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# The Diagnosis and Classification of Leprosy

## 1. Introduction

The accurate diagnosis of leprosy is of fundamental importance to all aspects of leprosy epidemiology, case management and the prevention of disability. Underdiagnosis will allow the continued transmission of the disease and much needless individual suffering, whereas overdiagnosis will involve overtreatment with antibiotics and unnecessary stress and stigma for some people; both will lead to misleading epidemiological statistics.

The diagnosis and classification of leprosy have traditionally been based on the clinical examination, frequently with additional information from skin-smears. Histopathologic examination, inoculation of the mouse foot pad, serologic tests, skin-testing and PCR have been largely confined to research studies, but attempts are being made to develop new tools that will make the tasks of diagnosis and classification easier and more reliable in the field.

The ideal diagnostic test would be simple, would identify all cases (100% sensitivity), and would be negative in people who do not have leprosy (100% specificity). Combining individual tests may improve the precision of a diagnostic procedure. Using the "OR" connector (only one sign of several is required for the diagnosis), sensitivity is increased at the expense of specificity, whereas using the "AND" connector (a combination of two or more signs must be present for the diagnosis) increases specificity at the expense of sensitivity.

The sensitivity and specificity of a test can be determined only by comparison with another test known to be reliable—a so-called "gold standard." The gold standard is rarely infallible, so the results will always possess a degree of error. It should be noted that, whereas the histopathologic examination may be the most reliable method for confirming a diagnosis of leprosy, it is by no means a perfect test in itself ([1–4]). Similarly, many practical problems affect the reliability of skin-smears ([5, 6]).

## 2. What are the Sensitivity and Specificity of the Diagnosis of Leprosy Based Solely on Various Combinations of Clinical Signs, Using Biopsy as the Gold Standard? What Contribution Can Skin Smears Make to the Sensitivity and Specificity of the Diagnosis?

Three cardinal signs remain the basis for the clinical diagnosis of leprosy ([7]):

- anesthetic skin lesions;
- enlarged peripheral nerves; and
- acid-fast bacilli in the skin smear.

Any one of these signs has been regarded as sufficient for the diagnosis of leprosy (the "OR" connector), so that sensitivity is high. Each sign is also quite specific in itself, so that specificity is high. The most important potential source of error is the reliability of the examination of the individual patient, referred to as inter-observer variation.

This was affirmed by the WHO Expert Committee on Leprosy ([8]) at its seventh meeting in 1997, which defined a case of leprosy as follows: "A case of leprosy is a person having one or more of the following features, and who has still to complete a full course of treatment:

- hypopigmented or reddish skin lesion(s) with definite loss of sensation;
- involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation;
- skin-smear positive for acid-fast bacilli.

This definition includes retrieved defaulters with signs of active disease, as well as relapsed patients who have previously completed a full course of treatment, but does not include cured persons with late reactions or residual disabilities" ([8]).

A widely quoted study in India ([9]) examined the agreement in the diagnosis of suspicious skin lesions in 811 children, who were examined separately by two experienced leprologists. Approximately half of

the children were eventually diagnosed with leprosy, whereas half were found not to have leprosy. In this group of patients, in which the leprosy was mainly tuberculoid or indeterminate, and which would be expected to include many doubtful cases ([10, 11]), the leprologists concurred in 90% of cases, indicating that, in experienced hands, these signs represent a reproducible means of diagnosing leprosy.

In a study of the diagnostic efficiency of paramedical workers (PMW) in India, the results were considered disappointing ([12]). However, reexamination of the data reveals that the sensitivity of the PMWs' examination was 97% and the specificity 92%. The 55 cases that were wrongly diagnosed were almost all children with few lesions, the most difficult group to diagnose accurately. The weakness of this study is that the gold standard was the diagnosis made by a medical officer, rather than the results of examination of a biopsy specimen. It can therefore be stated with some confidence that, as traditionally practiced, the cardinal signs represent good diagnostic tools.

As the clinical management of leprosy becomes integrated into the general health services, the majority of patients will be diagnosed and managed by non-specialists. For this reason, attempts have been made to simplify the guidelines for diagnosis by field staff using a single sign—the finding of a skin patch or patches with definite loss of sensation ([13]). Other suspect cases, not diagnosed by this single criterion, may be referred to an appropriate center for further examination. Such suspects will be people with skin lesions suggestive of leprosy, but without anesthesia; health workers can be taught to recognize such suggestive lesions by the use of photographs and atlases.

This simplified strategy for diagnosis, which could be used in especially difficult situations, and is being routinely applied in many national programs, may lead to significant underdiagnosis, particularly of multibacillary (MB) disease. Underdiagnosis of MB patients is important for two principle reasons:

- MB patients are thought to represent the major source of infection, so further transmission of *Mycobacterium leprae* may occur; and
- because they are at greater risk of reactions and consequent nerve damage, they may succumb to preventable disability, with the accompanying psychosocial sequelae.

Overdiagnosis will result in unnecessary treatment, but, more importantly, the psychosocial consequences of the diagnosis of leprosy should never be minimized. Therefore, the contribution of each of the cardinal signs will be examined.

### 2.1 Skin lesions with sensory impairment

Hypopigmented or erythematous macules are present in many newly diagnosed leprosy patients, and are often the first clinical sign of the disease. Many other conditions produce similar lesions, however. Therefore, to be specific for leprosy, the lesions must be accompanied by definite loss of sensation. This greatly reduces the sensitivity of the test, especially in MB cases, in which macules are less distinct and less likely to be anesthetic.

The most rigorous study performed in this area was carried out in Malawi, where sensory loss in paucibacillary (PB) lesions proved by histopathologic examination was examined ([14]). Although this study may reflect some of the limitations of the histopathologic examination already mentioned, the sensitivity as a diagnostic test of loss of light touch sensation in a lesion was 48.5% and the specificity 72%.

Other published studies give higher figures for the sensitivity of this test among PB patients. Figures of 93% in India ([15]), 92% in Bangladesh ([16]) and 86% in Ethiopia ([17]) have been reported. It is likely that the mixture of cases and the stage of disease at which they were examined account for some of these differences. Specificity was not calculated in these studies, as they were not population surveys. However, it is clear that hypesthetic lesions are occasionally seen in conditions other than leprosy, such as chronic dermatitis ([18]), which may lead to some overdiagnosis.

Fewer studies have examined anesthetic lesions in MB cases, because there is less perceived difficulty in the diagnosis, using the traditional cardinal signs, including skin-smears ([15]). Published figures for the sensitivity of anesthesia in the skin lesions

in MB patients are remarkably similar: 49% in Bangladesh ([16]) and 54% in Ethiopia ([17]).

In Ethiopia, the sensitivity of this single criterion taken alone was 70% for all patients. A large proportion (74%) of those whose lesions were not anesthetic were smear-positive, and, therefore, represented potential sources of *M. leprae* in the community ([17]). In other words, employing anesthetic skin patches as the single diagnostic criterion, 30% of patients may be missed, most of whom will be smear-positive.

### 2.2 Peripheral nerve enlargement

Thickened nerves generally appear later than do skin lesions. They were found in a greater proportion of new patients in Ethiopia (ulnar nerve enlargement in 68%) ([17]), where the patients typically present late, than in India (ulnar nerve enlargement in 23%) ([20]), where detection is generally much earlier. The finding of one or more enlarged nerves is more common among MB than among PB patients: in Bangladesh the figures were 96% and 86% respectively ([16]), whereas, in Ethiopia, the corresponding figures were 91% and 76% ([17]). One study in India, which included only early PB patients, found that only 20% had enlarged nerves ([15]).

The reproducibility and specificity of the examination for nerve enlargement have been questioned ([21]). One study in India found good agreement among three experienced senior examiners; it is interesting that the agreement for thickened nerves was better than that for typical macules with sensory loss ([22]). A second study in India found only moderate reproducibility among eight experienced PMWs ([20]).

False positive findings may occur because of poor examination technique ([21]) or because of non-specific enlargement of a nerve, seen in some manual workers ([23, 24]). A compromise proposed in the recent ILEP Learning Guide ([25]) is to teach health workers to examine just two nerves, the ulnar and the peroneal, thereby enabling them to detect the vast majority of cases of nerve enlargement ([17, 25]). The data show that, in Ethiopia, 451 (91%) of 496 new cases with nerve enlargement had involvement of either the ulnar (137 patients, 27.5%) or the peroneal nerve (48 patients, 10%) or both (266 patients, 53.5%). A balanced view may be to accept as diagnostic of leprosy a thickened nerve with at least one of the following additional signs ([17, 26]):

- a typical, hypopigmented skin lesion, with or without sensory loss; or
- nerve-function impairment (NFI) typical of leprosy, in particular, sensory loss on the palms of the hands or soles of the feet.

### 2.3 Neuritic leprosy

Primary neuritic ("pure neural") leprosy presents as a peripheral neuropathy, in which there are no skin lesions suggesting leprosy. The diagnosis depends on finding definite nerve enlargement and, often, NFI. In general, these patients would be diagnosed by the classical cardinal signs, but not by the single criterion of an anesthetic skin patch. In one study in India, biopsy of a cutaneous nerve was confirmatory in all 158 cases in which it could be done ([27]), indicating that, in experienced hands, the clinical diagnosis is very specific. In Ethiopia, this diagnosis was made in 3 (0.5%) of 594 newly detected patients ([28]), whereas in India, 179 (4.6%) of 3853 patients exhibited this form of the disease ([29]). In Nepal, 8.7% of new patients in the field were found to have neuritic leprosy ([30]).

### 2.4 Slit-skin smears

Skin-smears have traditionally represented one of the cardinal signs of leprosy: when positive, they directly demonstrate the presence of *M. leprae*. The specificity of this examination therefore approaches 100%. However, the sensitivity of smears alone is low, because smear-positive patients rarely represent more than 50%, and, sometimes, as few as 10% of all patients. On the other hand, positive smears indicate the most infectious group of patients. Smears are useful in diagnosing MB patients and relapses; their disadvantages are related to the logistics and reliability of taking, staining and reading the smears.

Whereas the standard of smear-taking and microscopy may not always be very high ([5]), every effort should be made to improve their quality by supervision and continuing education ([6]). The increased use of acid-fast microscopy for the diagnosis of tuberculosis may permit skin-smears for

TABLE 1. *Sensitivity (%) of various combinations of the cardinal signs in the diagnosis of leprosy.*

| Author | Signs | | | | | | |
|---|---|---|---|---|---|---|---|
| | #1 | #2 | #3 | #1 or #2 | #1 or #3 | #2 or #3 | #1 or #2 or #3 |
| Ponnighaus[14] | 49 (PB) | | | | | | |
| Groenen[15] | 92 (PB) | 86 (PB) | 36 | 100 | 95 | 91 | 100 |
| | 49 (MB | )96 (MB) | | | | | |
| Saunderson[17] | 86 (PB) | 76 (PB) | 45 | 95 | 92 | 87 | 97 |
| | 54 (MB) | 91 (MB) | | | | | |
| Lefford[59] | | | 41 | 82 | | | 84 |
| Sirumban[15] | 93 (PB) | 20 (PB) | | | | | |

Abbreviations: #1 - anesthetic skin lesions; #2 - enlarged peripheral nerves; #3 - acid-fast bacilli in the skin smear.

leprosy to be performed with greater reliability.

### 2.5 Sensitivity and specificity of combinations of cardinal signs for the diagnosis of leprosy

When all three cardinal signs were used in Ethiopia, the sensitivity was 97% ([17]). Specificity was not determined in this study, but the positive predictive value was 98%. Although few published studies contain sufficient data to permit calculation of the sensitivity of each cardinal sign, the figures presented in Table 1 suggest that any single sign is inadequate as a diagnostic test. The skin-smear does not add greatly to the sensitivity of the diagnosis, because the clinical diagnosis of MB leprosy employing two signs—anesthetic patches and enlarged nerves—is generally regarded as straightforward. Specificity is much more difficult to measure, because of the need to include details of all subjects examined who did not have the disease. Thus, it is rarely possible to determine the specificity of diagnostic tests for leprosy from published data.

A study in Malawi ([26]) examined the certainty of diagnosis, particularly of PB leprosy, assuming that the cardinal signs possess a high degree of specificity when used correctly. It was suggested that the diagnosis is "extremely likely" if any one of the following was found:

- a skin lesion of typical appearance, and definite anesthesia to light touch within the lesion;
- a skin lesion of typical appearance without evidence of anesthesia, but with a definitely enlarged nerve (near to or distant from the lesion);
- a skin lesion of typical appearance without evidence of anesthesia or nerve enlargement, but in a person with sequelae typical of leprosy neuropathy;
- a definitely enlarged nerve together with signs of damage to that nerve; or
- a skin lesion of typical appearance without evidence of anesthesia, but on the face.

Unfortunately, "skin lesions of typical appearance" were not defined. These criteria are very similar to a recent suggestion to use any two of five signs to make a firm diagnosis ([17]).

### 2.6 Biopsy

Material from a biopsy specimen may be used for a variety of purposes, including histopathologic examination, studies of immunohistopathology, and "culture" of *M. leprae* in the mouse foot pad. As already indicated, histopathologic examination cannot be regarded as the gold standard: even in the best of hands, a significant proportion of clinically obvious patients will yield negative or doubtful histopathologic pictures. In practice, most studies employ a combination of clinical and histopathologic criteria. The specificity of the histopathologic criteria is high, although it must be noted that it may be difficult to distinguish relapse from reaction in treated PB patients ([31]). Immunohistopathologic techniques offer the possibility of significantly increased sensitivity and specificity of the diagnosis of leprosy. A recent study of PB patients in

TABLE 2. *Sensitivity and specificity of various clinical criteria for classifying leprosy patients, compared with a bacteriological method as the standard.*

| | Criteria for classification as MB | | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| | Clinical | Bacteriological | | |
| Becx[60] | >5 lesions | BI >1 | 92 | 42 |
| Groenen[61] | >10 lesions or 4–9 lesions and >1 nerve | BI >0 (biopsy) | 92 | 41 |
| van Brakel[30] | >2 body areas | BI >0 (biopsy) | 93 | 39 |
| Croft[54] | >5 lesions | BI >0 | 89 | 88 |
| Dasananjali[55] | >5 lesions | BI >1 | 88 | 88 |
| Buhrer-Sekula[56] | >5 lesions | BI >0 | 85 | 81 |

China showed ([32]) that staining for the PGL-I antigen was very specific, whereas routine histopathologic examination was generally non-specific; this preliminary finding needs confirmation by additional studies.

### 2.7 Serology and PCR for diagnosis

The only serological test that has been widely studied is that for anti-PGL-I antibodies. Two methods have been employed: the *M. leprae* particle agglutination assay (MLPA); and an ELISA assay, which has been further refined into a "dipstick" assay. The ELISA or dipstick assay is preferred because of greater specificity ([33–35]). The disadvantage of this assay is its lack of sensitivity, especially for PB leprosy, although studies vary in how close a correlation is found with skin smears ([36, 37]).

PGL-I antibody testing has been reported to be helpful in the early detection of MB relapse ([38]). It may also provide an overview of the epidemiology of subclinical infection, as opposed to active disease ([39–41]). What has thus far proved more uncertain is application of this test to the early diagnosis of clinical cases ([42–46]), and to the prediction (either among contacts of known cases or in the general population) of who will develop clinical disease in the future ([47–50]). Newer serological tests based on recombinant technology may eventually overcome these difficulties and be useful in the field ([51]). Tests based on the polymerase chain reaction (PCR) are potentially highly sensitive and specific ([52]), but because they require a sophisticated laboratory, they are not currently applicable except as research tools.

### 3. What are the Sensitivity and Specificity of Classification Based Solely on Counting the Number of Skin Lesions, Using the Skin-smear Examination as the Gold Standard?

The spectrum of disease in leprosy has been characterized in a number of clinico-immunopathological classification systems, the most widely used of which is the Ridley-Jopling classification ([7, 53]). Since the introduction of MDT, however, the division of patients simply between PB and MB treatment groups has become normal practice. The most rigorous method of assigning patients to a treatment group is bacteriological, employing the slit-skin smear or biopsy. It should be noted that classification is required because there are two treatment regimens; if developments in chemotherapy lead to one regimen for all, classification will not be needed for this purpose, but it is important to remember that PB and MB cases have been shown to have very different risks for subsequent impairment and disability; classification may therefore remain an important tool.

When MDT was first introduced in 1981, the Ridley-Jopling classification was used as the basis of the new system of classification, with TT and BT cases termed PB, whereas BB, BL and LL cases were termed MB. A BI of 2 or more at any site required that the patient be classified MB, thereby changing the classification of some BT patients. By the time of the Sixth WHO Expert Committee Report in 1988, it was concluded that there were clinical and operational reasons for considering all smear-positive cases MB ([6]).

Since then, skin-smears have been done on all patients in some programs, with all smear-positive patients classified MB, and smear-negative TT and BT patients PB.

Because of the unavailability or unreliability of skin-smears in many programs, clinical methods of classifying patients have been developed. The recent WHO Guide asks the health worker to count the number of skin patches; if there are ≤5 patches, the patient is classified PB, whereas if there are >5 patches, the classification is MB ([13]).

The relevant published data comparing clinical classification with bacteriologic classification are presented in Table 2. Note that the exact criteria for classification (both clinical and bacteriologic) vary slightly among the studies. The sensitivity and specificity of the clinical criteria are stated with reference to the bacteriologic criteria as the gold standard.

Further analysis of data from Bangladesh showed ([16]) that specificity cannot be very much improved by any combination of purely clinical criteria. The authors also pointed out that the results of such studies vary in different countries according to the case-mix, making it difficult to set global standards. The lower sensitivity and higher specificity found in the last three studies, compared with the first three studies in Table 2, may be attributed to the greater proportion of smear-negative PB patients with ≤5 lesions in the samples (in the last three studies, PB patients comprise 41%–83% of all patients, compared with only 19%–23% of all patients in the first three studies).

As pointed out in a recent review ([54]), "The WHO system of classifying leprosy cases as MB is simple to apply and has a reasonable balance between sensitivity and specificity. However, it must be recognized that the system will lead to a small but significant number of smear-positive MB cases being treated with a PB treatment regimen." A study from Thailand also suggested that the risk of relapse may be greatest in the small group of MB patients wrongly classified PB and, therefore, undertreated ([55]). Also, there are larger numbers of PB patients who are unnecessarily treated with the MB regimen.

In a study carried out in Brazil ([56]), the anti-PGL-I antibody assay was found to have a sensitivity of 77% and a specificity of 93%, whereas the combination of the anti-PGL-I antibody assay and the number of lesions demonstrated a sensitivity of 94% and a specificity of 77% in the detection of true MB patients. However, a small group of patients remains who will be undertreated.

Another problem is identification of the small group of patients with an initially high BI (BI ≥4), who may be at greater risk of subsequent relapse ([57]). A study in Nepal ([58]), in which different methods of identifying highly smear-positive patients were examined, found three clinical features in various combinations (LL classification, more than five body areas involved, and skin infiltration) to be sensitive (>95%) but not specific predictors of this condition; by combining these features using the "AND" connector, specificity could be greatly increased, but sensitivity would be greatly reduced. Whereas the skin smear is the gold standard (i.e., it is taken to have 100% sensitivity and specificity), anti-PGL-I antibody assay in the same study demonstrated sensitivity of 84% but very low specificity ([58]).

## CONCLUSIONS

It is clear that at least two of the traditional cardinal signs are necessary to achieve a reasonable degree of sensitivity in the diagnosis of leprosy; using anesthetic patches as the only sign of leprosy is inadequate. One or more enlarged nerves is an acceptable additional sign, to be supplemented by skin-smears when available.

This has implications for training: peripheral health workers should be taught to suspect leprosy from the typical appearance of leprosy skin lesions; they should be able to diagnose leprosy in those patients with anesthetic skin patches. Patients with suspicious patches but without anesthesia should be referred, and health workers at the first referral level should be able to diagnose almost all cases of leprosy among suspects referred to them; therefore, they must know how to examine for enlarged nerves.

For classification, no other test, either clinical or serological, approaches the reliability of the skin-smear in classifying patients. However, because it is not reason-

able to expect that all new patients will be smeared for the purpose of classification, classification should be based simply on the number of skin lesions, as recommended by WHO.

*Recommendations.* The following recommendations are based on the evidence just described:

- Approximately 70% of leprosy patients can be diagnosed using the single sign of anesthetic skin patches, and this sign of leprosy should be taught as widely as possible.
- 30 per cent of all patients, including many MB patients, do not present with this sign, and health workers must be taught to suspect and refer other possible cases.
- Referral of suspects who do not have anesthetic patches, to a person with greater experience who has been taught to palpate the peripheral nerves, must be straightforward. Palpating just two nerves (the ulnar and the common peroneal) may permit diagnosis of as many as 90% of patients with any nerve enlargement.
- Classification should be based on the number of skin lesions: PB ≤5 patches; MB >5 patches. Skin-smears on a sample of new cases could provide quality control.
- Research into laboratory tests (for example, serological or skin tests) that could be useful in the field in identifying *M. leprae* infection, diagnosing active disease and classifying cases of leprosy, should be continued.

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