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## *EDITORIAL*

### **Classifying leprosy patients - searching for the perfect solution?**

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In medicine, the classification of a disease is used to identify the different aspects of disease presentation and this affects prognosis, treatment and scientific understanding. This is the only way in which the scientific community can share knowledge and improve patient care. Why do patients with leprosy need classifying according to disease type? Classification helps in understanding disease; clinical features can be better interpreted by linking them to the underlying pathology and immunology. Classification allows the risk of complications to be predicted; patients with borderline leprosy are at a much higher risk of developing reactions than patients with tuberculoid disease. The risk of ENL is also related to disease type with Lepromatous Leprosy patients having a odds ratio of 3.2 for developing ENL when compared with patients with Borderline Leprosy (BL).<sup>1</sup> Many studies have shown that borderline patients having the highest prevalence of Type 1 reactions.<sup>2</sup> The risk of disability is also related to clinical form of leprosy, also being higher in the borderline types.<sup>3</sup> The risks of these complications have practical consequences. Patients can be warned about them and so can take part in managing their own disease, clinicians will be alerted to the possibility and will recognise them more quickly and precious resources and manpower can be focused on the groups at greatest risk. Treatment schedules are determined by classification. Patients with high bacterial loads need and receive longer treatments with multi-drug therapy. Knowledge of the classification pattern within a leprosy-endemic district is important for health services, in terms of provision of anti-leprosy drugs and corticosteroids. Classification is also important for programme and evaluation and for epidemiological purposes in

monitoring the pattern of disease, trends over time, and international variations. This provides information that may indicate reduction in transmission or that there is under-diagnosis when only LL cases are being detected.

The need for an internationally accepted classification system for leprosy was recognised long ago. The first system proposed at an international meeting was in Manila in 1931. This was followed by systems proposed in Cairo in 1938, Rio de Janeiro in 1946, Havana in 1948 and Madrid in 1953, followed by an Indian classification in 1955.<sup>4</sup> These evolving classifications were based on clinical features with some support from histological and prognostic features and lepromin testing. They separated out the tuberculoid and lepromatous poles and recognised borderline, dimorphous or intermediate categories in between. In 1966 Ridley and Jopling published a paper<sup>5</sup> that used clinical, histological and immunological criteria to classify leprosy patients across the spectrum, and suggested five member groups: Tuberculoid (TT), Borderline Tuberculoid (BT), Borderline (BB), Borderline Lepromatous (BL) and Lepromatous (LL). This classification recognised the complex pathogenesis of the disease and, for the first time, made sense of the numerous clinical syndromes that leprosy presents, the validity of this classification was later confirmed by Meyers in a clinical-histological study.<sup>6</sup> The timing of this classification was important because it coincided with the initial laboratory work on the immune response to *M. leprae*, both in man and in the mouse. Key studies in patients confirmed that the immune response determines the clinical and histological manifestations of leprosy in all its different forms. Lymphocyte transformation test values to *M. leprae* antigens are strongest in TT patients and absent in LL patients.<sup>7</sup> Antibodies against *M. leprae* antigens are produced strongly in patients with LL disease and production is low in patients with TT disease.<sup>8</sup> These findings have been replicated with more sophisticated immunological studies such as those on cytokine production<sup>9</sup> and Toll like receptors<sup>10</sup> which again show that T cell activation is high at the tuberculoid end of the spectrum and low at the lepromatous end. This confirms the continuing scientific validity of the Ridley-Jopling classification. The classification has also been modified; an Indeterminate category was added and Ridley later outlined how patients might enter the disease process and move on the spectrum.<sup>11</sup>

In 1982, WHO recommended an additional classification, of paucibacillary (PB) and multibacillary (MB) types of leprosy, for operational purposes.<sup>12</sup> It was introduced to simplify disease recognition and to ensure that patients were appropriately treated with multi-drug therapy. As an operational classification it has been a great success, it has made classification simpler, determined by the number of skin lesions. This meant that expertise in defining the morphology of skin lesions ceased to be a prerequisite for field workers classifying leprosy patients, although health workers do have to recognise the wide range of presentations when suspecting leprosy. Treating leprosy patients has also been made simpler by the WHO classification with just two types of treatment that are now provided in blister packs. Simplification, however, has come with some implications. Since 1982 the WHO classification has changed. Initially it incorporated slit skin smears, and patients with a BI of 2+ were classed as MB. In 1988 a positive skin smear result at any site was sufficient for classification as MB.<sup>13</sup> Later the need for slit skin smears was dropped altogether, so the current classification of MB includes anyone with 6 or more skin lesions.<sup>14</sup> Individual countries have also made local modifications; in Brazil, for example, in reference centres where slit skin smears are performed, all patients with positive slit skin smears are classified as MB patients and, in field conditions whenever there is doubt about the classification, patients are treated as MB. In addition, in some regions patients are classified by counting

both skin lesions and enlarged nerves. Another impact has been on research. The repeated changes in the WHO classification means that it is almost impossible to compare the results of work that was done 20 years ago with work done more recently. Also, the different diagnostic criteria used complicate the comparison of data among countries and even within a country itself. There is also the risk of misclassification. This has been highlighted in a study done in Brazil, Nigeria and Nepal<sup>15</sup> where very different rates of PB/MB classification were found in these countries and also misclassification when using either slit skin smears or PGL antibody detection to assess bacterial status. Furthermore assessing skin lesions is not always easy and depends on the amount of skin examined, and the quality of the light. Furthermore the number of skin lesions may change over time. For example a study from the Philippines comparing WHO classification with the Ridley-Jopling classification found that in patients whose leprosy was classified as paucibacillary, 38%–51% of them had multibacillary leprosy according to Ridley-Jopling criteria and were thus at risk of under-treatment.<sup>16</sup> Both groups are heterogenous. The PB category comprises patients with indeterminate, TT, BT, BB and even early BL leprosy types. The MB category is equally heterogenous and comprises BT, BB, BL and LL patients. In a recent study in Northern India where new MB patients were recruited histological examination found that 60% of these new MB patients were smear negative BT patients.<sup>17</sup> These patients were thus at risk of being over-treated. However it should also be noted that both clinicians and pathologists show intra and inter observer variability in assignment of patients to the Ridley-Jopling groups. The two classifications, Ridley Jopling and WHO, should be seen as being complementary rather than exclusive. It is best to focus on the situations where each classification performs best. In the field the WHO classification is appropriate, especially in highly endemic, low resource settings. It is easy to use and teach, general health care workers can be confident in their diagnosis and it is easy to allocate patients to the appropriate treatment regimen. Referral centres should probably use both classifications. The WHO classification remains useful for allocating patients to treatment groups. In the context of research, however, it is better to use the Ridley-Jopling classification, which promotes a better understanding of the disease pathology, prognosis and the risk factors for complications. In research a classification is needed that provides reflects the spectrum of the immune response and provides standardisation and comparability over time and place. It is more complex and requires access to at least slit skin smears and should be supported by histopathology where ever possible. The original classification was proposed over 40 years ago and has some development.<sup>11</sup> However it has never been standardised, the large study done by Meyers *et al.*<sup>6</sup> was never formally published. It would now be timely to establish agreed clinical and histological case definitions for classification together with protocols for patient classification. It would also be important to consider how newer tests such as PGL 1 as well as future tests such as T cell based tests and skin tests using new antigens fit into the Ridley-Jopling classification.

It is strongly recommended that the Ridley-Jopling classification is used for any study looking at immune processes in leprosy and for genetic studies identifying genes for susceptibility to either the disease or its complications.<sup>18</sup> It has also been agreed at the Editorial Board that research papers submitted to *Leprosy Review* should use the Ridley-Jopling classification unless there is a good reason not to such as in field based operational studies.

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