THE VALUE OF THE HISTOLOGICAL CRITERION FOR THE CLASSIFICATION OF LEPROSY.

A STUDY OF REPORTS BY SEVERAL EXAMINERS OF THE SAME HISTOLOGICAL PREPARATIONS

R. Kooij, M.D.
Research Officer, Westfort Institution
Pretoria, Union of South Africa

According to the resolutions adopted by the Sixth International Congress, held in Madrid in October 1953, the criteria which bear on the classification of leprosy cases are: (1) clinical, (2) bacteriological, (3) immunological (the lepromin test), and (4) histopathological.

The committee on classification agreed unanimously, and in adopting the committee's report the congress as a whole concurred, that the basic criteria of primary classification should be *clinical*, comprising the morphology of the skin lesions and the neurological manifestations.

The scheme adopted recognizes two distinct types of leprosy, lepromatous (L) and tuberculoid (T), thus maintaining the concept of polarity. It also recognizes two groups of a lesser order, indeterminate (I) and borderline (B) or dimorphous. Type connotes the existence of clinically and biologically stereotyped features characterized by marked stability and mutual incompatibility. Group connotes less distinctive or positive characteristics, less stability, and less certainty with respect to evolution.

There are descriptions of these clinical types and groups, and the congress transactions also have recommendations for the reading of the lepromin reaction. There are, however, no descriptions of the histological pictures of typical lesions of types and groups, nor are there exact histological definitions of "lepromatous" and "tuberculoid." In practice, therefore, there is no unanimity on these matters.

For this reason I have recently submitted for examination a number of histological preparations, stained by hematoxylin and eosin, from cases of different forms of leprosy, to several men in certain countries who are familiar with the histopathology of skin lesions, certain of whom have had some experience with leprosy. The patients from whom these specimens derived had been classified clinically by Dr. A. R. Davison, medical superintendent of this institution. In alphabetic order the examiners were:

Dr. R. Camain, histopathologist of the Institut Pasteur, Paris (experience with leprosy when stationed at Dakar).

Dr. R. van Dam, histopathologist of the Binnengasthuis, Amsterdam.

Dr. B. Duperrat, histopathologist of the Hôpital St-Louis, Paris (where there is a leprosy department).

Prof. Dr. W. Lutz, professor of dermatology, Basel, Switzerland.

Dr. W. J. Pepler, histopathologist of the South African Institute for Medical Research, Johannesburg (where leprosy specimens are frequently examined).

Prof. Dr. J. R. Prakken, professor of dermatology, University of Amsterdam.

Dr. G. K. Steigleder, chief assistant of the University Clinic for Skin Diseases, Frankfurt am Main, Germany. (Head, Prof. Dr. O. Gans.)

TABLE 1.—*Summary of the reports of findings on histological specimens from 45 cases of leprosy, as reported by seven examiners.*

Case data[a]			Examiner's number and histological findings[b]						
No.	Bacteriology	Lepromin	1	2	3	4	5	6	7
Lepromatous leprosy **(9 cases)**									
12124	+	—	T	.....	L	L	T	T	L
12110	+	—	T	.....	N/L	L	L	L	L
11982	+	—	T	.....	.....	.....	.....	T+L	L
12177	+	—	N	L	.....	.....	.....	.....	N
12108	+	—	N	L	.....	.....	.....	.....	N
12243	+	—	T	T	.....	.....	.....	L	.....
12243[c]	+	—	N	N/T	.....	.....	.....	.....	N
12184[d]	+	—	N	N/T	.....	.....	.....	.....	N/T
12246	+	—	T	L+T	.....	.....	.....	.....	L
Borderline leprosy **(18 cases)**									
12041	+	—	N	L	L	L	L	T	L
12041[c]	+	—	N	N	N/T	N/T	T	T	N
12044	+	±	T	L	.....	L	.....	.....	L
12026[e]	+	+	T	T	T	T+L	T+L	T	T
12026[f]	+	+	.....	L	L+T	L+T	L+T	N	L
12112	+	+	T	T	N/T	L	L+T	T+N	N/T
12101	+	—	T	T	T	L	T	T	T
11760[g]	+	—	N	T	T/L	L	L/T	N/T	T+L
12147	—	—	N	N/T	.....	.....	N/T	N	N
12141	+	±	N	N+L	.....	.....	.....	N	N
12156	+	+	N/T	L	.....	.....	.....	N/T	N/T
12206	+	—	T	L	.....	.....	.....	.....	N
12182	+	—	N	N/L	.....	.....	.....	T	T
11999	+	—	N+T	L	.....	.....	.....	.....	N
11835	+	—	N/T	L+T	.....	.....	.....	.....	N
11774	—	—	N	N/L	.....	.....	.....	.....	N
12220	+	—	N	L	.....	.....	.....	.....	N
12233	+	—	N	L	.....	.....	.....	.....	N
Tuberculoid leprosy **(18 cases)**									
12040	—	+	N	N	N/T	N	N	N	N
12114	+	±	T	.....	T	N/T	N/T	T	T
11207	—	+	N	N/L	N	L+N	N	N	N/T
11898	+	+	T	T	T	L+T	T	T	T
690	—	+	T	T	T	T	T	T	T
10257	+	±	T	T	.....	.....	.....	T	T
12157	+	—	N	N/L	.....	.....	.....	N	N
11460	—	—	N	L	.....	.....	.....	N	L
12198	—	—	N	N/L	.....	.....	.....	.....	N
12196	—	—	N/T	N/L	.....	.....	.....	T	T
12209	—	+	T	T	.....	.....	.....	.....	T
12179	+	+	T	T+L	.....	.....	.....	.....	T
11869	—	—	N	T+L	.....	.....	.....	.....	N
12045	—	+	T	T+L	.....	.....	.....	.....	T
12217	+	+	T	T	.....	.....	.....	.....	N/T
12209	—	+	T	T	.....	.....	.....	.....	T
12210	—	+	N	N	.....	.....	.....	.....	N
12236	—	+	N+T	T	.....	.....	.....	.....	T

a For explanation, see text.

b T = tuberculoid; L = lepromatous; N = nonspecific; N/L (etc.) = the first condition with tendency to the second; T + L (etc.) = both conditions found.

c A second specimen from the same case as the preceding one, taken two weeks later with no treatment in the interval.

d This case was later classified as borderline.

e The first of two specimens from this case, of a macule on the trunk.

f The second specimen from the same case as the preceding one, taken two weeks later with no treatment in the interval, of a swollen earlobe.

g The histological diagnosis of this case, in another laboratory, was tuberculoid.

The intention of this investigation was to test the value of the histological criterion in classification. Consequently, no information was given the examiners concerning the clinical, bacteriological or immunological data of the cases; only Examiner No. 7 (Table 1) had this information in some instances. They were asked, after having examined a few sections, to state if they considered the histological picture to be tuberculoid, or lepromatous, or nonspecific.

The results of these examinations are given in Table 1. It will be seen that the specimens comprised 9 from clinically lepromatous cases, 18 from borderline cases, and 18 from tuberculoid cases, a total of 45. Not every examiner saw or reported on all of the specimens; in fact, none of them did, although two missed out on only one each, and another on only four.

Further about Table 1, the bacteriology column refers to findings in smears, not sections. The lepromin reaction was called positive if either the early (Fernandez) or late (Mitsuda) phase was positive. The numbers assigned to the examiners do not at all correspond to their order in the alphabetical list. As for the symbols signifying their reports which are not obvious, two letters separated by an oblique line, as for example N/L, signify the former condition with a tendency to the latter one; two letters connected by the plus sign (+) signify the finding of both histological pictures in the same section. In either case the finding is regarded as "mixed."

For the specimens from the 9 lepromatous cases, on which 33 reports were made, only 12 diagnoses were of "lepromatous." In 8 instances "tuberculoid" was diagnosed and in 7 instances "nonspecific"; mixed diagnoses were made 6 times, twice both lepromatous and tuberculoid together.

For the 18 borderline cases there were 87 reports: lepromatous 18 times, tuberculoid 21 times, and nonspecific 22 times. A mixture was indicated in the largest number of all, 26 reports, 8 of them signifying both tuberculoid and lepromatous.

For the 18 tuberculoid specimens there was a total of 77 reports, 37 of them tuberculoid, 22 nonspecific, and 2 lepromatous. Mixed was reported 16 times, in 4 instances lepromatous and tuberculoid together.

These data on results are assembled in Table 2.

TABLE 2.—*Summary of the examiners' histological classification of specimens, by clinical classification of cases.*

Clinical classification of cases	Examiners' histological classification of specimens				Total
	Lepromatous	Tuberculoid	Nonspecific	Mixed	
Lepromatous	12	8	7	6	33
Borderline	18	21	22	26	87
Tuberculoid	2	37	22	16	77
Total	32	66	51	48	197

In Table 3 the histological reports have been tabulated in relation to the bacteriological findings and the results of the lepromin reaction—information which was not available to the examiners. Not much correlation can be found with the bacteriological status of the cases, and there are obvious discrepancies with the immunological status.

TABLE 3. *Correlation of the examiners' histology findings with the bacteriology and immunology (lepromin reaction) of the cases.*

Histological findings	Bacteriology		Immunology		Total
	Positive	Negative	Positive	Negative[a]	
Lepromatous	30	2	4	28	32
Tuberculoid	47	19	34	32	66
Nonspecific	27	24	14	37	51
Mixed	35	13	21	27	48
Total	139	58	73	124	197

a Including 4 doubtful (±) readings.

From these figures we may conclude:

1. That different cases of the same type or group of leprosy may show different histological pictures, and even the same section may show both lepromatous and tuberculoid changes.
2. That the investigators differed, sometimes markedly, in their opinions on the same section.
3. That one cannot exclude the diagnosis of leprosy on the finding of a nonspecific histological picture.
4. That when the histological picture is not in agreement with the classification based on the other criteria, one does not necessarily have to change the classification.
5. That agreement of the histology with clinical criteria of a definite type or group of leprosy gives support, and should be helpful in doubtful cases.

COMMENT

It is not logical in a classification based on four criteria to use terms derived from one of them, as in this case they refer to the histological one. This applies particularly when, as in leprosy, the most weight is put on the clinical criteria.

In my opinion one must drop these histological terms for the general classification and use names not related to any of the basic criteria. In the meantime, until unanimity is achieved, we must continue using the terms adopted by the Madrid congress.

The histological investigation is important, especially in doubtful cases.

It is also important for scientific purposes, to aid in the understanding of the processes.

Judgment of histological specimens can probably be improved by defining more accurately the histological pictures to which the terms "tuberculoid" and "lepromatous" are applied, and also the different cells involved—the Virchow cell, the foamy cell, and the vacuolated hydropic epithelioid cell. The significance of the location of the infiltrate with regard to the epidermis must be further investigated by means of serial sections. Some authors, among them Cochrane, state that in tuberculoid lesions the infiltrate presses up against the epidermis, but that in lepromatous lesions there is a free subepidermal zone.

Study of changes in the nerves, and the staining of the bacilli, fat, collagen, elastin and reticulin, may also be helpful in doubtful cases.

It must be remembered that the histological section represents only a small piece of the lesion, and that other sections of the same lesion may be different. Sections from other lesions may also differ. The earlobe, especially, often differs histologically from lesions of other parts of the body (see Table 1, second section, Case 12026). Therefore the earlobe is not suitable for this purpose, as Wade has pointed out.

Not all individuals of each clinical type or group are identical, so it is not to be expected that the four criteria will be identical in each type. In classifying a case we find it useful to express the criteria as a formula. Thus a straightforward tuberculoid case would be negative (–) bacteriologically, tuberculoid (T) clinically, positive (+) immunologically, and tuberculoid (T) histologically—expressed in an abbreviated form as – T + T. A lepromatous case would be + L – L. Cases could still be called tuberculoid that showed the formula – T + N (N denoting that the histology was nonspecific). Multiple combinations are possible. (The indeterminate type is left out of consideration in this article because it seldom occurs in South Africa). It would lead to a better understanding of cases if the formulas were used in scientific publications.

I have endeavored to show that no single one of the four criteria is absolute in itself, but that a close approximation to the truth can be obtained by using all four. It must be pointed out that in this inquiry the histological criterion did not get its optimal chance, because the majority of the examiners did not have much experience in the histology of leprosy. They were chosen, however, in order to obtain judgments on purely histological grounds. For some of them, too, the time of examination was rather short. In any case, from the results obtained, one may conclude that the histology of leprosy, even for these competent histopathologists, was very difficult. The results would probably have been better if they all had had much previous experience with leprosy. Nevertheless, one can expect great discrepancies under any condition. By chance, an outstanding leprologist examined histological specimens from a number of our leprosy patients. His results were no better; in fact, they were rather worse.

SUMMARY

There are reported the results of a study of the same histological preparations from cases of leprosy by several histopathologists from several countries whose experience has been with general dermatological material, few having had any experience at all with leprosy material.

There were great differences in opinion, showing that the judgment of the histopathology of leprosy is very difficult. The practical consequences are stressed.

RESÚMEN

Preparaciones histológicas procedentes de casos de lepra fueron examinadas por varios histopatólogos familiarizados con el material dermatológico general, pero dotados de poca experiencia con material leproso. No se suministraron datos de los casos a los examinadores, a fin de que sus dictámenes se basaran exclusivamente en la histopatología.

Los casos, clasificados clínicamente, con datos bacteriológicos e inmunológicos (reacción de la lepromina), eran: 9 lepromatosos, 18 colindantes y 18 tuberculoideos. El número de examinadores que dictaminaron sobre los distintos ejemplares varió sobremanera, de todos los siete (10 ejemplares) a no más de tres (22 ejemplares); en conjunto hubo 197 dictámenes sobre los 45 cortes.

Las relaciones entre los diagnósticos por clasificación clínica y los hallazgos histológicos comunicados por los examinadores aparecen en las tablas; y también la correlación de los hallazgos histológicos y el estado bacteriológico e inmunológico de los casos.

Hubo amplias diferencias entre los dictámenes relativos a algunos de los ejemplares y discrepancias notables dentro de los grupos clínicos. Dedúcese, entre otras cosas, que las grandes diferencias de opinión demuestran que es muy difícil juzgar la histopatología de la lepra.