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Transfer Factor as a Probe in the Immune Defect in Lepromatous Leprosy

TO THE EDITOR:

Thank you for allowing me to respond to the letter of Dr. Gerald L. Stoner of 9 March 1978, regarding the above editorial. In an area as complex and controversial as the nature of the fundamental defect in lepromatous leprosy, one hardly expects a consensus and Dr. Stoner's comments are most appropriate in expressing alternate views.

One can only agree with Dr. Stoner's desire for more critical evidence bearing on genetic factors influencing susceptibility to leprosy. The editorial in question was certainly not intended to be interpreted as an attempt to present any original concepts regarding this time-honored view. Indeed in references 30 and 31 of the editorial, Dr. Rotberg's hypothesis is reviewed at some length; Dr. Beiguelman's work is reviewed in reference 33; and that of Dr. Godal *et al,* in reference 15 of the editorial.

Obviously this writer strongly disagrees with Dr. Stoner's statements that imply that nothing is known about the mechanism of action of transfer factor and hence its activity in lepromatous leprosy "tells us next to nothing about the nature of the immune defect." As referenced in the editorial, this writer feels there is adequate evidence to allow one to believe that transfer factor acts specifically and in the fashion indicated. If so, in light of the other possibilities for the fundamental defect in lepromatous leprosy, the results with transfer factor in leprosy appear relevant to this writer's judgment.

Dr. Stoner apparently prefers a very narrow definition of an Ir gene to mean only those defined in inbred strains of animals studied by their responses to synthetic polypeptides. As indicated and referenced in the editorial (references 38 and 39), this writer is comfortable with a perhaps more imprecise use of the term to refer to the more than 30 Ir genes identified in animals and the quite large number of known associations between diseases and HLA antigens in humans. To be sure, there are alternate explanations for these HLA-disease associations in humans, but, in this writer's mind, the evidence that these associations are likely to be on the basis of Ir genes appears persuasive at the moment. The interested reader may wish to read Dupont *et al* (1976), for a review of the evidence on this point.

Dupont, B., Hansen, J. A. and Whitsett, C. Association between HLA and diseases. *In:* Clinical Evaluation of Immune Function in Man, Litwin, S. D., Christian, C. L., and Siskind, G. W., eds., New York: Grune & Stratton, 1976, pp 97-132.

As to the evidence presented against the leprosy Ir gene hypothesis, this writer prefers to think of indefinite or subpolar lepromatous leprosy patients as being fundamen-

tally borderline cases. The remarks concerning lepromatous leprosy were intended to exclude borderline disease and as was pointed out in the editorial, a number of control mechanisms "are very attractive as significant mechanisms for the dynamic changes occurring in borderline leprosy."

Regarding the observation that there were "at least 4, and possibly 5" of 37 pairs of monozygotic twins who were discordant for the type of leprosy, this writer is perhaps naively impressed with the converse, namely that 32 and possibly 33 of the 37 pairs were concordant for the type of leprosy (particularly if one classifies subpolar lepromatous or subpolar tuberculoid cases as lepromatous or tuberculoid rather than borderline disease.

Dr. Stoner describes an interesting study which is apparently in press and this writer looks forward to the opportunity of examining the data in more detail when the paper is published. As this writer understands the study described, Dr. Stoner has failed to demonstrate an association between HLA-D antigens and lymphocyte blast transformation responses to *M. leprae* in siblings of leprosy patients. This writer can not by any means accept this finding as proof that there is no association between lepromatous leprosy and genetic factors. As was pointed out in the editorial: "Considering the enormous number of genes in the total complement of human chromosomes, it is obvious that the demonstration of an association between a given disease susceptibility gene and any of the relatively few available genetic markers is indeed fortuitous. The inability to demonstrate convincing correlations to date between leprosy and the limited markers available attests perhaps more to the incompleteness of currently available methodologies than to the lack of the existence of a disease susceptibility or Ir gene for leprosy." In a more philosophical vein, it is usually impossible to prove that something does not exist simply because one does not demonstrate it experimentally. One can usually only say that the experiment failed to demonstrate the phenomenon.

This writer quite agrees with Dr. Stoner that alternative explanations are plausible for all the points brought out in the editorial as supporting the genetic hypothesis of susceptibility to (polar) lepromatous leprosy. In fact, in most instances, attempts were made to point out these alternative explanations, as witnessed by the inordinate length of the editorial. This writer is not persuaded that the alternative explanations offered by Dr. Stoner are more likely than the original interpretations that these findings support the genetic hypothesis of susceptibility to lepromatous leprosy.

This writer, in defense of the editorial, would prefer that Dr. Stoner quote at least the entire sentence he refers to in his final paragraph, namely: "If the results of TF trials in leprosy are an indication that the fundamental defect in lepromatous leprosy resides in a genetic location, then there is little hope in attempting immunization of prelepromatous individuals with *M. leprae.*"

Finally, this writer would like to thank Dr. Stoner for pointing out the shortcomings of the editorial and to express his wish that Dr. Stoner were correct in his conclusions. This currently pessimistic writer would be very happy indeed if the fundamental lepromatous defect turns out to be at a site other than a genetic one.

—Robert C. Hastings, M.D., Ph.D.

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Test for Carcinogenicity of DDS

To The Editor:

Regarding the carcinogenic activity of dapsone (DDS) (IJL **44** [1976] 383), a very simple and rapid way to resolve this controversial matter is to use the rapid and *in vitro* test systems to investigate the carcinogenic and/or mutagenic activity of chemicals as is being used by Dr. Ann D. Mitchell, of the Biochemical Cytogenetics Program of Stanford Research Institute, Menlo Park, California 94025.

—Meny Bergel, M.D.

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