patient with lepromatous leprosy aggregated liposomes containing 9 μg of glycolipid at dilutions of 1:10, 1:20 and 1:40 but another such serum failed to aggregate the liposomes. Neither of two sera from *M. lepraemurium*-infected mice aggregated the liposomes.

Liposomes are simple models of biological membrane vesicles, consisting of a double layer of lipid whose hydrophilic ends are outermost in aqueous media. They have been used as carriers for immunological studies on natural ([2]) and synthetic ([5]) glycolipids. It seems that in the case of the leprosy-specific glycolipid they also allow expression of the antigenic determinant in an aqueous system. The leprosy-specific glycolipid is an abundant product of the bacteria ([3, 7]). Our demonstration that it is serologically active even when highly purified suggests many possible experimental uses for this material.

We are grateful to Mr. R. Butler for supplying the mouse sera. The supernatants used to prepare the lipid were "by-products" formed in the production of purified *M. leprae* for the UNDP/World Bank/WHO IMMLEP Programme.

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Indeterminate Leprosy—A Valid Clinical Concept

To the Editor:

The letter of my good friend, John H. S. Pettit, under the heading "Should Indeterminate Leprosy Ever Be Diagnosed?", which appeared in the Journal ([15]), calls for a serious and considered answer. The doubts expressed in the letter appear to be a reflection of the clinical experience of a consultant dermatologist practicing in a town where the prevalence of leprosy is not high, and seeing patients referred to him. Doctors working in areas of very high leprosy prevalence, especially if they conduct whole population surveys or contact examinations at frequent and regular intervals, are familiar with the early skin mani-

festations of leprosy conveniently classified as "indeterminate." It was in situations of high concentration of virtually untreated patients with bacilliferous types of leprosy (such as Culion leprosarium in the pre-sulfone era, certain villages in Tamil Nadu, or in areas of equatorial rain forest in the former Belgian Congo) that the majority of children exposed to repeated and massive infection with viable leprosy organisms would develop skin lesions—possibly implantation lesions corresponding to the radiographically demonstrable early lesions of the pulmonary parenchyma due to infection with *Mycobacterium tuberculosis*. These lesions were the "hazy patches" of juvenile or adolescent leprosy.

I would assure Dr. Pettit that in the areas where spontaneous regression occurred in 2873 patients diagnosed as having early leprosy ([13]), there was a correspondingly large number of patients suffering from persistent "determinate" forms of leprosy, as a report indicated ([1]): that is, 3889 with tuberculoid leprosy and 1104 with lepromatous leprosy in a population of 43,035 persons. In view of prevalence rates as high as 119 per 1000, the doubts expressed by Dr. Pettit were shared by such experienced clinicians as Zanetti and R. G. Cochrane. The doubts of these observers were dispelled when they visited the hyperendemic area in the former Belgian Congo and examined some hundreds of patients.

The present writer was not unaware of the existence of other dermatoses besides leprosy, characterized by congenital or acquired hypopigmentation. Not only did I write the chapter on "Differential Diagnosis" in Cochrane and Davey's *Leprosy in Theory and Practice* ([5]), but I contributed to the literature numerous articles on the subject, for example, on dermatological conditions mistakenly attributed to leprosy ([9]), conditions mistakenly thought to indicate nerve damage due to leprosy ([7]), and less common neurological findings in leprosy ([10]). After wider experience in many countries, I wrote articles on "The variegated clinical pattern of leprosy" ([4]), "Confluent macular lepromatous leprosy" ([8]), and "Observations on the macular series in African leprosy" ([12]).

Other depigmenting dermatoses were common in African clinical practice, such as nutritional hypochromia, idiopathic macular hypopigmentation, onchocercal depigmentation ([2]), and depigmentation in yaws ([3]). Fixed eruption ([13]), toxic epidermal necrolysis ([14]), and Kaposi's sarcomatosis also attracted attention ([11]).

When the diagnosis of "indeterminate leprosy" is made by an experienced clinician, this valid clinical concept can be substantiated by histopathological studies, provided that the biopsy material includes the deep layers of the dermis and the observer can devote sufficient time to the examination. We found (at the Leprosy Study Centre, London) that if every fifth section is examined and a small dermal nerve fibril is followed, sooner or later a single acid-alcohol-fast organism or a small clump of such organisms is discovered. Recent studies of the dermis and of the posterior auricular nerves in close contacts of patients suffering from bacilliferous forms of leprosy have disclosed acid-alcohol-fast bacilli, sometimes after prolonged search. Staining with Nyka's method may reveal organisms previously not visible.

Knowledgeable chiefs and "medicinemen" recognized the very early macules of "indeterminate leprosy." Those scarcely visible macules that they called "the mother of the bad leprosy" ([16]) would be found to contain innumerable leprosy bacilli; according to them, the other kinds would usually disappear, but might occasionally be followed by evidence of peripheral nerve damage.

Demonstrable diminution of sensation in a circumscribed area of skin (as judged by relatively crude clinical testing) does not occur in the early stages of macular lepromatous leprosy.

By closely observing these different types of lesions in the skin, the medically qualified practitioner is enabled to build up a composite and comprehensive picture of the response of the skin to leprosy infection. In some parts of India, however, the clinical entity of primary persistent polyneuritic leprosy, in which skin lesions are consistently absent, may account for a variable but definite proportion of early leprosy infections; the diagnosis is confirmed and the classification established by histopathological and microbiological examination of a sliver of nerve.

The clinical concept of indeterminate leprosy is useful in those large areas in the world where facilities for histopathological examination by experienced pathologists with adequate time to spend on each series of sections are just not available. Where reliable techniques for taking, staining, and reading dermal smears are in use, the demonstration of the presence of *M. leprae* (perhaps in unexpectedly large numbers) will indicate those cases of "indeterminate leprosy" that are in reality early lepromatous leprosy; while histopathological examination may reveal a typical microscopic picture in a dermal nerve fibril that is pathognomonic of early tuberculoid leprosy. When the proportion of cases clinically diagnosed as "indeterminate leprosy" is thus reduced by these two considerations, there remains a group of skin lesions that clinicians experienced in this field will recognize. Should doubt remain, then of course the excellent advice proffered by Dr. Pettit should be followed: temporize, await indubitable signs of leprosy, and do not saddle the patient and his family with the stigmatizing diagnosis of leprosy.

In these young patients, the lepromin test is of limited value, and its degree of positivity bears little relation to the type of skin lesion observed. Unfortunately, a persistently negative lepromin test does not always indicate the absence of any potential for cell-mediated immunity; in some such patients, spontaneous resolution of indeterminate leprosy lesions occurs.

In conclusion, I would submit that the clinical concept of indeterminate leprosy is both valid and valuable and would invite Dr. Pettit to visit some hyperendemic areas and see for himself. The practical advice I would give is: make a definite diagnosis on clinical grounds, backed up if at all possible by bacteriological and histopathological findings, and then, in the absence of any positive indication that the lesion (or lesions) will spontaneously regress, treat for leprosy. It goes without saying that the more conversant the clinician is with the local appearance of the numerous dermatoses frequently confused with leprosy, the more precise and accurate will be his diagnosis of "indeterminate leprosy."

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