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Classification of Nerves is Modified by the Delayed Recognition of *Mycobacterium leprae*[1]

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Although the pathology of nerve damage in leprosy and the injury to the patient are not in dispute ([4, 5]), the nature of the relationship between *Mycobacterium leprae* and nerve tissue has not been elucidated. The Schwann cell has been referred to as the "target" of *M. leprae* ([9, 25]), which it selectively ingests ([9, 11, 22]). But nerve is not always the optimal site for *M. leprae* ([15]) and, apart from the affinity between them, nerve involvement has been attributed to the immunological protection afforded to the organism ([2, 4, 12]). The opportunity to compare concurrent biopsies of nerve and skin, with reacting and nonreacting lesions across the spectrum of leprosy, allowed us to approach the problem from the viewpoints of classification and bacterial load in nerves relative to skin lesions.

The Ridley-Jopling classification ([19]) is now widely accepted, but its histological component refers only to skin, not to nerve lesions. Although there have been many studies of the histology, ultrastructure, and histochemistry of nerves in relation to general classification, and the perineurium has been studied in detail ([13]), there appears so far to have been only one serious attempt to determine whether nerve and skin classification could be considered identical: Srinivasan, *et al.* ([24]) found discrepancies in 21 out of 36 cases. However, it is generally believed that there is no significant difference between nerve and skin classification, and the material for the present study has already been reported to show no difference ([14]). Here we reconsider the matter, using slightly modified group definitions suitable for application to nerve. Immunohistology will be the subject of a separate study.

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MATERIALS AND METHODS

The biopsies of nerve and skin were taken by the late Dr. J. C. Pedley from leprosy patients at the United Mission Hospital at Tansen, Palpa, Nepal ([14]). The nerves selected for biopsy were of the sensory type, and usually they were clinically visible or palpable. The majority were the terminal radial or terminal ulnar nerve at the wrist, and a few were superficial peroneal or sural nerve in the leg. In some cases more than one nerve and/or skin biopsy was taken from different sites. The intention had been to study the mode of transmission of leprosy.

From these cases, we selected nerve and skin biopsies of 42 untreated patients. The two biopsies were taken concurrently, the skin biopsy coming from an area supplied by the nerve. In most cases, there was reported to be a skin lesion at the site. The paraffin blocks, obtained from the Leprosy Study Centre in London, had been fixed in FMA (Harman's modification, with fixation in the mixture of Formalin, mercuric chloride, and acetic acid for 18 hr). Fresh sections of skin and nerve were cut and stained with hematoxylin and eosin (H&E), and by a modified Fite stain for acid-fast bacilli (AFB) ([18]).

AFB in the skin lesions were indexed on a logarithmic scale, the bacterial index (BI) of the granuloma being corrected for the size of the granuloma (logarithmic index of biopsy, LIB; biopsy or histopathological index). In the nerve sections, the granuloma fraction was irrelevant since the bacilli, more often than not, were outside the granuloma in relatively normal nerve tissue. The bacilli in nerves, therefore, were estimated by the BI, as in smears, over the whole area of the nerve. The result is referred to for convenience as the LIB, the two indices being identical in this instance. When organisms in skin sections were very scanty, they were counted arithmetically and the count was then converted to the LIB scale ([18]).

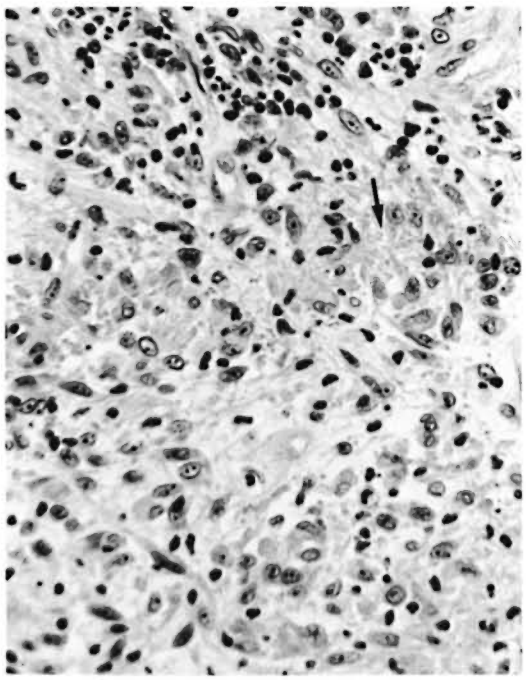

FIG. 1. Immature epithelioid cells in granuloma in nerve. The patch of fibrinoid necrosis (→) indicates TT (H&E ×300). (Fribrinoid is not well seen in black and white.)

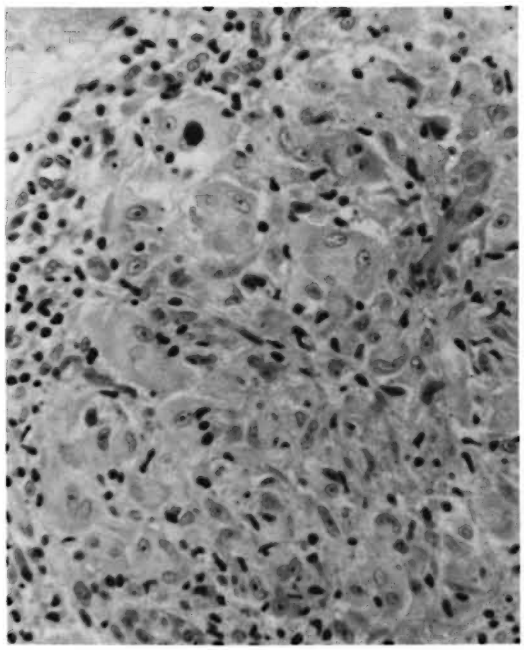

FIG. 2. Mature epithelioid cells in a dermal nerve, TT (H&E ×300).

The skin and nerve lesions were classified separately, skin lesions as previously ([16]), and nerve lesions by a slightly modified scheme. Insofar as there were differences, the two were correlated by a classification ratio which was calculated in two ways: a) By number of cases. From the number of cases deviating in the predominant direction (e.g., nerves more tuberculoid than skin) was subtracted any cases deviating in the opposite direction (nerves more lepromatous than skin); the difference was divided by the total number of cases in the group to be compared, including any cases in which there was no difference in classification, the answer being expressed as a percentage. b) The group difference was the mean of the number of groups by which the two classifications differed, e.g., if one was BT and the other BL, the group difference was two.

RESULTS

Classification of nerves. Some histological features normally used in the classification of skin (e.g., erosion of the epidermis) were inapplicable to nerve biopsies. To compensate for this, and to obtain full data on nerve classification at the tuberculoid end of the spectrum, it was found necessary to place emphasis on the distinction between mature (fully differentiated) and immature epithelioid cells, a point which has already been employed in the delineation of polar tuberculoid skin lesions ([18]). By comparison with immature epithelioid cells (IEC) (Figs. 1 and 3), the less-common mature epithelioid cell (EC) has a larger, more solid cytoplasm and a larger nucleus with more emphatic margination of chromatin, and a more prominent eosinophilic nucleolus ([1]) (Fig. 2). The difference was more conspicuous in nerves than in skin.

The classification used for nerves was as follows:

TTp = EC (with or without a few IEC) plus lymphocytes (lc) +++.

TTs = EC (with or without some IEC) plus large Langhans' giant cells (GC), and/or fibrinoid necrosis or caseation.

TT-BT = EC and IEC only; or IEC plus a small patch of fibrinoid.

BT = IEC plus some lc or small or foreign-body type GC.

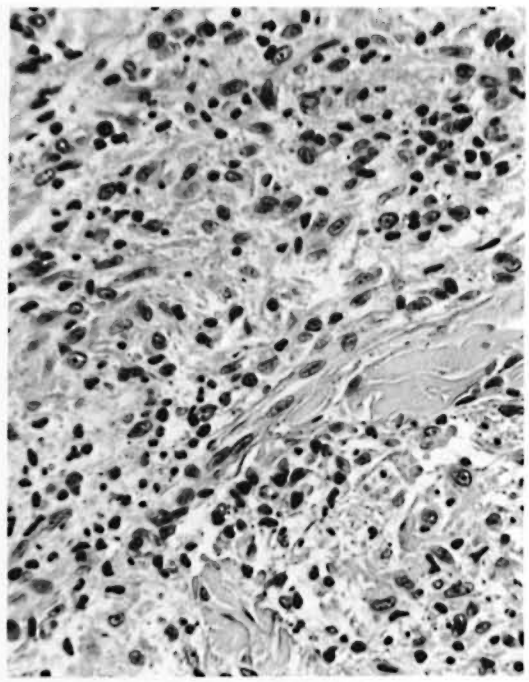

FIG. 3. Immature epithelioid cells and some lymphocytes in a skin lesion, BT, for comparison with Figs. 2 and 4 (H&E ×300).

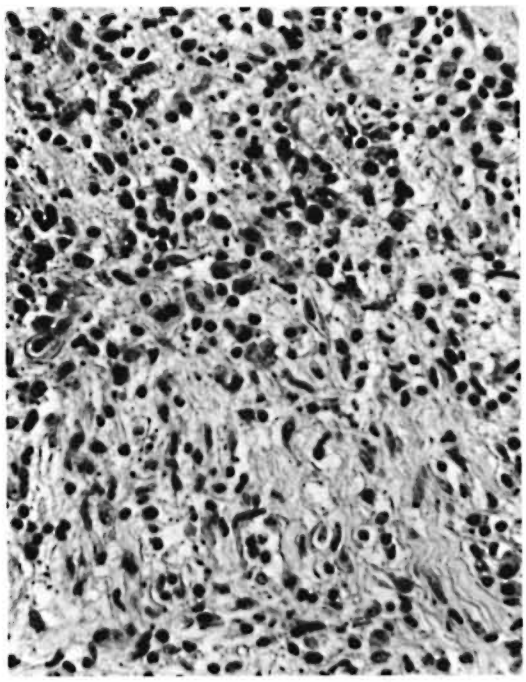

FIG. 4. BL nerve lesion from same case as Fig. 3. Fairly numerous lymphocytes but few macrophages (many AFB in Schwann cells) (H&E ×300).

BB = IEC only (BB); or mixed features of BT and BL (BT-BL), i.e., IEC plus macrophages (Mø) with some lc.
BL = Mø plus lc ++ (lc > Mø).
LLs = Mø plus lc + (Mø > lc).
LLp = Mø with bulky cytoplasm and scanty lc.

The more lepromatous the classification, the greater was the proportion of AFB in neural elements rather than in inflammatory cells. Macrophages might not be easy to identify in many cases (Figs. 4 and 5).

Lesions in reaction, characterized mainly by heavy edema, were classified on the same principles as above and designated accordingly, e.g., BT/R. Reactions in BB, BL, and LLs were all mild in this series of cases; they are not designated separately. All except one of the lesions placed for convenience in the BB group were, in fact, of the alternative BT-BL type.

The classification of the 42 cases, for nerve and skin, is shown in The Table.

Skin biopsies: granuloma fraction. The majority of biopsies showed good sized granulomas, indistinguishable from those of ordinary skin lesions, despite the fact that there was not invariably a clinical lesion at the site. Of the nine groups and categories, reacting and nonreacting but excluding indeterminate, seven gave mean granuloma fractions in the range 0.27 to 0.55 (the maximum possible being 1.0). By contrast, 11 cases of nonreacting BT gave mean granuloma fractions of 0.08 and the one case of BL, 0.02.

Biopsy index. The logarithmic index of bacilli (LIB) was markedly higher in nerve lesions than in skin lesions of the same classification (Fig. 6). This was true irrespective of any modifications introduced here for the classification of nerves. The LIB was also markedly higher in nerve biopsies than in concurrent skin biopsies, irrespective of any differences in classification between the two (The Table). The greatest difference was in the mid-borderline region; it was absent at the lepromatous end of the spectrum (Fig. 6); at the tuberculoid end, AFB were virtually absent. Only in 3 of 42 cases was the LIB greater in skin than nerves: one LLp and two BT/R.

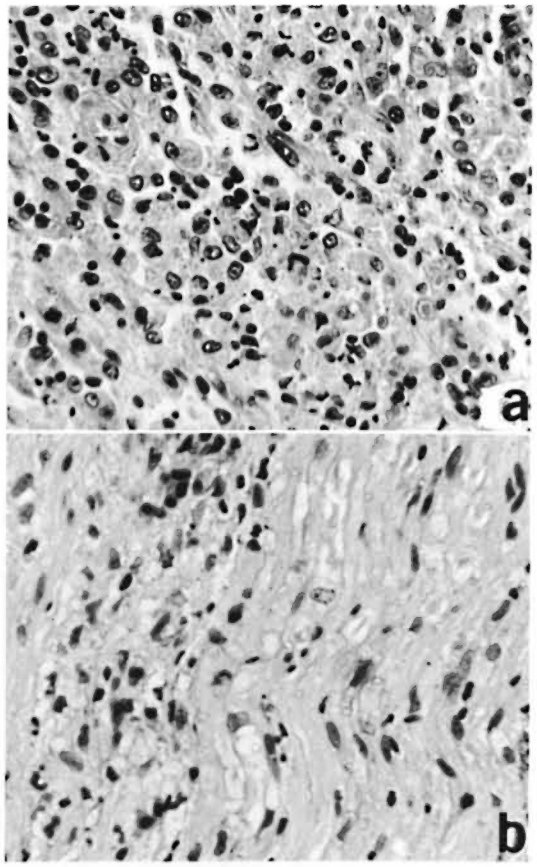

FIG. 5. a) Macrophage granuloma, LLs, in nerve; b) more usual pattern of LLs nerve lesion with few macrophages. Note swollen Schwann tubes, and band of endoneurium on the left (H&E ×300).

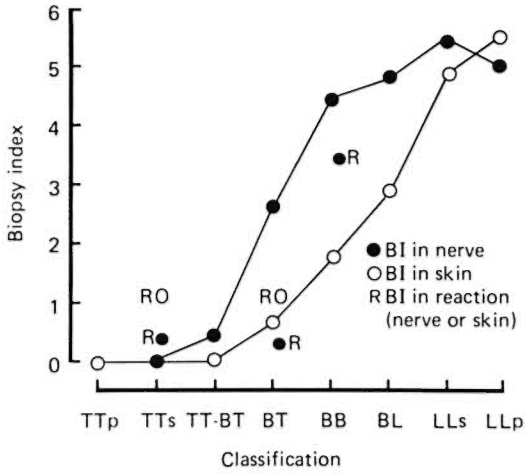

FIG. 6. Correlation between LIB of nerve and skin lesions. Reacting lesions are shown separately.

Correlation of classification: skin and nerve. The classification of skin and nerve lesions was not always identical (Fig. 7). Ignoring the two indeterminate cases, 20 out of the other 40 lay off the axis X–X, which represents identity of classification. The nature of the discrepant cases was examined and the results compared when nerve classification and skin classification were used as the base line. The mean size of the discrepancies of nerve against skin (taking skin as the base line) was 1.38 groups; that of skin against nerve, 1.43 groups. There was, therefore, no significant difference in size,

THE TABLE. *Correlation of the bacterial index (LIB) in nerve and skin lesions across the leprosy spectrum.*

Nerve class	No. cases	LIB nerve		LIB skin concurrent	Skin class	No. cases	LIB skin		LIB nerve concurrent
		Range	Mean				Range	Mean	
TTp	1	0	0	0	TTp	1	0	0	0
TTs	1	0	0	0	TTs	0	—	—	—
TTs/R	2	0–0.4	0.2	0	TTs/R	2	0–2	1.0	2.3
TT-BT	2	0–0.8	0.4	0	TT-BT	4	0	0	0.3
BT	11	1–3½	2.6	0.8	BT	10	0–2½	0.6	2.3
BT/R	4	0–2	0.6	0.2	BT/R	9	0–3½	1.0	2.6
BB	4	3–5	4.5	2.4	BB	4	0–2.8	1.7	5.3
BT-BL/R	1	3½	3.5	0.4	BT-BL/R	0	—	—	—
BL	6	4–5	4.8	1.9	BL	2	1.2–2.8	2.0	4.5
LLs	8	5–6	5.5	4.2	LLs	7	3.7–5.8	4.8	4.8
LLp	1	5	5.0	4.2	LLp	1	5.6	5.6	5.0
Idt	1	0	0	0	Idt	2	0	0	3.1
	42					42			

but the discrepant groups were unevenly distributed. When the axis X–X was bisected by the line Y–Y in such a way that the number of cases above and below Y–Y was equal (or as near as possible equal with 16 above, 19 below, and 5 on the line), it was seen that the distribution of cases in the four quadrants thus formed was 12 cases in C + D against 3 in A + B. This is because when skin lesions are taken as the base line the discrepancies above and below X–X are about equal, but when the nerve is taken as the base line the discrepancies above and below X–X are unequal. Thus, when nerve classification is compared to skin classification (skin as base line), the random variance in nerve classification is unpredictable; but when skin is compared to nerve (nerve as base line), the discrepancies show a definite trend. When nerve is tuberculoid (TTs or TT-BT) skin is less tuberculoid, and when nerve is borderline (BB or BL) skin is more tuberculoid. These relationships or classification ratios are brought out in Fig. 8. At the poles of the spectrum, there is no difference between skin and nerve. The only significant spike in Fig. 8b is due to a single biopsy.

If TT-BT had been omitted as a separate group the number of discrepant classifications would have been 18 instead of 20 out of the 40 cases. The mean size of the discrepancies would have been smaller, but there would still have been five cases in which the discrepancy was two groups, all of them due to the nerve being more lepromatous than skin, e.g., BL nerve and BT skin (Figs. 3 and 4). Combining the TTp and TTs groups and the LLp and LLs groups to make a five-group spectrum would not have further diminished the discrepancies.

Reactions. Seven nerve biopsies and 11 skin biopsies were considered to show definite reactions of the delayed hypersensitivity type or Jopling type 1 (The Table). Some of the other biopsies showed evidence of a less marked reactional tendency. Reactions in nerve and reactions in skin did not always correlate with one another, the total number of reacting patients being 14 (Fig. 7).

The LIB of reacting and nonreacting lesions did not show a universal correlation. In nerve lesions, the LIB was significantly lower in reaction in BT, and also lower in one case of BB; but in TTs the only AFB, though few in number, were found in reacting lesions (Fig. 6). In skin lesions, the LIB appeared to be higher in reaction in BT, which was the only group in which reacting and nonreacting lesions could be compared. Thus, the LIB of the reacting skin lesions was actually higher than in the reacting nerve lesions, although substantially lower than in nonreacting nerve lesions (Fig. 6). In 3 out of 10 cases, the LIB in the reacting skin lesions was 1.8 against 5.0 in the nonreacting nerve lesions.

DISCUSSION

It is of interest that some differences were found between the classifications of nerve and concurrent skin lesions in about half the cases, most of which would have been present on the usual five- or seven-group spectrum. This confirms very well the findings of Srinivasan, *et al.* ([24]) and, like them, we found that nerve lesions generally tended to be more lepromatous than skin lesions. However, there were exceptions, and the previous workers did not take into account the implications for the role of nerves in the pathogenesis of the infection. The present study presents some complex results which, individually, are open to a variety of interpretations. Collectively, we suggest that they point to one determining factor, namely, the level of antigen at the time of its immunological detection in nerve and skin, detection in nerve being delayed. The results to be considered are the following.

1. The bacterial index (LIB) was higher in nerve lesions than in concurrent skin lesions irrespective of any differences in classification. In itself, this is not unexpected. It is commonly interpreted as an expression of the affinity of *M. leprae* for nerves. However, the observation that the LIB was not higher in nerve than in skin in lepromatous patients is against such an explanation. It supports a similar finding in early lesions, in which it was noted that the optimum site for growth when immunity was low was the macrophage granuloma around the superficial blood vessels of the dermis ([15]). This study also demonstrated that the nerve was a favored site at the tuberculoid end of the spectrum, as expected. In the present study, however, this is not seen because bacilli are

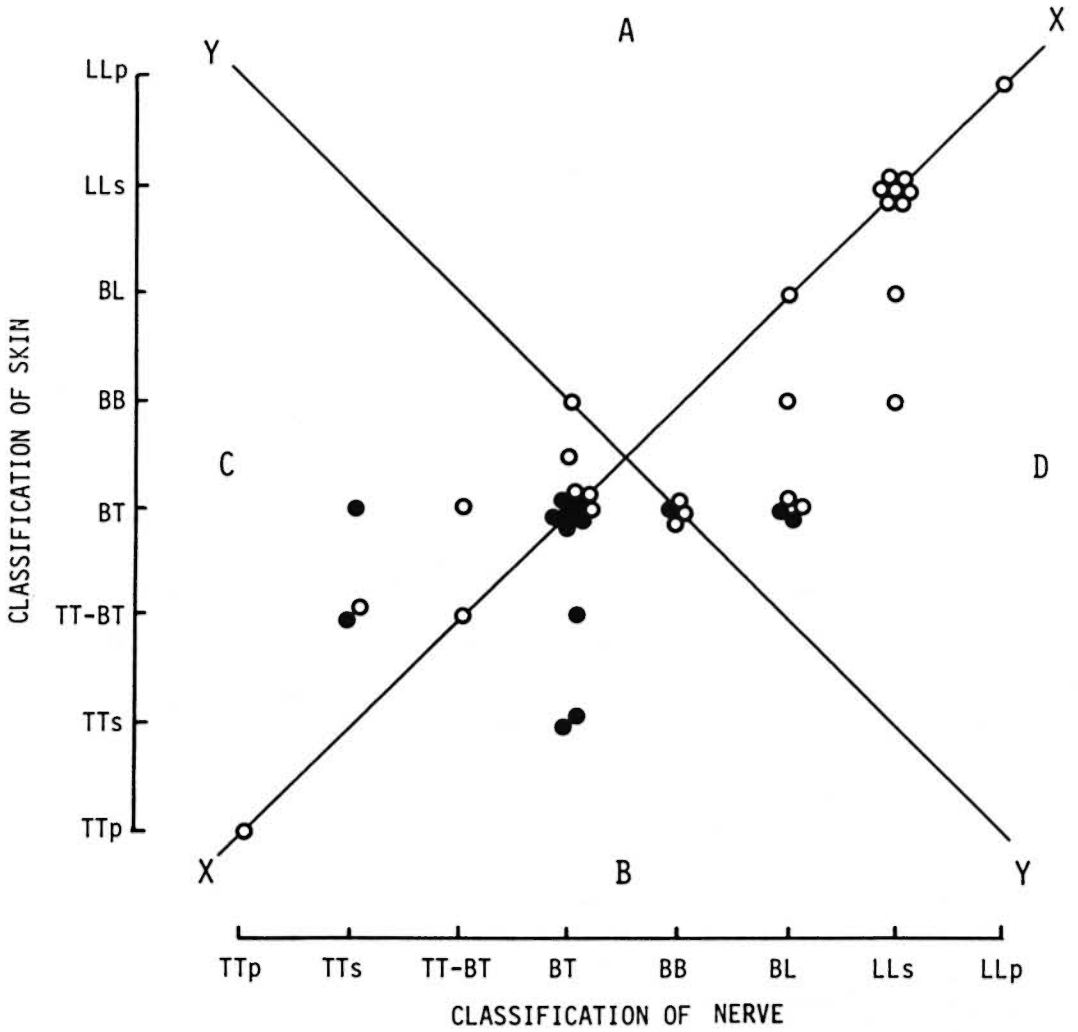

FIG. 7. Correlation between classification of lesions in nerve and skin. Nonreacting = ○; reacting = ●.

so scanty in tuberculoid lesions. The finding that the nerve is a preferred site for bacterial growth only in moderate or high-immune patients is in keeping with the protected site hypothesis, not with the affinity to nerves.

2. The LIB in each of the classification groups, except LL, was higher for nerve lesions than for skin lesions of the corresponding group, reactions excepted. This is explained by a delayed detection of bacilli and, consequently, greater build up of the load in nerves at any given level of response. To simplify, a tissue response that could detect 2+ bacilli in nonprotected sites might only be able to detect 3+ in nerves.

3. Discrepancies in the classification of nerve lesions compared to those of concurrent skin lesions were random; those of skin lesions compared to nerve lesions were not. Nerve lesions vary in a somewhat random manner, probably because of the unpredictability of the reactions which determine nerve classification. Skin lesions are not randomly discrepant because the skin, in established infections such as these, harbors the main mass of *M. leprae* in the body, and skin classification reflects better than nerve classification the immune state of the patient as a whole. When the nerve classification was TTs (or TT-BT), the skin was less tuberculoid, usually BT, which suggests a local upgrading in nerves relative to skin.

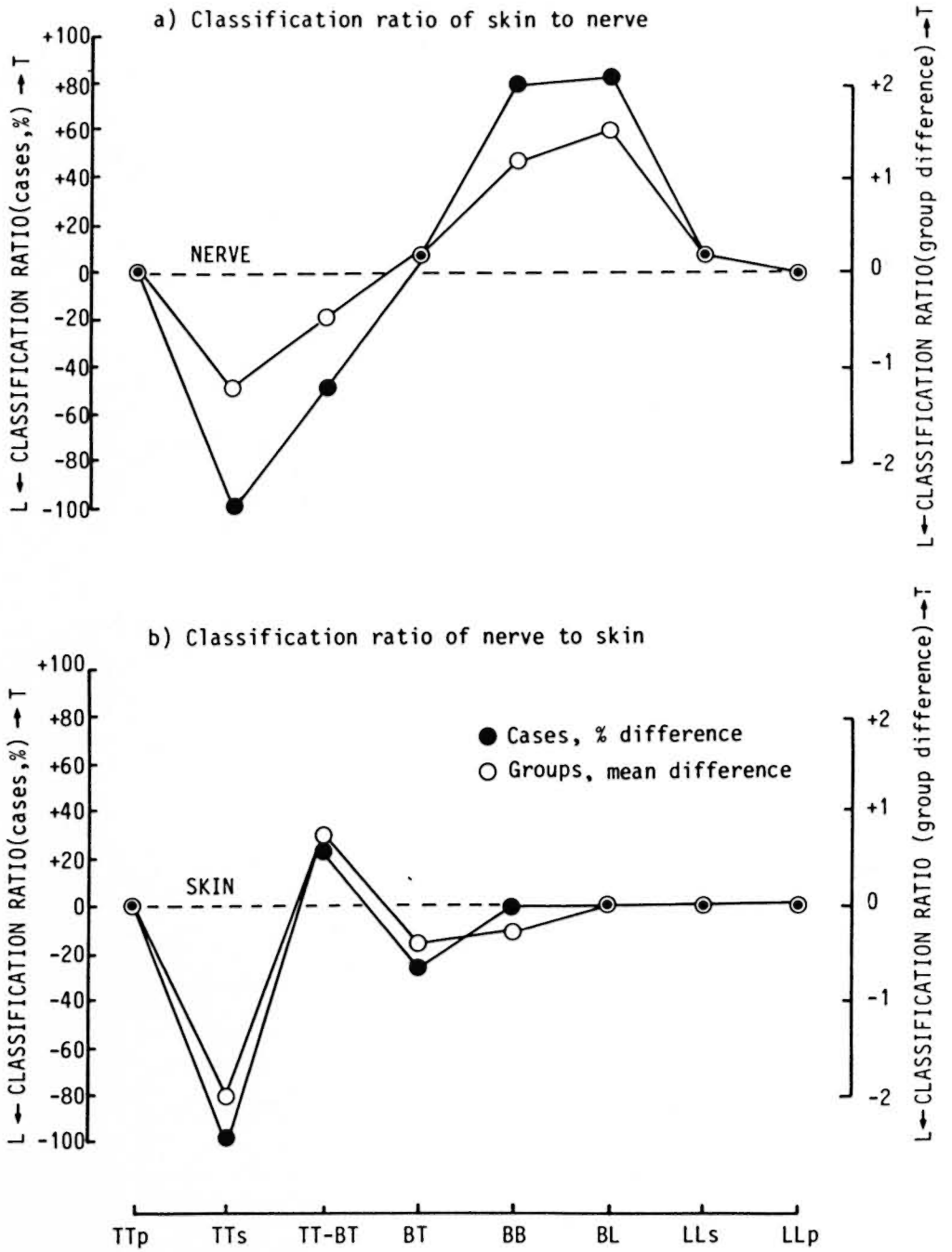

FIG. 8. Relationship between classification of nerve and skin lesions: a) skin in relation to nerve; b) nerve in relation to skin.

More commonly, when the nerve classification was BB or BL, the skin lesion was again BT, presumably because of a local downgrading in nerves relative to the skin. These conclusions are consistent with the bacterial loads in the reaction phase (see below). At the LLp and TTp poles, there is probably no difference between skin and nerve (the number of cases was very small), the reason being that these are primary

groups which do not originate by up or downgrading ([17, 21]).

4. The LIB of a reacting BT nerve was lower than that of a nonreacting BT nerve, yet in TTs the only bacilli were found in reacting lesions. As regards TTs, the explanation might be that the reaction takes place in a lesion, perhaps BT with scanty bacilli, and that histological upgrading occurs before the bacilli are completely eliminated. But when a BT lesion in nerve was itself in reaction it appeared that bacilli might be eliminated without a significant change in the classification. Reactions in nerves take place following immunological recognition of their antigen load ([2]). In a high-immune response, recognition occurs relatively early when the load in nerves is still fairly low. Recognition then is associated with a local flare up of hypersensitivity ([3]), and the nerve lesion becomes even more tuberculoid than the skin. Vice versa, with a relatively weak immune response, antigen build up in nerves is heavy at the time of recognition, and it is followed by local immunodepression. Thus, BT represents a critical point in the spectrum from which local up- or downgrading may occur in nerves following a reaction, although it is not clear to what extent this influences the course of the infection as a whole. Most cases originate as BT ([15]), which explains the present observation that the granuloma fraction in BT is small.

BT skin lesions in reaction were associated with heavy bacterial loads in nerves. In 3 out of 10 cases, the LIB in nerves was 5, and it seems likely that such cases would ultimately downgrade. This suggests that downgrading reactions may be more common than was thought to be the case and, at the same time, suggests an interpretation for a type of reaction that has always been difficult to account for immunologically ([6]). It would appear that a reaction of the delayed hypersensitivity type ([10]) in a borderline lesion that is ultimately associated with stagnation or downgrading ([20]) may represent persisting reactivity in the skin of a patient in whom the bacterial load in nerve prohibits upgrading. There is an impression of a small degree of local autonomy in the evolution of the local tissue response, but with the ultimate outcome determined by the mass of antigen present elsewhere.

These results help to substantiate the hypothesis that nerves function as protected sites which are only of real benefit to the leprosy bacillus under adverse conditions. The benefit occurs both in the early stage of the infection when the infection is not yet established ([8]), and later if there is a high-immune response. The organism then is unable to sustain itself at its optimal growth sites, preferably in macrophages in cool tissues with a good blood supply, e.g., in superficial dermis ([15]), where multiplication and immunological detection are both easier. Schwann cells are not professional antigen presenting cells, and bacilli are often situated free in the cytoplasm ([7, 23]). They are also long-lived cells, protected by a basement membrane from which antigen is slow to escape ([4, 12]). The environment within nerves is protected also by the perineurium ([4, 13]). Nerves are the most important but not the only protected site. The epidermal zone and arrector pili muscle are others, although they are less favorable than nerves to bacterial multiplication ([15]). However, it is not excluded that bacilli in these sites are not in fact situated in fine nerve fibers. The present results do not favor the hypothesis of an affinity between *M. leprae* and the Schwann cell or axon as a major factor in the pathogenesis of leprosy, although obviously there is an affinity in that *M. leprae* can sustain itself in nerves whereas other mycobacteria cannot, partly perhaps because it is less cytotoxic. Its uptake and growth in Schwann cells is greater than that of other mycobacteria *in vitro* ([11, 22]). Without such an affinity, nerves would be of no service to the leprosy bacillus as a protected site. But it is the latter consideration that is significant in pathogenesis.

As regards the practical application of these results, the small but significant differences between the classification of nerves and skin do not, on our interpretation, upset the validity of skin classification for the evaluation of the current immune state or for the management of the patient. The classification of nerves is important for the understanding of the pathogenesis of leprosy and, if available, might well be of prognostic value for individual patients. More needs to be known. The results emphasize a point that was apparent before, that paucibacil-

lary patients may harbor multibacillary loads in their nerves. It is now clear that this load is unpredictable.

SUMMARY

Biopsies of 42 concurrent nerve and skin lesions across the spectrum of leprosy were classified and compared histologically and bacteriologically. Observations were made as follows: a) The bacterial load was higher in nerve than in skin lesions of the same histological classification, and it was higher in nerve than in concurrent skin lesions irrespective of classification, although not at the lepromatous pole. b) There was some discrepancy between the histological classification of nerve and skin lesions in half the cases. Skin classification appeared to represent the general tissue response and, insofar as discrepancies existed, the skin classification was thought to give the better evaluation. Nerve classification was subject to minor variations of a random nature which were thought to be the outcome of local reactions due to the build up of antigen as a result of delayed recognition in an immunologically protected situation. Upgrading or downgrading ensued locally, depending on the level of antigen at the time of its detection. In such cases, the corresponding skin classification was usually BT, which occupied a critical point in the spectrum. A certain autonomy of the response between lesions of skin and nerve suggests an explanation for downgrading reactions. Although *Mycobacterium leprae,* alone among mycobacteria, has some sort of affinity for Schwann cells, it is the role of the nerves as protected sites which is fundamental to the course of the disease.

RESUMEN

Se estudiaron, clasificaron y compararon histológica- y bacteriológicamente las biopsias de 42 nervios y lesiones de piel concurrentes correspondientes a las varias formas del espectro de la lepra. Las observaciones se hicieron como sigue: a) la carga bacteriana fue mayor en los nervios que en la piel de la misma clasificación, aunque no en el extremo lepromatoso; b) hubo cierta discrepancia entre la clasificación histológica de los nervios y las lesiones en piel en la mitad de los casos. La clasificación de la piel pareció representar la respuesta tisular general y no obstante las discrepancias observadas, la clasificación de la piel permitió la mejor evaluación. La clasificación de los nervios estuvo sujeta a menos variaciones debidas al azar las cuales, pensamos, son el resultado de las reacciones locales debidas al reconocimiento tardío del antígeno en una situación inmunológicamente protegida. El mejoramiento o el empeoramiento de las lesiones apareció localmente dependiendo del nivel de antígeno al momento de su detección. En tales casos, la clasificación en piel correspondiente fue generalmente BT, la cual ocupó una posición crítica dentro del espectro. Una cierta autonomía de la respuesta entre las lesiones de piel y nervios sugirió una posible explicación a las lesiones de empeoramiento. Aunque el *Mycobacterium leprae* tiene cierta afinidad por las células de Schwann, es el papel de los nervios como sitios protegidos el factor fundamental del curso de la enfermedad.

RÉSUMÉ

On a classifié et comparé par des méthodes histologiques et bactériologiques les biopsies prélevées au niveu de 42 lésions combinées neuro-dermatologiques, relevant des différentes formes de la lèpre. Les observations ont été faites de la façon suivante: a) la charge bactérienne était plus élevée dans les lésions nerveuses que dans celles de la peau lorsqu'il s'agissait de lésions appartenant à la même classification histologique; cette charge était plus élevée dans les nerfs que dans la peau sans égard à la classification, encore que ceci ne fut pas le cas pour les lésions lépromateuses polaires; b) une discordance entre la classification histologique des lésions nerveuses et des lésions dermatologiques dans la moitié des cas. La classification des lésions de la peau paraissait refléter la réponse tissulaire générale; pour autant que des discordances existent, on estime que la classification dermatologique fournit une meilleure évaluation. La classification nerveuse peut subir des variations mineures dûes au hasard; on pense que ces variations sont en rapport avec des réactions locales dues à la production d'antigènes à la suite d'une reconnaissance tardive dans une situation de protection immunologique. Il en résulte des réactions progressives ("upgrading") ou régressives ("downgrading"), selon le taux de l'antigène au moment de sa détection. Dans de tels cas, la classification dermatologique correspondante était généralement BT, donc un carrefour crucial dans le spectre. Le fait que l'on ait observé une certaine autonomie de la réponse entre les lésions de la peau et celles des nerfs suggère une explication pour les réactions régressives ("downgrading"). Quoique *Mycobacterium leprae,* cas unique parmi les mycobactéries, témoigne d'une certaine affinité pour les cellules de Schwann, ce sont les nerfs, en tant que site protecteur, qui jouent un rôle fondamental dans l'évolution de la maladie.

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APPENDIX

The minor amendments introduced for the histological classification of nerves should be of practical value. They are not essentially new, being based on the same principles as the classification of tuberculoid skin ([17]). It is not proposed that the eight-group classification used here should become standard. It was useful for analysis, but the results would have been the same without it. The differentiation of mature and immature epithelioid cells requires experience as well as good technique. It is described in detail by Adams ([1]), and

will be the subject of a future report. In case of difficulty, mature epithelioid cells are almost invariably associated with either very many lymphocytes (TTp) or fibrinoid change (TTs). The latter is best demonstrated by Martius scarlet blue (MSB) stain, with which an orange-red color is specific. With familiarity, fibrinoid can be seen in hematoxylin-eosin preparations (although it is difficult to demonstrate in black and white photographs). MSB also helps in the identification of mature epithelioid cells.