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Certainty Levels in the Diagnosis of Leprosy[1]

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Of fundamental importance in any study is a clear definition of a "case" of the disease under investigation. The more difficult and controversial the diagnosis, and the more variation there may be in methods of ascertainment, the more important is this step of clarifying case criteria.

Ideally, a case definition should state explicitly all criteria which lead to the inclusion of a particular individual into a defined category. Although a case definition should be clear and acceptable to experts in the field, it need not necessarily be universally applicable. This is true insofar as the criteria used to define a case will have to suit local circumstances and will depend on the types of information and staff available. Case definitions may also differ according to their purpose. For example, a disease control program must consider the implications of its case definition for decisions concerning treatment, whereas this may not be of major concern for an epidemiological research project. In the latter circumstance, diagnostic specificity is often of particular importance. The inclusion of false-positives biases relative risk measures towards unity, thereby obscuring risk factors under study ([2, 11]).

Recognition of the important implications of case definitions has led recently to attempts to assign levels of certainty to the diagnosis of a number of different diseases. For example, a recent study of childhood infections in Kenya considered the diagnosis of pertussis as "unlikely," "possible," "likely," or "definite" on the basis of a scoring system ([13]). And the Expanded Programme of Immunization has produced guidelines according to which a diagnosis of measles, neonatal tetanus, polio, or childhood tuberculosis may be graded as "suspect," "probable," or "certain" ([3]).

It is widely recognized that the diagnosis of leprosy is often difficult. Given this difficulty, it is surprising that few publications in the leprosy field specify precisely the criteria upon which diagnoses are made. It has even been commented that the absence of clearly stated case definitions calls into question much of the leprosy literature insofar as it renders results uncomparable and unreproducible ([4, 8]).

We have become acutely aware of the difficulty of defining a "case" of leprosy in the course of the Lepra Evaluation Project (LEP), a total population epidemiological study in Karonga District, Northern Malawi ([10]). The clinical evidence was often too meager for the diagnosis of leprosy to be established, and yet too suggestive for it to be precluded. Keeping unresolved "suspects" on observation for long periods proved to be expensive and impractical due to frequent changes of residence. Although it was hoped initially that histopathological information could resolve uncertain diagnoses, it was found that many histopathological results were themselves inconclusive. Findings were often "compatible" with clinical leprosy but by no means conclusive, and might in fact have been due to some other skin disease ([7]). In addition, we became increasingly aware of the problem of false-negative histopathology results in individuals whose clinical findings had been overwhelming or in suspects whose follow-up showed clear signs of leprosy both clinically and histopathologically.

These experiences have led us to develop a procedure for grading the degree of confidence with which it can be held that a diagnosis of leprosy is in fact correct. According to this system, individuals in whom clinical leprosy is suspected are allocated to one of four groups: a) a "narrow" (certain leprosy) group in which the diagnosis of leprosy should be almost invariably (>99%) correct; b) a "middle" (probably leprosy)

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TABLE 1. *Criteria for assignment of levels of clinical certainty.*

Typical skin lesion(s)	Definite anesthesia in lesion(s)	Definite nerve enlargement (no history of trauma)	Typical sequelae of (leprosy) neuropathy	Clinical certainty	Code
Yes	Yes	Yes	—[a]		
Yes (or slightly less than typical)	—	Yes	Yes	Certain	5
Yes	Yes	—	—		
Yes	—	Yes	—		
Yes	—	—	Yes	Extremely likely	4
—	—	Yes	Yes		
Yes (on face)	—	—	—		
Yes	—	—	—		
Slightly less than typical	Yes	—	—	Most likely	3
—	—	Yes	—		
Less than typical	—	—	—	To be considered seriously	2
Untypical	Yes	—	—		
—	—	—	Yes		
Untypical lesions for which no other diagnosis can be made	—	—	—		
—	—	Slight nerve enlargement	—	Possibly	1

[a] (—) indicates that the sign is not clearly present, or not present at all.

group in which we expect that most of the individuals included are or were actual cases of clinical leprosy; c) a "wide" (possibly leprosy) group which may contain only a small proportion of individuals with actual clinical leprosy; and d) an "out" (not leprosy) group, in which the initial suspicion of leprosy is discarded.

Our method for assignment of these overall levels of certainty in the diagnosis of leprosy is presented in this paper.

SOURCES OF INFORMATION

The basic aims and procedures of the Lepra Evaluation Project (LEP) are described elsewhere ([10]). For the purposes of this presentation, it may be noted that the project began in 1979 as a total population epidemiological survey in Karonga District, Northern Malawi. In the course of the survey, 112,000 individuals were examined for signs of leprosy by paramedical Leprosy Control Assistants (LCAs). All newly found suspects were seen also by a Medical Officer (JMP or, on a few occasions, Dr. Gjalt Boerrigter). Slit-skin smears were taken by the LCAs, and biopsies were taken by the Medical Officer. In addition, the LEP had access to all records of cases who had been treated by the Lepra Control Project (LCP), which had been in the district since 1973 ([1]). Thus, there were several types of information on which to base the overall certainty of a diagnosis of leprosy:

Levels of clinical certainty. When examining a suspect, the Medical Officer assigned a code describing the strength of the clinical evidence in favor of leprosy. The criteria for assigning these levels of clinical certainty are given in Table 1. For example, the clinical certainty was considered "extremely likely" if there was: a) a skin lesion of typical appearance (for paucibacillary leprosy) and definite anesthesia to light touch within the lesion; or b) a skin lesion of typical appearance without evidence of anesthesia but with a definitely enlarged nerve (near or far from the lesion); or c) a skin lesion of typical appearance without evidence of anesthesia or nerve enlargement, but in a person with typical sequelae of leprosy neuropathy; or d) a definitely enlarged nerve together with signs of damage to that nerve; or e) a skin lesion of typical appearance (for paucibacillary leprosy) without evidence of anesthesia but on the face.

No clinical certainty level was assigned if a positive (bacterial index [BI] >2 from at

TABLE 2. *Protocol for coding of histopathological certainty as used in the Lepra Evaluation Project.*[a]

Diagnosis code	Meaning
1	"Leprosy confirmed beyond reasonable doubt" (or "almost certain but slight element of doubt remains").
2	"Consistent with but not diagnostic of leprosy" (or "pathological and possibly due to leprosy, but lacking specific diagnostic criteria").
3	"Definitely pathological but completely nonspecific," or "normal or near normal tissue."
4	"Pathological but indicative of specific disease other than leprosy."

[a] This is an abbreviated version of the protocol which has been described in full in references 5 and 7.

TABLE 3. *Agreement code used when reviewing Lepra Control Project records.*

Code	Meaning
1	Agree with original diagnosis of leprosy.
2	Original diagnosis doubtful.
3	Original diagnosis of leprosy very unlikely.
4	Unknown (insufficient information available).

least one site) slit-skin smear result was already known at the time of examination. In addition, no clinical certainty level was assigned to patients who were currently or previously under treatment by the LCP, unless there was a suspicion of relapse. In such cases the assigned level of clinical certainty referred to the relapse, and not to the original diagnosis. Patients who had received treatment elsewhere, that is, by an institution or service other than the LCP, were assigned a level of clinical certainty only if there were sufficient findings on which to base it. Since such patients were not routinely examined by the Medical Officer, their clinical certainty was often assigned retrospectively, on the basis of findings reported by the LCAs. This was the only circumstance in which a clinical certainty was assigned without the patient being examined in person by the Medical Officer.

Slit-skin smear results. Slit-skin smears were taken by the LCAs or the Medical Officer if there was any suspicion of multibacillary leprosy ([10]). Two smears were usually taken from the earlobes and two from the lesion or lesions. The results were coded both as average BI ([12]) and as percentages of solids, fragments, and granules.

Histopathology results. Skin biopsies were obtained by the Medical Officer from >90% of all leprosy suspects newly found in the course of the LEP after 1980. These were routinely taken using a 4-mm punch (Steiffel Laboratories) from the most active part of a lesion ([7]). Occasionally, a split-nerve biopsy was obtained if the only sign of leprosy was an enlarged peripheral sensory nerve. If a biopsy was not taken, the reason for its omission was recorded. Biopsies were also obtained from suspected relapses, but only very occasionally from patients while still on treatment. In the latter cases, the biopsies were usually taken because it was suspected that the original diagnosis had been wrong. The processing of these biopsies is described elsewhere ([7]). The histopathologist's report was provided in standard form as shown in Table 2.

Repeat biopsies were taken if an initial negative or inconclusive histopathology result contrasted markedly with the level of clinical certainty and antileprosy treatment had not yet been initiated on the basis of the clinical findings. Repeat biopsies were also taken if an initial negative or inconclusive biopsy result was consistent with the assigned level of clinical certainty but the individual self-reported or was found later with additional signs suggestive of leprosy.

Lepra Control Project (LCP) records. The LCP records contained clinical findings, classification, and smear results (smears having been taken only if multibacillary leprosy had been suspected) on all cases registered by the LCP since it began in the district in 1973. Many also contained review notes and additional comments by the LCP Medical Officer (Dr. Gjalt Boerrigter). These records were reviewed by JMP, and a retrospective "agreement code" was assigned with reference to the original diagnosis of each case. These codes and criteria are given in Table 3.

History given by patient. All individuals with clinical signs of leprosy were asked for any history of antileprosy treatment. In addition, a number of individuals without signs

volunteered such information. All reported places of prior treatment were recorded, and the most reputable such institution was coded.

All of this information was recorded on specially designed forms, coded, and analyzed on computers at the London School of Hygiene and Tropical Medicine. Several different methods of amalgamating the variables were explored over a period of 4 years. The procedure ultimately developed is presented below.

ASSIGNMENT OF CERTAINTY LEVELS

The Figure is a flowchart illustrating the steps used (by the computer) to assign each suspect—excluding relapses—to the "narrow," "middle," "wide," or "out" group. The procedure for relapses is identical, except that it neglects all information collected prior to the date when the relapse was first suspected. Although the basic logic should be clear from the flowchart, it is described briefly below. Numbers on The Figure refer to decision points as described in the text.

Any LCP or LEP slit-skin smear result with an average BI >1 places the individual automatically in the narrow (N) group (point 1). In the absence of slit-skin smear results, or if the average BI is ≤ 1, histopathology results are then considered. First, any histopathology result with a code 1 (Table 2) places the individual in the narrow (N) group (point 2). If an individual has no code 1 biopsy results, the computer searches for any histopathology result with conclusive evidence solely of another skin disease (Table 2, code 4). If found, the individual is assigned to the out (O) group (point 3). If not, but there are two or more nonspecific biopsy results in the presence of some clinical activity, then the individual is still assigned to the out (O) group (point 4).

The logic of interpreting biopsy and clinical results then differs according to whether or not the individual was on treatment at the time the biopsy was taken (points 5, 6, and 7). Any individuals on treatment with nonspecific biopsy results (Table 2, code 3) are assigned according to the review of their records (point 8).

Individuals from whom no biopsy was taken, or from whom the biopsy was unsatisfactory, are considered separately, as shown on the left side of The Figure. If the individual was known to the LCP, then the clinical certainty is assigned on various combinations of current clinical signs and record review (points 9, 10, and 11). It will be noted that the reason for a biopsy not having been taken from inactive cases is considered here—if the biopsy was considered unnecessary because of typical sequelae of neuropathy then the overall certainty is higher than if there was no residual evidence or only inactive lesions (point 12).

Lastly, there is a group lacking biopsies and not previously known to the LCP, in which case the overall certainty is assigned on the basis of clinical signs, if present (point 13), or on history of past treatment, if clinical signs are not present (point 14).

ILLUSTRATION

Table 4 shows a breakdown of the diagnostic certainties assigned to 2292 leprosy patients and suspects ascertained in the first LEP survey, illustrating the frequency of allocations at each point in the decision tree (The Figure). Relapses are excluded from this tabulation. Of the 2292 suspects, 1043 (45.5%) were allocated into the narrow group. The main reasons for this allocation were definite histopathological evidence of leprosy (410, 39.3%); typical sequelae of leprosy neuropathy (302, 28.9%); strong clinical evidence alone (167, 16.0%); and bacteriological evidence of leprosy (107, 10.3%). Of the 167 who were graded on clinical grounds only, 67 were previously treated and thus not new suspects, while 100 were newly found suspects. The majority (57) of these 100 new suspects were found by the LEP in 1979 and 1980, before it was attempted to take biopsies as a matter of routine. The majority (455 out of 744) of individuals allocated to the middle group were registered patients with no remaining evidence of leprosy and no history of a positive slit-skin smear (decision point 10). These patients are discussed further below.

VALIDATION

Validation of diagnostic criteria such as are described here presents a difficult problem, insofar as there is no fully reliable standard against which they can be assessed. On

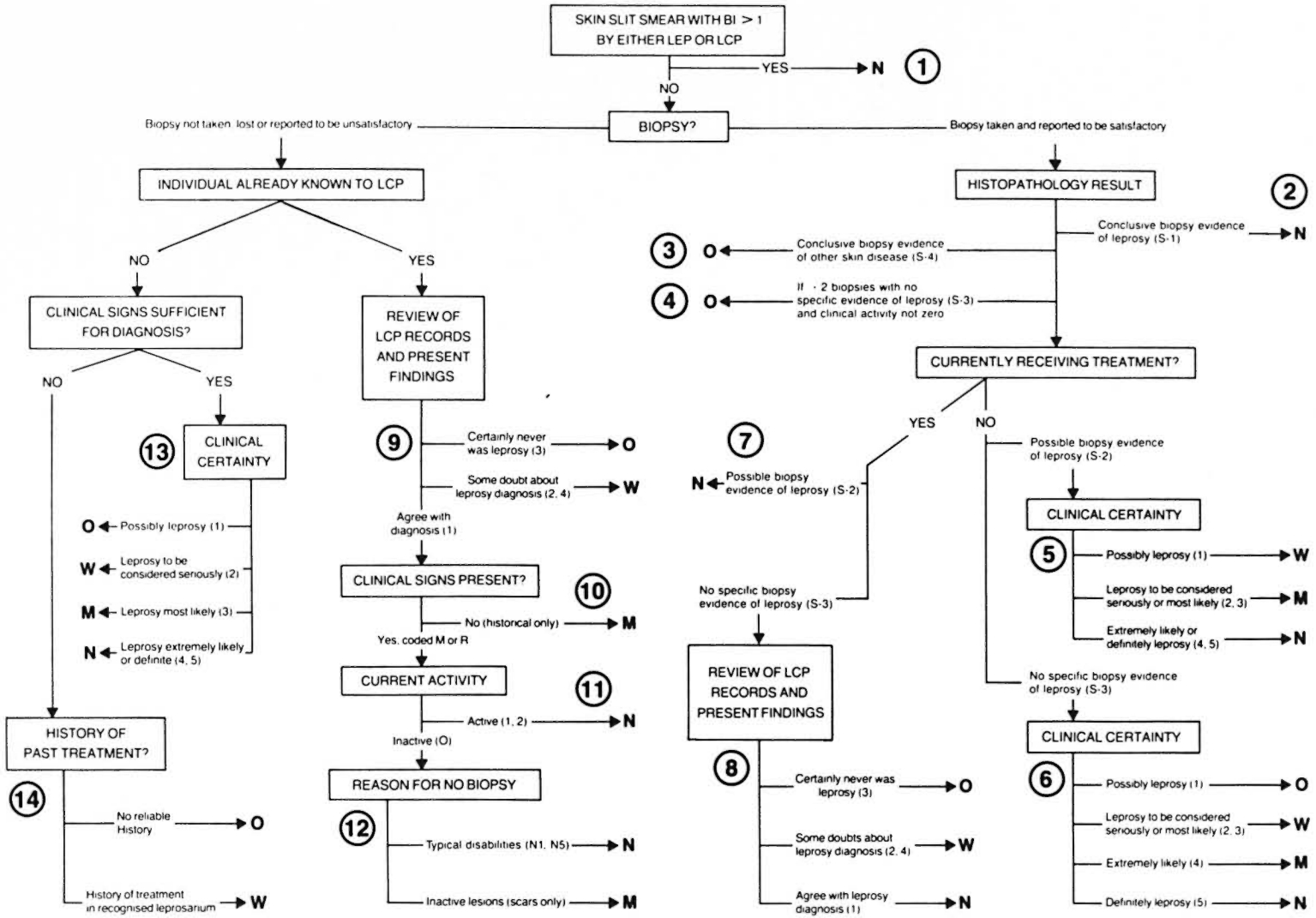
SKIN SLIT SMEAR WITH BI > 1 BY EITHER LEP OR LCP
YES → N (1)
NO
BIOPSY?
Biopsy not taken, lost or reported to be unsatisfactory
Biopsy taken and reported to be satisfactory
INDIVIDUAL ALREADY KNOWN TO LCP
NO
YES
CLINICAL SIGNS SUFFICIENT FOR DIAGNOSIS?
NO
YES
(13) CLINICAL CERTAINTY
O ← Possibly leprosy (1)
W ← Leprosy to be considered seriously (2)
M ← Leprosy most likely (3)
N ← Leprosy extremely likely or definite (4, 5)
HISTORY OF PAST TREATMENT?
(14)
No reliable History → O
History of treatment in recognised leprosarium → W
REVIEW OF LCP RECORDS AND PRESENT FINDINGS
(9)
Certainly never was leprosy (3) → O
Some doubt about leprosy diagnosis (2, 4) → W
Agree with diagnosis (1)
CLINICAL SIGNS PRESENT?
(10)
No (historical only) → M
Yes, coded M or R
CURRENT ACTIVITY
(11)
Active (1, 2) → N
Inactive (O)
REASON FOR NO BIOPSY
(12)
Typical disabilities (N1, N5) → N
Inactive lesions (scars only) → M
HISTOPATHOLOGY RESULT
(2)
Conclusive biopsy evidence of leprosy (S-1) → N
(3) O ← Conclusive biopsy evidence of other skin disease (S-4)
(4) O ← If < 2 biopsies with no specific evidence of leprosy (S-3) and clinical activity not zero
CURRENTLY RECEIVING TREATMENT?
YES
NO
(7)
N ← Possible biopsy evidence of leprosy (S-2)
No specific biopsy evidence of leprosy (S-3)
REVIEW OF LCP RECORDS AND PRESENT FINDINGS
(8)
Certainly never was leprosy (3) → O
Some doubts about leprosy diagnosis (2, 4) → W
Agree with leprosy diagnosis (1) → N
Possible biopsy evidence of leprosy (S-2)
CLINICAL CERTAINTY
(5)
Possibly leprosy (1) → W
Leprosy to be considered seriously or most likely (2, 3) → M
Extremely likely or definitely leprosy (4, 5) → N
No specific biopsy evidence of leprosy (S-3)
CLINICAL CERTAINTY
(6)
Possibly leprosy (1) → O
Leprosy to be considered seriously or most likely (2, 3) → W
Extremely likely (4) → M
Definitely leprosy (5) → N

TABLE 4. *Breakdown by certainty level and organogram decision point (The Figure) of 2292 individuals in whom leprosy had been diagnosed before—or was suspected during—the first Lepra Evaluation Project survey.*

Decision point	Description	Certainty level				Total	%
		N	M	W	O		
1	Average BI > 1	107	—	—	—	107	4.7
2	Conclusive biopsy evidence	410	—	—	—	410	17.9
3	Other skin disease	—	—	—	14	14	0.6
4	Two negative biopsy results	—	—	—	2	2	0.1
5	Inconclusive biopsy result	26	75	33	0	134	5.8
6	No biopsy evidence of leprosy	2	25	142	93	222	9.7
7	Inconclusive biopsy, on treatment	0	—	—	—	0	
8	No biopsy evidence, on treatment	2	—	0	0	2	0.1
9	Registered cases, diagnosis doubtful	—	—	114	4	118	5.1
10	Registered cases, no signs left	—	455	—	—	455	19.8
11	On treatment, still active	27	—	—	—	27	1.2
12	Inactive lesions and/or sequelae of neuropathy left	302	143	—	—	445	19.4
13	Clinical certainty grading only	167	46	18	17	248	10.8
14	History of treatment	—	—	50	58	108	4.7
Totals		1043 (45.5%)	744 (32.5%)	317 (13.8%)	188 (8.2%)	2292 (100%)	

the other hand, the validity of the certainty levels can be tested in relation to a specific risk factor which is recognized to be associated with leprosy. Table 5 shows the protective efficacy of BCG against N, M, W, and O cases, as derived by case control analyses by methods described elsewhere ([6]). The lower the specificity, i.e., the lower the percentage of true cases in a certainty group, the lower is the observed protection imparted by BCG (χ^2, for trend = 9.24; $p < 0.005$).

DISCUSSION

The procedure described in this paper illustrates one way of tackling the difficult problem of diagnostic criteria for leprosy. The complexity of the method reflects the difficulty of diagnosing leprosy and the need to take into consideration several different types of information. In our case, it also reflects the availability of a considerable amount of relevant information on computer files where it can easily be accessed and analyzed.

The validity of the method can be supported both on intuitive grounds and by relating cases classified into different groups to a recognized risk factor. The correlation between protective efficacy of BCG and overall certainty level (Table 5) provides supportive evidence that the certainty level is a direct reflection of diagnostic specificity ([2, 6, 11]). The lower vaccine efficacies in lower certainty groups occur insofar as BCG's effect is against leprosy per se, and not against other conditions which are included in increasing proportions in the M, W, and O groups. These results also suggest that the difference in specificity between successive groups is not uniform. The greatest difference in vaccine efficacy occurs between the middle (M) and wide (W) groups. This indicates that the specificity of the middle group is quite high and that of the wide group, quite low. More direct validation

←

THE FIGURE. Organogram showing how individuals are allocated into "narrow" (N), "middle" (M), "wide" (W), and "not leprosy" (O) groups. Numbers indicate decision points discussed in the text.

TABLE 5. *Efficacy of BCG in protecting against clinical leprosy, according to level of certainty of the diagnosis.*[a]

Certainty group	No. cases	Protection imparted by BCG	
		Estimate	95% Conf. int.[b]
N	213	37%	16% to 53%
M	47	31%	−36% to 65%
W	58	2%	−122% to 56%
O	47	−4%	−130% to 53%

[a] Estimates derived by stratified (for age, sex, and schooling status) case control analysis as described in reference 6. Cases restricted to those registered during first Lepra Evaluation Project survey, after 1 January 1980. Controls matched for age, sex, and schooling status.

[b] 95% Confidence interval.

would require some alternative—and not yet available—test of proven and very high specificity.

Although intuitively reasonable, the structure and criteria of this system are arbitrary. There are several decision points at which a different allocation might be used. For example, one might argue that the "narrow" group includes subsets with varying strengths of evidence. An average BI > 1 on its own may seem to be stronger evidence of leprosy than either a histopathology result with a code 1 or an "extremely likely" clinical certainty level associated with an inconclusive biopsy result. The latter criteria might permit a small number of non-leprosy cases to be included in the "narrow" group. However, the procedure described here was decided upon so as not to sacrifice too much sensitivity for only a slight increase in specificity.

It may be noted that most of the patients known to the LCP were allocated into the "middle" or "narrow" groups solely on the basis of whether or not they had typical sequelae of neuropathy at the time of examination by LEP staff (The Figure, points 10–12, and Table 4). We have found it difficult to define criteria according to which treated patients without typical sequelae of leprosy neuropathy can be allocated reliably to either the "narrow" or the "middle" group. The assignment of an agreement code to the original diagnosis was often difficult and less reproducible than we would wish. We suspect that this will be a problem when reviewing case records of most leprosy control programs.

It may be noted that a finding of typical sequelae of neuropathy on its own was weighed differently, depending upon whether the individual concerned was a newly found suspect or a known leprosy patient. In known patients, such sequelae were considered sufficient for a narrow group allocation if the individual had a prior credible history of leprosy (decision points 9 and 12). In newly found suspects, on the other hand, the same sequelae were grounds for a clinical certainty grade of 2 ("to be considered seriously," Table 1) only. This reflects our view that sequelae of neuropathy in the absence of enlarged nerves and in the absence of a history of antileprosy treatment can arise from other causes (e.g., trauma) and should not, on their own, be sufficient for M or N overall certainty levels (decision point 13).

It should be evident from the allocation procedure that the overall diagnostic certainty does not reflect simply current clinical signs of leprosy. This is important insofar as it means that the cases so defined cannot be translated directly into current prevalence rates of clinical or active leprosy, let alone of infection with *Mycobacterium leprae*. We have discussed the implications of diagnostic certainty on the assessment of leprosy prevalence in a separate publication (9).

Although scoring systems have been used as an alternative to the flowchart approach in assigning diagnostic certainty for some diseases, we found such methods to have two disadvantages in this context. One problem arose because of the dependence between variables. For example, it seemed reasonable to weigh the clinical certainty grade differently dependent upon other, e.g., histopathological, information (e.g., points 5 and 6). Although such assumptions can be handled numerically, it makes a scoring system impracticably complicated. Furthermore, the flowchart representation makes the procedure's logic explicit. Given the complexity of the problem, we find this preferable to the implicit logic of a numerical scoring method.

It is difficult to avoid terminological difficulties when discussing a problem such as

this. In particular, it may be pointed out that the term "certainty" has been used in this paper in three distinct contexts: a) with reference to the clinician's diagnosis, b) with reference to the histopathologist's diagnosis, and c) with reference to the aggregate of all relevant information. This implicitly recognizes that all the evidence and opinions relating to a diagnosis of leprosy need not agree, but allows us nevertheless to arrive objectively at an overall decision as to the status of each individual. It is this aggregate or overall decision which is then used for determining treatment and/or for epidemiological analysis.

It should be emphasized that this is not presented as a universal solution to the problem of defining a case of leprosy. The form and content of the data upon which our procedure is based are probably unique. However, analogous circumstances are found in many leprosy-endemic areas and research projects, and the general approach described here could be modified to fit most situations.

SUMMARY

This paper describes a procedure for grading the degree of confidence with which it can be held that a diagnosis of leprosy is in fact correct, after considering all available clinical, historical, bacteriological, and histopathological information. Individual suspects are assigned to one of four categories corresponding to different levels of overall certainty of the diagnosis. The method is illustrated using data from the Lepra Evaluation Project in Northern Malawi, and validated in the context of an analysis of BCG's protective efficacy against clinical leprosy. Although the procedures described in this paper were designed for a specific epidemiological study, the method could be adapted for use in most leprosy research or control programs.

RESUMEN

Este trabajo describe un procedimiento para valorar el grado de confianza con el cual se puede sostener que un diagnóstico de lepra es correcto. El procedimiento considera la información clínica, histológica, bacteriológica, e histopatológica. Los individuos sospechosos son asignados a una de 4 categorias que corresponden a diferentes niveles de certidumbre en el diagnóstico. El método es ilustrado usando datos del Proyecto de Evaluación de la Lepra en Malawi del Norte, y es válido aplicado al análisis de la eficiencia protectora del BCG contra la lepra clínica. Aunque el procedimiento descrito en este trabajo se diseñó para un estudio epidemiológico específico, el método se puede adaptar para usarse en la mayoría de los programas de investigación o control de la lepra.

RÉSUMÉ

On décrit ici une méthode pour renforcer le degré de confiance que l'on peut accorder à une diagnostic de lèpre, en considérant toute l'information disponible sur les plan clinique, historique, bactériologique, et histo-pathologique. Les sujets soupçonnés d'être malades ont été divisés en quatre catégories, qui correspondent aux différents niveaux de certitude global du diagnostic. La méthode est illustrée en utilisant les données recueillies dans le Projet d'Evaluation mené au Malawi du Nord; il a été validé dans le contexte d'une analyse du pouvoir protecteur du BCG contre la lèpre clinique. Quoique les procédures décrites aient été établies dans le cadre d'une étude épidémiologique spécifique, la méthode pourrait être adaptée et utilisée dans la plupart des programmes de recherche et de lutte contre la lèpre.

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