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Editorial

PRIMUM NON NOCERE,[1] THE ETHICS OF TRIALS OF LEPROSY CHEMOTHERAPY

It has always been my view that the demand that the physician does no harm applies to the chemotherapy of leprosy as to every other area. This communication has been stimulated by two recent events. In response to a paper[2] describing a trial of combined chemotherapy, in which one of the regimens included pyrazinamide, a drug previously shown[3] to be without effect against *Mycobacterium leprae*-infection of mice, I discussed,[4] 'the *injunction* [emphasis added] against the use in patients of drugs not already shown effective in mice . . .'. My discussion elicited a response,[5] in which the writer, who had not been involved in the original paper, objected strongly to my use of the word 'injunction'. After permitting me to defend my choice of words,[6] the editor declared the issue closed.

The second event that moved me to produce this communication was my participation in a recent international meeting, at which mention was made of two ongoing clinical trials: one in which an inhibitor of dihydrofolate reductase, which had previously been shown to be ineffective in *M. leprae*-infected mice, was administered both alone and in combination with dapsone or dapsone + rifampicin; and the second involving rifampicin and isoniazid, a drug previously shown[3] to be ineffective in mice, together with a commercially available combination of a long-acting sulphonamide with a dihydrofolate reductase inhibitor. The ethics of these trials were not discussed.

According to my understanding, developed when serving on several committees concerned with the ethical aspects of clinical research, the ethics of experimental chemotherapy in man revolve about two primary considerations: the freely given and informed consent of the subjects; and a judgement with respect to the relative weights of potential risks to the subjects participating in the study, and potential benefits to the individual and to society. Although the requirement to obtain the subject's informed consent has been dealt wtih extensively elsewhere,[7] much remains to be said with respect to the issue of risk *vs* benefit.

Administration of any drug imposes risks of toxicity and other side-effects, known or unexpected. Of this, everyone is aware, and all acceptable clinical trial protocols contain provisions for periodic interviews, clinical examinations, and laboratory procedures that are intended to obtain evidence of any undesirable effects of the drug before these have become clinically apparent. Perhaps a less obvious risk is that inherent in withholding established treatment. Once the efficacy of dapsone in the chemotherapy of leprosy, or of isoniazid in the chemotherapy of tuberculosis, had become established, it was no longer ethical to include in clinical trials groups of subjects to whom only placebos were administered. Similarly, because of the striking efficacy of rifampicin, the THELEP

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Scientific Working Group recognized that it would be unethical, in the trials of combined chemotherapy then being planned,[8] to include a control regimen of dapsone monotherapy.

Obviously, risks are relative, and must be carefully weighed against the benefits expected. The patient with leprosy may certainly expect to benefit from participating in a clinical trial, and, therefore, may ethically be exposed to the risks inherent in the trial of any new drug, including that resulting from the withholding of drugs of proven efficacy, should this be required. At the same time, it is incumbent upon those responsible for the trial both to minimize these risks and to maximize expected benefits. These requirements require elaboration.

The risks of exposure to a new drug and the withholding of established treatment may be reduced by minimizing the numbers of patients involved in the trial, the duration of the exposure to the new drug, and the period during which the proven drugs are to be withheld. To measure the efficacy of a new bactericidal drug, it may be deemed necessary to administer it as monotherapy to patients with previously untreated multibacillary leprosy. In such a case, the risks to patients may be minimized by recruiting the minimal number of patients—approximately 10—required to yield a reasonably precise measure of the rate at which *M. leprae* are initially killed, and by minimizing the duration of the monotherapy. If, for example, the drug is expected to exhibit bactericidal activity similar to that of rifampicin, it need be administered for no longer than 1 month, measuring the proportion of viable organisms within several days of the first dose, and at weekly intervals thereafter.

To place patients at risk in a clinical trial so inappropriately designed that no possible benefit can result is clearly unethical; unavoidable risks must be balanced by certain benefit. Yet, it is debatable how often the capability of a given trial-design to yield meaningful results is considered as a component of the benefit to be expected. Take, as an example, a field trial of a new regimen, in which the endpoint is to be relapse or failure to relapse. In designing the THELEP field trials at Karigiri and Polambakkam, the numbers of patients to be recruited were determined only after decisions had been taken with respect to the rate of relapse expected and the degree of precision desired. It became clear that a minimum of 400 patients was required per regimen, if we wished to be able to distinguish between relapse rates of 1% and 2% per year, with an *alpha* error of 0·05 and a *beta* error of 0·20. Clearly, to have allocated fewer patients per regimen, in order to test more regimens among a limited number of patients, might have resulted in an inconclusive trial, i.e, the patients would have been placed at risk without the possibility of benefit.

A similar case was that of the disposition of the patients who had been recruited into the THELEP controlled clinical trials at Bamako and Chingleput, once the 2 years of treatment had been completed.[8] At that time, there was considerable interest in observing these patients during an additional period without treatment. Regretfully, however, the Steering Committee decided that, on ethical grounds, it could not support such an additional study. Although it felt that it might be acceptable to follow, without additional treatment, those patients who had been treated by 1 of the 2 'maximal' regimens—rifampicin + dapsone + clofazimine or prothionamide administered daily for 2 years, the same could not be held to be true for those patients who had been treated by the 'minimal' regimen—a single large initial dose of rifampicin followed by daily dapsone for 2 years. Even more important, however, was the recognition that, because the endpoint was to be relapse, the numbers of patients involved (215 patients distributed among 6 regimens)

were so small that the follow-up study was unlikely to yield information of any value. Thus, no benefit could be expected that would justify the expected risk, particularly to those patients who had not been treated by a maximal regimen.

The injunction against the use in man of drugs not already shown to be effective against *M. leprae* in mice should be understood in this context. More than once in the recent past, considerable effort has been invested to justify clinical trial of a drug that was shown not to be effective against *M. leprae* in mice. The arguments advanced in favour of trying the drug, despite the lack of activity in *M. leprae*-infected mice, have included the compelling need for new drugs, and the logic of employing a drug with a given mechanism of action.

Whenever a new antimicrobial is to be tried, especially if it is to be administered alone, not only must the toxic potential of the drug be considered, but also the possibility that the drug will prove not to be effective, at the same time that established therapy is withheld. That a drug will prove not to be effective in the chemotherapy of leprosy appears particularly likely in those cases in which the drug has been demonstrated to be without effect against *M. leprae* in the mouse.

That the drug was shown to be inactive in mice has been attributed to shortcomings of the *M. leprae*-infected mouse as a test system. That the mouse footpad system possesses shortcomings is without question. However, these may not simply be assumed, but must be demonstrated in the case of a drug which ought logically to be active against *M. leprae*, but is found inactive. In any event, for the reasons noted above, and in the absence of a widely accepted substitute for the *M. leprae*-infected mouse, proceeding to clinical trial in the absence of evidence that a drug is active in the mouse cannot be considered ethical. The interested investigator could better, and more ethically, employ his skills in the search for an explanation of the unexpected failure of a drug to be active. In fact, such a search may itself yield important information.

Department of Dermatology L. Levy*
Hadassah University Hospital
Jerusalem, Israel

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* Correspondence: Department of Dermatology, Hadassah University Hospital, POB 12000, 91120 Jerusalem, Israel.