Again on "Indeterminate Leprosy" (Alias Immature Hanseniasis)

TO THE EDITOR:

The present polar concept of leprosy enunciated by Rabello in 1938 ([22, 23]) conceptually prompted as an immediate and necessary consequence the existence of a nonpolar or unstable group which was then called "uncharacteristic" ([8, 24, 25]). This was soon found to be quantitatively important by Pupo ([1]) who found that 68.7% of his 583 patients were "uncharacteristic." These concepts were widely accepted in the 1940s ([5, 19]) at the Pan-American Conference in Rio de Janeiro in 1946 and at the Havana Congress of Leprosy in 1948 ([7]).

This "uncharacteristic" group or group I or "indeterminate" group was accepted in classifications of the disease at the International Leprosy Congresses held in Madrid in 1953, in Rio de Janeiro in 1963, and in Mexico City in 1978 ([6]). The subject has been recently reviewed on these pages ([26]).

Thus the concept of this group I ("uncharacteristic," "indeterminate," "immature") has been well accepted. Recently two points of view have been put forth which, to our dismay, question the importance or even the existence of group I. We believe that this may be due to semantic misunderstandings due to the ambiguous expression "indeterminate" leprosy. Dr. Pettit ([21]) questioned the validity of making the diagnosis of leprosy in the absence of bacilli in cutaneous lesions. Recently Dr. Jopling ([14]) indicated that these clinical cases of group I could not be included in a classification such as the Ridley-Jopling classification which is based in immunity since the very designation "indeterminate" implies that the immunologic characteristics of the case have not yet developed.

In our view, the absence or scarceness of a specific agent in infectious cutaneous lesions cannot be considered as unusual. As examples, in both cutaneous tuberculosis and in the late gummatous lesions of tertiary syphilis; the infectious agents are only exceptionally observed and can usually not be demonstrated even in inoculation experiments. The difficulty in demonstrating acid-fast bacilli in cutaneous tuberculosis is well documented ([10, 20, 28]) even when large fragments of tissue are inoculated into guinea pigs. The concept of disease without readily demonstrable infectious agents is in keeping with the classical aspects of the general pathology of the mycobacterioses as laid down by Jadassohn in 1913–1928 ([13]). The principle of "inverse proportions" was used at that time to explain the finding of very few bacilli along with very destructive lesions. Jadassohn himself described a "leprosy without bacilli" which was then called "tuberculoid leprosy." Although this was controversial at the time ([12]), the concept of "leprosy without bacilli" is now well accepted in the T quiescent forms (TT) with no more than 0.7% of cutaneous lesions having demonstrable bacilli ([3]).

To our minds it seems reasonable to include these I cases ("indeterminate," "immature," "uncharacteristic" patients) in the classification of leprosy based on immunology. There seems to be ample evidence on clinical, epidemiological, and immunologic grounds for the existence of these forms and for the development of the polar lesions from these immature forms of the disease. The instability of these I cases and their behavior in lepromin tests indicate an immune response as indicated in the classical work of de Souza Compos-de Souza Lima in 1950 ([9]). As much as 41% of these I cases persist as such during clinical and immunological follow up from 23–35 years ([2]). Lymphocyte blast transformation responses have been used as a means of defining "strictly indeterminate" cases ([15]). Garrido Neves ([11]) has termed the histopathologic findings in these cases as not being "indeterminate" but rather "suggestively diagnostic." Scott, *et al.* ([27]) showed shifts towards lepromatous or tuberculoid and clinical five-year remissions in 28% of their cases. Belda ([4]) reported a series of 4139 cases with impressive data concerning the clinical features of these patients. Mshana, *et al.* ([16]) showed evidence of recognition of *M. leprae* antigens in 40% of I cases compared to 88% of BT cases and no recognition of these antigens with patients with BL and LL disease.

Dr. Pettit ([21]), on the other hand, suggests

that in the presence of a single hypopigmented lesion which is not yet anesthetic, even when observed in areas endemic for leprosy, the diagnosis of the disease should wait until more definitive lesions of lepromatous or tuberculoid disease develop. In our view, in all endemic areas for the disease, the diagnosis of leprosy should be made in such cases and treatment begun before a not unusual lepromatization occurs (especially in Mitsuda negative I cases). In our view, Dr. Pettit's position is unacceptable since it results in denying these patients, not rarely children, the benefits of sulfone treatment which is capable of stopping the disease at its onset. In view of the 4139 cases of Belda ([4]) and the 4605 I cases reviewed by Noussitou in Burma ([18]), we see such I cases as representing an integral part of the endemic matrix of hanseniasis. In regard to Dr. Pettit's position it might be useful to obtain an early prognosis based on the Mitsuda test since, in the presence of macular lesions, a negative test in individuals between 16 and 20 years old is highly suggestive of leprosy in our experience and makes specific treatment mandatory. If a child with a hypopigmented macule in an area endemic for leprosy has that macule change into definite bacilliferous hanseniasis (LL) it seems to us impossible to state that another child, in the same endemic area, with the same type of macule is free from any known disease (Noussitou, personal communication, 1983).

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Reply to Dr. Rabello, *et al.*'s Letter to the Editor

TO THE EDITOR:

My Brazilian colleagues are asking me to accept, in a classification of leprosy, the inclusion of an indeterminate form, and because I have consistently refused to accept this proposition they imply that my position is unreasonable. One of their arguments to justify their view that an indeterminate macule can be diagnosed as a leprosy lesion, in spite of absence of bacilli, is that skin lesions in syphilis may be devoid of treponemata, skin lesions in tuberculosis may be devoid of tubercle bacilli, and leprosy bacilli cannot be demonstrated in skin lesions of tuberculoid leprosy. This argument is spurious, for in these three conditions there are other ways of establishing the diagnosis; whereas there are no other ways of establishing that an indeterminate macule, free from acid-fast bacilli, is due to leprosy. The writers claim that there are "ample clinical, epidemiological and immunologic grounds" for establishing that an indeterminate macule is due to leprosy and can be classified as such; in fact, they go so far as to claim that "it seems reasonable to include these I cases ('indeterminate,' 'immature,' 'uncharacteristic' patients) in the classification of leprosy based on immunology." If this is what they really believe, then, on this question, the gulf between us is indeed great.

I maintain that a diagnosis of leprosy cannot be made on a macule in which no sensory deficit can be demonstrated, no bacilli found, and in which histologic examination reveals only a mild non-specific histiocytic and lymphocytic infiltrate. In such a case, however, a pre-leprosy condition must be suspected, especially if the patient lives in, or has lived in, a country where leprosy is endemic, provided that alternative possible diagnoses have been excluded. In such circumstances, I advocate a policy of ensuring that the patient reports for examination at regular intervals, and of instituting treatment if and when evidence of determinate leprosy is found.

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Reply to Dr. Rabello, *et al.*'s Letter to the Editor

TO THE EDITOR:

My letter entitled "Should indeterminate leprosy ever be diagnosed" ([3]) was meant to stimulate your readers, and in my answer to Dr. Browne's defense I pointed out that from what was written in India and the Philippines, as well as from Africa, it is clear that different authors use the diagnosis in different ways ([4]).

South America has now joined the fray ([5]). Dr. Rabello and his colleagues quote a paper ([1]) in which 41% of indeterminate cases persisted as such during clinical and immunological follow up for 23–35 years. I quoted a paper ([2]) in which 2749 cases all regressed spontaneously. Does Dr. Rabello really believe these papers were discussing the same thing?