INTERNATIONAL JOURNAL OF LEPROSY
and Other Mycobacterial Diseases

OFFICIAL ORGAN OF THE INTERNATIONAL LEPROSY ASSOCIATION

EDITORIAL AND PUBLICATION OFFICE
National Hansen's Disease Center
Carville, Louisiana 70721, USA

VOLUME 50, NUMBER 4 DECEMBER 1982

EDITORIALS

Editorial opinions expressed are those of the writers.

Macrophages versus Lymphocytes in Leprosy

Our studies on the distribution of the Mitsuda reaction in families free of leprosy[1,2,3] and in those composed of couples including at least one leprosy patient[4] have shown that individuals born to Mitsuda-negative parents are more prone to exhibit a negative reaction to lepromin injection than persons born to at least one Mitsuda-positive parent. Additionally, the proportion of Mitsuda-negative individuals in the offspring of couples composed of a Mitsuda-positive person married to a Mitsuda-negative partner is significantly larger than that observed in the offspring of couples both of whom are Mitsuda-positive.

Taking into account this familial association, and considering that the Mitsuda reaction evaluates, though not perfectly, the macrophages' capacity to lyse phagocytized leprosy bacilli, we advanced the hypothesis that this lysogenic ability is inherited autosomally. People could be classified as lysers or non-lysers according to their macrophages' capacity to destroy *Mycobacterium leprae*; the lyser being dominant over the non-lyser phenotype[4]. Obviously, this would also mean that resistance to the proliferation of leprosy bacilli and, in consequence, resistance at least to lepromatous leprosy would occur as a dominant trait. Conversely, the permanent incapacity of macrophages to destroy phagocytized leprosy bacilli, which would enable their intracellular proliferation, would be inherited recessively.

This monogenic hypothesis was not supported, however, by data from families in which both parents were lepromatous patients. In fact, among 81 individuals born to 24 lepromatous couples, 30.9% were strong lepromin reactors[4] when, according to the monogenic hypothesis, all of them should have been Mitsuda-negative like their parents. Therefore, the monogenic hypothesis was submitted to criticism[5,6] and a more elaborate hypothesis, which was named the lysing threshold hypothesis, was proposed

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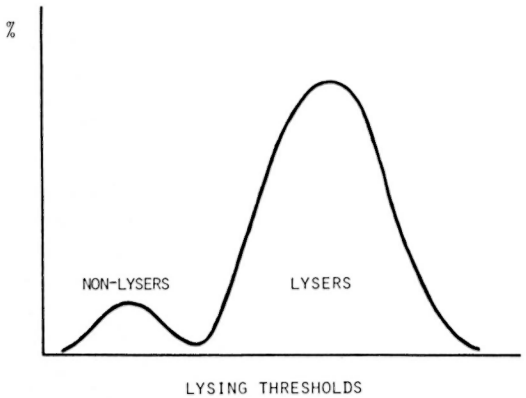

THE FIGURE. Hypothetical bimodal distribution of a human population according to the degree of lysogenic ability of the macrophages towards *M. leprae* (lysing thresholds).

to explain both the familial distribution of the Mitsuda reaction and the manifestations of the different forms of leprosy[2].

According to the lysing threshold hypothesis, both lyser and non-lyser phenotypes are represented by individuals whose macrophages exhibit different degrees of lysogenic ability towards *M. leprae* (lysing thresholds). Therefore, among the lysers there are individuals whose macrophages express their lysing capacity for leprosy bacilli more strongly than the macrophages of others. The non-lyser phenotype includes individuals with macrophages exhibiting no activity at all for phagocytized *M. leprae*, as well as persons whose macrophages show, or can be stimulated to disclose, various degrees of an incipient lysing activity against leprosy bacilli. This possibility was later supported by the observations that the macrophages of some lepromatous patients (non-lysers) were able to destroy injected heat-killed leprosy bacilli after 90–120 days, while the macrophages of others conserved the bacilli undestroyed after 120 days[7]. In contrast, the macrophages of Mitsuda-positive individuals completely destroy injected leprosy bacilli in 3–4 weeks.

If one accepts that either the lysers or the non-lysers are unimodally distributed according to the lysing threshold, then one can also accept that the lysing capacity of human macrophages for phagocytized *M. leprae* is a semi-discontinuous trait, being represented by a bimodal curve. Therefore, the lysers and non-lysers would be discriminated by the threshold corresponding to the antimodal area (The Figure). Individuals falling at this critical threshold would, of course, pose difficulties in their classification, since they might be considered either as lysers or as non-lysers. On the other hand, they would be expected to be rare in any population and, in any case, for prognostic purposes it would be safer to include them among the non-lysers.

The assumption that the non-lyser phenotype is an autosomal recessive trait is maintained in the lysing threshold hypothesis. It is implicit that the frequency of this phenotype varies in different populations, most probably due to selection pressure and/or genetic drift. However, the non-lyser phenotype may be determined by more than one allelic pair of genes. This possibility is easy to accept if, for example, one assumes that the macrophages' incapacity to destroy *M. leprae* might be a consequence of either an overall genetic reduction of the functional capacity of the macrophages or a deficiency of any one of the several enzymes that intervene in the lysis of phagocytized leprosy bacilli.

According to the lysing threshold hypothesis, some individuals are non-lysers because they have a certain homozygous genotype, say *aa*; while others have the same phenotype, in spite of being *AA* or *Aa*, as a consequence of being homozygous for a gene that belongs to another allelic system (*bb* or *cc* or *dd*, and so on) but brings about the same final effect on the macrophages (genocopy). If one of these genotypes were more common than the others, most marriages between non-lysers would generate only non-lysers since both parents would have the same, frequent genotype. On the other hand, a fraction of these couples would be expected to generate lysers since, for instance, one parent might have genotype *AAbb* and the other genotype *aaBB*.

At any rate, whatever the gene pair considered, the proposed bimodal distribution

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of human populations according to lysing thresholds requires accepting that the alleles responsible for the dominant and recessive phenotypes are major gene pairs, that is to say, alleles with an expressivity highly dependent upon both genetic and environmental modifying factors. The genetic modifying factors would be represented by the particular genetic constitution of each individual, while the immunological experiences with antigens found in *M. leprae* and in other common mycobacteria would play the most important role among the non-genetic factors. Such experiences would accelerate the contact and the engulfment of leprosy bacilli by the macrophages, as well as the release of hydrolytic enzymes and antibacterial substances from the lysosomes.

The influence of genetic variations of *M. leprae* on the expression of the lyser or non-lyser genotypes is not taken into account in the lysing threshold hypothesis, since there is no evidence that different strains of *M. leprae* have different degrees of resistance to biological destruction by human macrophages. This does not mean, of course, that different antigens liberated by different strains of *M. leprae* might not play an important role for producing clinical variants of leprosy. Moreover, different persons may react differently to them and this variation, if real, might be dependent upon another genetic system.

The hypothesis that the non-lyser phenotype is inherited recessively does not mean that, under special circumstances, individuals who are genetically determined to be non-lysers could not be transformed into lysers, particularly if their lysing threshold is near the antimodal value. By analogy, although the ability to taste phenylthiourea and related compounds is undoubtedly determined by a major allelic autosomal pair, it is possible to change the individual threshold by learning[8]. In this regard, indeterminate leprosy patients as well as healthy contacts who were persistently Mitsuda-negative individuals can be transformed into Mitsuda-positive reactors after being injected with a mixed suspension of BCG and heat-killed *M. leprae*[7].

In the lysing threshold hypothesis there can be transient and slight variations in the lysing thresholds of human beings due to exogenous and endogenous influences. For instance, it is well known that hormonal influences and drugs may temporarily accelerate or depress the lysing capacity of macrophages[9, 10, 11, 12]. Such slight variations would be insignificant in individuals whose lysing threshold is far from the antimodal value, since their lyser or non-lyser phenotype would not be modified. In contrast, the same variations might lead to dramatic changes when acting on people with lysing thresholds near the antimodal value since, under these circumstances, their phenotypes could change from non-lyser to lyser or vice versa.

In keeping with the lysing threshold hypothesis, the following possibilities exist for explaining the finding of a small proportion of Mitsuda-positive reactors among individuals born to lepromatous couples, both of whom are undoubtedly non-lysers:

a) Some lepromatous couples could be genocopies; that is to say, they would have the same phenotype brought about by different genotypes with the same final effect.

b) Some Mitsuda-positive individuals born to lepromatous couples would be phenocopies, i.e., in spite of having the non-lyser genotype they could have been transformed into lysers, e.g., because of being more intensely exposed to BCG vaccination and repeated lepromin injections[13, 14, 15]. This

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transformation would be expected to be more common among persons whose lysing threshold is near the antimodal value.

c) Some Mitsuda-positive reactors would not exhibit histological correspondence, i.e., the macroscopical late reaction to lepromin would have occurred without active participation of the macrophages. This situation can be observed in about 15% of positive + and ++ Mitsuda reactors[16, 17, 18].

d) An appreciable fraction of Mitsuda-positive reactors born to lepromatous parents would be composed of illegitimate children[19].

The lysing threshold hypothesis also offers a simple but coherent explanation for the occurrence of different forms of leprosy. Thus, the non-lyser phenotype is the source of the lepromatous cases, since *M. leprae* are able to survive and to multiply only within macrophages which are not capable of lysing the bacilli. When lysers are infected with *M. leprae* they either do not manifest leprosy at all or have the tuberculoid type of the disease, depending on environmental and/or endogenous variables. People whose lysing threshold is near the antimodal value have the tendency to manifest borderline leprosy when infected with *M. leprae*. This explains not only the instability of borderline patients, but also why they are less frequently found among leprosy cases in all populations.

Besides explaining the origin and low frequency of borderline cases, the lysing threshold hypothesis provides an explanation for some intriguing epidemiologic data concerning lepromatous and tuberculoid leprosy cases. As will be seen, such data can be explained if the source of lepromatous patients is circumscribed to a specific and small fraction of the human population composed of individuals whose macrophages are genetically unable to destroy *M. leprae* (non-lyser phenotype). In that case, in highly endemic areas the proportion of lepromatous cases would tend to a limit, that is to say, to a stable value. In contrast, the tuberculoid cases would be positively correlated to the global prevalence of leprosy, since the lyser phenotype is considered to predominate in all human populations.

For a long time it has been known that the lepromatous rates in areas where leprosy is highly prevalent never surpass 1 per 1000[20, 21]. Some epidemiologic data show clearly that the proportion of lepromatous cases decreases as the global prevalence of leprosy increases, indicating that the proportion of lepromatous patients tends towards a stable value[22, 23].

In spite of its coherence, the lysing threshold hypothesis has not been generally accepted. This has apparently been due to the demonstration that peripheral blood lymphocytes from lepromatous patients exhibit an impaired *in vitro* blastoid reaction towards *M. leprae* antigens which seems to be specific to this bacillus[24, 25, 26, 27, 28, 29]. The

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specificity of this impairment is indicated by the fact that the impaired reactivity to nonspecific mitogens, which is shown *in vitro* by the lymphocytes of some lepromatous patients, is usually associated with leprosy activity or can be attributed to the effect of dapsone (DDS)[30, 31, 32]. In contrast to the concordant results seen in these lymphocyte transformation tests, the *in vitro* reaction of blood-derived macrophages from leprosy patients and healthy individuals has given controversial results, probably as a consequence of technical differences[5, 6, 33, 34, 35, 36, 37, 38, 39, 40, 41].

Thus, the apparent specificity of the impaired blastoid reaction of lymphocytes from lepromatous patients to *M. leprae* antigens, together with the discrepant results concerning the *in vitro* reaction of blood macrophages with leprosy bacilli, was considered by most immunologists as sufficient evidence for assuming that the primary defect in lepromatous leprosy lies with the lymphocytes. Consequently, the lysing threshold hypothesis, which considers the primary defect in lepromatous leprosy as inherited and located within the macrophages, was neglected. The hypothesis was not generally accepted despite the arguments that:

a) *In vitro* systems may not reflect *in vivo* reactions. The discordant results concerning the *in vitro* macrophage behavior toward *M. leprae* are not essential for proving or disproving the hypothesis.

b) The most striking difference between the lepromatous and the tuberculoid lesions results from the difference in their macrophage function; the former being infiltrates where Virchow cells predominate, the latter being granulomata of epithelioid cells.

c) The lysing incapacity of macrophages of lepromatous patients is specific for *M. leprae*, since other mycobacteria are destroyed by them after phagocytosis *in vivo*[42, 43, 44, 45, 46, 47, 48, 49] or *in vitro*[6].

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d) The Mitsuda reaction which evaluates, though not perfectly, the lysing ability of the macrophages for leprosy bacilli has a prognostic value. A positive reaction indicates resistance at least to the lepromatous type of leprosy[50, 51].

e) The Mitsuda reaction is a familial trait[1, 2, 3, 4, 52].

Time has provided more elements in favor of the lysing threshold hypothesis. One of them was the demonstration that the lack of *in vitro* response of lepromatous patients' lymphocytes to *M. leprae* antigens is secondary, and due to failure of their macrophages to present these antigens in an immunogenic form to the lymphocytes. Hirschberg[53] has shown that when lymphocytes of lepromatous patients were incubated with macrophages from leprosy or healthy contacts whose lymphocytes respond well to *M. leprae* antigens, they also respond well to those antigens. In contrast, when lymphocytes of leprosy patients or healthy contacts who respond well to these antigens are incubated with macrophages from lepromatous patients, they fail to react to *M. leprae* antigens.

The vaccination experiments developed in Venezuela by Convit and coworkers[7, 43, 54] have given additional support to the hypothesis which considers the primary defect in lepromatous leprosy to lie with the macrophages. These authors were able to show that persistent Mitsuda-negative contacts as well as Mitsuda-negative indeterminate leprosy patients became immunologically reactive to leprosy bacilli when they received intradermal injections of a mixture of heat-killed *M. leprae* and viable BCG. Such individuals gave positive early and late reactions to standard and concentrated integral lepromin, as well as to soluble antigen extract of *M. leprae*[55]. Their lymphocytes showed blastoid reactions *in vitro* in the presence of *M. leprae*. Moreover, the indeterminate patients developed inflammatory reactivity in the hypochromic lesions, and a papular rash with a tuberculoid structure was often observed at the sites where leprosy bacilli were present. The same vaccination procedure provoked less dramatic changes in lepromatous patients, but it was able to also induce their macrophages to lyse both mycobacterial species and enabled them to develop positive early and late reactions to standard lepromin.

The experiments of Convit and coworkers[7, 43, 54] have shown that individuals who are destined to be permanently nonlysers of *M. leprae* can be transformed into lysers of this bacillus by allowing their macrophages to phagocytize a mixed suspension of mycobacteria containing a species which they are unable to destroy (*M. leprae*) together with another which they are able to lyse (BCG). These authors have also shown that in special cases, which cannot be sensitized by BCG, a mixed suspension of *M. vaccae* and heat-killed *M. leprae* may be used.

It seems, therefore, that when macro-

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phages of non-lyser individuals phagocytize simultaneously *M. leprae* and another mycobacterial species they are able to lyse, such macrophages can become activated by the mycobacteria they can lyse. As a consequence, these macrophages also destroy the phagocytized *M. leprae*. Thus, the primary and inborn error of the macrophages of non-lyser individuals can be corrected, and the antigens of the leprosy bacillus can be presented to lymphocytes in an immunogenic form.

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