lapsed in 2 years of follow up after stopping treatment; 4 of these 5 patients were lepromin (Mitsuda) positive.

On the other hand, the significant observation of our study was that by further continuation of treatment with dapsone for another 6 months (Regimen II of our paper), no worsening of the disease status was observed in any of the paucibacillary cases, whatever their classification or immunological status. Further, the incidence of relapses was also minimized.

We thank Dr. Jopling for his valuable comments, and hope that our reply will clarify the questions raised by him.

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Allergy and Immunity in Leprosy: Are these Concepts Becoming Obsolete?

TO THE EDITOR:

Science advances by observation and experiment. For both of these, technology is necessary and when it is inadequate, progress may be retarded. However, as investigators into artificial intelligence (AI) are now finding, conception and creativity are also required, but the ideas that these introduce may not be immediately susceptible to confirmation or refutation by existing techniques. In the absence of new ideas, not only may real advances be blocked, but false conclusions may be reached due to persistent misinterpretation of observations and experimental results already obtained.

In the exact science of inorganic chemistry, Stenberg, *et al.* ([9]) pointed out that the solid-state chemistry of superficially mundane A_2BX_4 compounds with β-K_2SO_4-related structures was "*a can of worms*" characterized by prolific polymorphism and, despite careful single-crystal X-ray diffraction studies, *persistent uncertainty* about exact space groups and atom positions. They referred to *50 years of (confusing) literature* and proposed that *wrong structural models might have been refined* (my italics).

It is tempting to believe that similar considerations may apply in the less exact science of "leprology." The interesting editorial by Maier ([5]) gives an excellent review of knowledge of the subject to date, but appears at several points to avoid addressing some crucial longstanding problems. Although on p. 133 Maier states: "There is as yet no immunological explanation for tuberculoid leprosy, in which cell-mediated responses to *M. leprae* seem to be intact." He then cites two possibilities for the appearance of this form of the disease: "Firstly, there may be a delay before the onset of cell-mediated immunity so that when it appears the bacilli are established in vulnerable tissues which are then damaged by the inflammation. Secondly, cell-mediated immunity could be directed against antigenic components which are released only by or-

ganisms that have been killed, so that the immunological attack occurs in the wrong place around dead or leaking bacilli."

The two immunological explanations proposed by Maier are not entirely new and something akin to them in general terms is mentioned in a review of the subject of nerve involvement in leprosy by Pearson and Ross ([6]). The explanations take little account of other important phenomena mentioned in the editorial but which appear to be conceptually dissociated from the heading on p. 129 ([5]) of "Acquired cellular immunity." These phenomena are: a) failure of Hansen's bacilli to replicate *in vitro*; b) lack of axoplasmic damage at the histological loci where these bacilli appear to be replicating *in vivo,* in Virchowian hanseniasis ("lepromatous leprosy"); c) failure to find Hansen's bacilli at the site of axoplasmic damage in early polar tuberculoid macules characterized by the presence of granulomatous activity *in vivo* and a similar failure where the axoplasmic damage is unaccompanied by granuloma formation, as in late polar Virchowian Hansenian damage ("secondary neural lepromatous leprosy"); d) highly specific failure of Virchowian ("lepromatous") macrophages to lyse even denatured Hansen's bacilli *in vivo,* the negative Mitsuda response.

Maier's second suggestion avoids the question of what may have killed Hansen's bacilli in the first place (lysosome enzyme digestion by a host macrophage? antibody from a lymphocyte?) and whether there is a link between the supposed killing mechanism and axoplasmic damage. If such a link exists, the finding (b) above suggests that it is an inverse one. Unless one assumes that in the absence of spore formation every nonreplicating Hansen's bacillus is dead, the corollary is that a mechanism that induces the resting prokaryote to replicate may be directly related to the mechanism that is protecting adjacent axoplasm from progressive damage, or even the same one.

This would only be understandable if each individual Hansen's bacillus carried not only epitopes recognizable by immunocytes but, in order to retain its genotype after each fission, a vertically transmitted (heritable) element pathogenic to axoplasm and laterally transmitted thereto in the absence of bacillary replication. If damage is simply due to leakage or transfer of a nonreplicating antigen to the axoplasm as Maier seems to imply on p. 133 ([5]) ("vulnerable tissues," "wrong place"), this might partly explain a small limited lesion like the positive Mitsuda response, but it fails to explain the massive size, sensory loss, progression, and virtual absence of Hansen's bacilli, from its inception, of a polar tuberculoid macule.

A more likely explanation is that Maier's leaking antigen is in fact a mycobacterium-borne fragment of DNA that can and does leave its prokaryote host and, using the ribosomes of the axoplasm to which it transfers and in which it replicates, induces the axon to synthesize pathogenic polypeptides and/or proteins implicated in surface alterations and in neurological deficit on a molecular scale. The altered axon is regarded as "self" by the Virchow ("lepra") cells and by the Schwann cells of a Virchowian ("lepromatous") human host, just as is the cell wall of the live or denatured Hansen's bacillus. However, it is recognized as "foreign" by the tuberculoid host's epithelioid, giant, and Schwann cells, which mount a progressive autodestructive response to its presence and hand over the breakdown products to the "memory" lymphocytes of the lymphoreticular system. Again, the altered (infected) axoplasm is treated by the cells of the tuberculoid host in the same way as is the cell wall of the live or denatured Hansen's bacillus.

There is no reason why a human host should not be able to differentiate functionally Virchowian ("lepra"), epithelioid, and giant cell macrophages almost simultaneously in the same areas of skin, sensory nerve plexuses, and unmyelinated nerve terminals. Both tuberculoid and Virchowian dynamic processes would then overlap, giving rise to the much disputed microscopic and macroscopic types of intermediate and borderline pathology.

The language of immunology is really quite inadequate for expressing what amounts to molecular parasitosis of each Hansen's bacillus in the deleterious (for it) microenvironmental cellular ecosystem of the human host. I have proposed elsewhere a theoretical model of a mycobacterial hyperparasite [Corcos, M. G. HD; a disorder of mycobacteria? The Star 39:2–3, 6–7 (1979–1980) and Molecular biology of HD;

the case for the involvement of a transferable plasmid. The Star 40:6 and 41:16 (1981–1982)] avoiding so far as possible the language of conventional immunology, but using the semeiotics of Hansen's bacilli in an attempt to derive a logical connection between phenomena (a), (b), (c), and (d) above.

It seems justifiable to question a part of the first sentence on p. 116 of Maier's paper ([5]) containing the statement that: "Leprosy is a chronic infectious disease caused by the intracellular *Mycobacterium leprae* . . . ." Despite the continued failure of Hansen's bacillus to satisfy Koch's postulates, that statement and numerous variations of it have become so widely accepted as to render its inclusion in many publications almost mandatory. This is a pity, because its continued use may lead unintentionally to the concealment of a hitherto unsuspected molecular pathology, that in the light of improving investigative techniques is at least worthy of consideration.

Is leprosy a chronic disease of man, or are there two responses to the different types of behavior of two organisms living in a state of loose mutualism? Are the reproductive properties of a Hansen's bacillus so fixed in each individual prokaryote cell as to justify implied speciation of a genus of mycobacterium? If, in fact, each bacillary cell is a host–parasite complex, owing some of its observed *in vivo* and *in vitro* behavior to a transferable DNA parasite, then perhaps it may be helpful to begin to think in terms of the (hyper)parasite responsible for a disease or disorder of mycobacteria being the ultimate pathogen causing damage to the human host, rather than of the mycobacteria themselves fulfilling this role.

For ethical, humanitarian, and historical reasons Rotberg ([7]) has been a consistent advocate of a change of terminology whereby words having the highly pejorative prefix "lepr . . ." are discarded in favor of others which I am using in this letter, which as well as being non-pejorative may also have value in the critical assessment of experimental molecular findings as they relate to clinical observations. Thus, "Virchowian" is a useful non-tautological term covering both the proliferative cellular response to live Hansen's bacilli and the almost acellular lack of lysis of denatured bacilli found in the negative Mitsuda response. "Hanseniasis" (cf. Leishmaniasis) is more accurately descriptive of functioning Hansen's bacilli, whether replicating or regressive, than is "leproma" which implies true tumor formation hardly justified by the observed cytology. "Hansenian damage," "Hansen's disease," or "HD" (covering damage remotely but equivocally associated with nonreplicating and disintegrated or absent Hansen's bacilli *in vivo*) are at least reasonable neutral descriptions of the axoplasmic damage occurring early in tuberculoid lesions and late in Virchowian ones. The terms have the advantage of not excluding possible natural—although pathological—cross species transfer of functioning DNA from prokaryote to eukaryote cells ([4, 8]), and even of an exceptional cycle of transfer of DNA in the opposite direction from axon to prokaryote, perhaps more frequent though less damaging to all participants many thousand years ago.

On p. 139 ([5]) Maier considers that an animal model would be invaluable to enable a study to be made of why some forms of the disease produce granulomas and how these granulomas damage the victims' nerves. To anyone looking below the surface of what histology reveals, the proposition that granulomas damage the victims' nerves is a nonsequitur and its unwarranted assumption may even inhibit logical consideration of why granulomas are present in Hansen's disease and just what is their relationship to axon damage.

On p. 119 ([5]) Maier points out that at the lepromatous pole patients exhibit a selective immunological unresponsiveness to antigens of *M. leprae* leading to widespread lesions of, among other tissues, peripheral nerves. He also notes that the lepromatous pole of leprosy is characterized by a massive bacillary infiltration of the tissues and continuous bacteremia, but that tissue destruction is minimal and appears late. This is a far cry from the usually observed finding of ingravescent damage to victims' nerves (axons) coterminously with the regression, either spontaneously or in association with therapy, of the bacillated Virchowian infiltrate (granuloma) ([2, 3]).

What is not mentioned is that epithelioid, lymphocyte, and multinucleate giant cell granulomas in a large number of patholog-

ical conditions, though otherwise resembling those of Hansen's disease, are not associated with nerve damage. It may be that this very frequent consignment by various authors, of long recognized observations important in the etiology of HD to different parts of the same paper, is due to our unwillingness to visualize spatial events measurable in cu μm and below, in a time frame measured in weeks, months, and years. As a result, we tend to ignore the fact that in tuberculoid lesions microscopic axoplasmic damage and granuloma formation are so closely associated in time and place as not to exclude the possibility that the former may precede and cause the latter, rather than the reverse [Corcos, M. G. Molecular biology of HD; the case for the involvement of a transferable plasmid. The Star 40:6 and 41:16 (1981–1982)].

So long as observations and experimental results are misinterpreted by their division into the logic-tight compartments to which I have elsewhere referred ([1]), so long will each one continue to add to the already substantial fabric of misunderstanding.

There is much forgetting to be done. At the time of this writing it is beginning to look as if molecular biological and biotechnological methods are becoming incompatible with "leprosy," the "lepra" cell, "lepromin," "lepra" reactions, "leprosy" patients, and "*Mycobacterium leprae.*" These older words were in use long before there had been any investigations into the relationship between bacterial genetics and the molecular pathology of higher plants and animals. Would it not be better to substitute words more in keeping with the newer technology for the older ones, rather than to attempt to fit terms that may have outlived their scientific as well as their social usefulness, into a new and hopefully advancing field of knowledge? Failure to do this could be instrumental in slowing the advance, in opening a larger "can of worms," in perpetuating further uncertainty and more confusing literature, and even perhaps in increasing the refinement of wrong structural models ([9]).

—Michael G. Corcos, M.R.C.S., L.R.C.P., D.T.M.&H.

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Photoactivated Topical 8-Methoxypsoralen in Repigmentation of a Tuberculoid Leprosy Lesion

To the Editor:

We have reported a case of tuberculoid leprosy in which repigmentation was accelerated by use of systemic 8-methoxypsoralen followed by exposure to sunlight (PUVASOL) ([2]).

An 18-year-old female with a tuberculoid leprosy lesion over the extensor aspect of the right elbow was treated with 600 mg of rifampin once a month for 6 months and 100 mg of dapsone daily for 2 years. Treatment was then discontinued and she was kept on 3 monthly follow up. During her second follow-up visit she complained of persistence of hypopigmentation. She was advised to take 20 mg of 8-methoxypsora-