a dû tenir plus ou moins compte du degré d'activité ou de régression.

Cinq groupes ont été définis: TT, BT, BB, BL et LL. Le dernier est subdivisé soit en forme polaire (LLp) soit en forme sous-polaire (LLs), celle-ci étant identique au sous-groupe précédemment appelé LI. Ce changement a été rendu nécessaire par le fait que LL avait auparavant deux significations légèrement différentes selon qu'on envisageait un système de 5 ou 6 groupes.

L'étude du comportement de malades dans ces groupes semble indiquer que la cytologie du granulome reflète le potentiel antibactérien, qui est lié au taux de transformation des lymphocytes, tandis que la présence d'un grand nombre de lymphocytes dans les lésions est plutôt un indice de la résistance à l'aggravation ou du potentiel d'évolution favorable avec l'aide de la chimiothérapie. Ces deux aspects histologiques sont indépendants, si ce n'est qu'un certain nombre de lymphocytes est indispensable à l'activation des macrophages et au développement des cellules épithélioïdes. De légères modifications ont été apportées à la définition de certains des groupes histologiques pour tenir compte de ces données.

La présente classification s'est révélée comme un instrument de travail applicable à tous les groupes ethniques étudiés jusqu'à présent et on a noté une concordance remarquable des résultats obtenus par les histologistes qui l'ont utilisée.

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