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Conferências / State of Art

Mesas Redondas / Round Table
Introduction:

My subject is an easy one to discuss on one level. On the other hand, it is an extremely difficult one at a more basic level. The state of the art in therapeutics in Hanseniasis is, in practice, the application of the World Health Organization multi-drug treatment regimens (WHO/MDT) in the World Health Organization's campaign to eliminate hanseniasis as a public health problem by the year 2000. This is the easy part. On a more basic level, however, I have deep concerns about the WHO elimination campaign. This difficult part is what I want to share with you.

The Leprosy Unit of WHO has been supported by almost unlimited funding from an extramural source for a number of years. It has taken the initiative in therapy, based on the scientific advice of consultants. Its deliberations are translated as standard practice and followed by any number of national leprosy programs. Some of what WHO has accomplished has been beneficial. Now, however, I believe the WHO elimination campaign is causing more harm than good. I think it is time to address some of these issues.

So, I have prepared a talk that will begin with some general comments on the available drugs for the treatment of Hansen's disease. I will then make some observations on the elements of the elimination campaign and multi-drug therapy in the nature of a spoof about what we have to believe in order to follow the lead of the World Health Organization. I will then examine some of the underlying presumptions upon which the WHO multi-drug regimens are based and give you evidence that I believe shows some of these presumptions to be incorrect. We will then look at the current thinking about multi-drug regimens and the overall elimination program. Finally, I will talk about the future directions of the elimination campaign and the future of the leprosy unit of WHO itself.

I wish to make it perfectly clear that my remarks represent my personal views. My views will not in any way represent official views of the International Leprosy Association, the International Journal of Leprosy, the U. S. Public Health Service Gillis W. Long Hansen's Disease Center at Carville, the Louisiana State University in Baton Rouge, or the Tulane Medical Center in New Orleans.

General remarks:

I think we can all agree that the main three drugs are dapsone, clofazimine, and rifampin. I think dapsone is the most valuable of the three, followed by clofazimine, and finally rifampin. Why do I think this? Dapsone and clofazimine are clearly superior to all other known anti-leprosy drugs because there are no pre-existing drug-resistant bacilli. Int. Special 98
going cell division. Newer fluoroquinolones may show even better activity against *M. leprae* than those currently available. If persisters are a problem with *M. leprae*, and I believe they are, then work with analogs of pyrazinamide is important to attempt to develop a drug which will be active against persisters. Finally, there are likely to be promising new leads for leprosy from the current massive screening underway to find new drugs against tuberculosis.

There are fundamentally two approaches to treating a leprosy patient. The first is the traditional approach of treating each patient individually with the optimum known treatment available. This approach, for example, would involve lifelong treatment of lepromatous patients to ensure that they do not relapse and become re-infected. Shorter durations of treatment are known to be adequate for patients with more cell-mediated immunity, i.e. borderline and tuberculoid patients.

The other approach is a public health approach. Inherent in this approach is the notion that it is best to spend the limited available resources to treat the maximum number of patients with the minimally effective regimens. Inherent in this approach is the presumption that the overall burden of the disease on a population will be reduced by this activity. This public health approach is that of WHO with their multi-drug treatment (MDT) regimens. Basically these regimens were initially of an individualized duration in so-called multibacillary patients and fixed duration in paucibacillary patients. Now they are of fixed duration in all types of the disease and the duration is being shortened even further for multibacillary patients. Finally there are newer regimens being tried which are of even shorter durations.

The WHO elimination campaign with MDT or what we must believe to believe that it will be successful:

From time to time for the last several decades there have been meetings of leprosy experts, usually in Geneva at WHO headquarters, followed by proclamations which change the definitions of what we have traditionally thought of as leprosy. As more and more WHO-defined terms accumulate I have difficulty following what are the traditional meaning of words and what are the new WHO definition. This has created enormous confusion.

WHO has abandoned traditional classifications of the disease. All leprosy is now simplified to multibacillary (MB) or paucibacillary (PB). At first this was defined based on results from skin smears. This was later changed to a clinical classification. This lumps some BT, BB, BL, and LL cases as multibacillary and everyone else as paucibacillary. There is no mention of the patient's cell-mediated immunity and no mention of the progression of the disease. Thus some paucibacillary could be Mitsuda negative indeterminate cases; some could be early lepromatous cases with a single macular lesion. The value of traditional classifications such as the Madrid or Ridley-Jopling was that they gave some notion as to the probable clinical course of the disease. TT and some BT, BB and BL cases self-heal. LL and some BL, BB, and BT cases have a progressive course unless treated.

A leprosy patient has been redefined by WHO to mean an individual who is currently recommended by WHO to be receiving WHO/MDT.

Prevalence has been redefined by WHO to mean now the number of human beings currently recommended by WHO to be receiving WHO/MDT per unit of total population.

The elimination of leprosy has been redefined by WHO to mean that the number of human beings currently recommended by WHO to be receiving WHO/MDT is < 1 per 10,000 of the population.

We are told that the number of human beings currently recommended by WHO to be receiving WHO/MDT is less than the number of human beings who used to be considered as having leprosy. Therefore leprosy is being eliminated. What has happened, of course, is merely a change in the definition.

WHO has accepted mouse foot pad experimental data as being clinically relevant. I believe that these data are frequently misinterpreted, particularly with regard to the so-called bactericidal and bacteriostatic properties of drugs. These mouse foot pad definitions are quite different from traditional definitions based on in vitro cultivation of other organisms under optimum growth conditions.

The WHO leprosy elimination plan:

The WHO leprosy elimination plan is nothing more than an uncontrolled clinical trial on a global basis involving millions of leprosy patients.
patients. It tests the hypothesis that the application of WHO/MDT will interrupt the transmission of leprosy. Because it is uncontrolled, if the number of new leprosy patients had decreased, we would never know whether or not WHO/MDT had anything to do with it. When something follows something else does not mean that what follows was caused by what happened before. The formal dictum, taught to graduate students all over the world, is called the falsity of the post hoc ergo propter hoc argument. In this case, the number of new case detections has remained at about 500,000 per year despite the widespread application of WHO/MDT. Thus, it can be correctly argued that because the new case detection rates have not decreased in the last 15 years, it is not likely that WHO/MDT is acting to interrupt leprosy transmission. It would therefore be logical that it would not be expected to do so in the next 3 years, by the year 2000.

It should be emphasized that "elimination" when used by WHO is a new definition, and does not mean eradication. "Elimination" is defined arbitrarily as the number of cases currently recommended by WHO to be receiving WHO/MDT per unit of population or the newly defined "prevalence." As the recommendations of WHO change to shorter treatment durations, then "prevalence" falls and "elimination" becomes more likely. I believe it is not truthful to compare current "prevalence" numbers with former prevalence numbers and claim that WHO/MDT is successful in "elimination." Unfortunately this is being done, and this is having an impact on decision makers to decrease resources allotted to leprosy work since they believe WHO "elimination" is the same as actual elimination, i.e. eradication.

As it currently stands, I believe the WHO elimination campaign will be announced as being successful by the year 2000. I believe that the transmission of leprosy will continue, as before. I believe that support for leprosy work in general will be needed, as before. I wonder how leprosy can successfully compete for limited funds if it is announced that it has been "eliminated."

Underlying presumptions of WHO/MDT:

At the time the WHO/MDT regimens were developed, there were a number of underlying presumptions that were more or less generally accepted as representing a consensus of the group when they met in Geneva. I believe a number of these presumptions are not valid and will point out why.

It was presumed that primary dapsone resistance was common and was increasing. Rifampin was thought to be a highly effective drug and resistance to it was to be avoided. Rifampin's "bactericidal" activity in mouse foot pad experiments was thought to be clinically relevant. Daily rifampin was thought to be too expensive and it was presumed that once monthly rifampin would suffice. By analogy to directly observed therapy in tuberculosis, it was presumed that directly observed therapy on a monthly basis was necessary in leprosy. Finally it was presumed that therapy for leprosy had be simple enough so that it could be delivered to the patients by non-professional staff.

Was primary sulfone resistance really a problem? Dapsone resistance has always been confirmed by the growth of *M. leprae* in mice fed dietary dapsone. Clinical dapsone resistance arose after many years of interrupted dosing of dapsone either based on the notion that stopping dapsone would benefit patients with reactions or by non-compliant patients. It arose after many years of low dose dapsone, based in part on the efficacy of dapsone in low doses in mice. In a series from Carville, secondary dapsone resistance arose an average of 16 years after sulfones had been initiated. Resistance to clofazimine has never been documented despite decades of use as monotherapy. These time periods are longer than the incubation period of leprosy, generally accepted as 3 to 5 years as an average. Thus secondary sulf one resistance did not arise from a pre-existing mutant of *M. leprae* that was resistant to dapsone, but rather it arose after many years of low dose, interrupted treatment with sulfones, and clofazimine resistance has never been seen.

Does low-level dapsone resistance in mice mean that the patient has clinically relevant dapsone resistance? In a study from Carville, 180 consecutive new lepromatous patients were screened by standard dapsone sensitivity tests in mice fed dietary dapsone in the customary doses of 0.01, 0.001, and 0.0001%, corresponding to the customary full, partial, and low-level dapsone resistance. Of these 180 biopsies, bacilli from 27 grew in mice at levels of 0.0001% dietary dapsone or higher.
Of these 27 patients, over half were treated with dapsone, 100 mg daily, as monotherapy. In all of them, by all the customary criteria, their response to dapsone was normal. (Jacobson, Int. J. Lepr. 52:710, 1984). We later extended this series to almost 500 new lepromatous patients. About 15% grew in mice receiving 0.0001% dietary dapsone and about 1-2% at 0.001% corresponding to low and intermediate resistance respectively. We never saw a new patient’s bacilli grow in mice fed 0.01% dapsone; i.e. we never saw a primary full-resistance isolate. If “primary dapsone resistance” is caused by patients with full clinical resistance, i.e. resistant to 100 mg daily doses, transmitting the disease to new individuals, then we should have seen a bimodal distribution of dapsone sensitivities. There should have been a peak of fully susceptible isolates and another peak of fully resistant isolates, corresponding to new patients who acquired their disease from cases with dapsone sensitive bacilli and those who acquired their disease from cases with dapsone resistant bacilli. We did not see this bimodal distribution. What we saw was more compatible with a normal distribution of dapsone sensitivities among native isolates of M. leprae. I do not believe that primary dapsone resistance was ever a problem clinically.

Now let us examine the role of rifampin in leprosy therapeutics. It was presumed that rifampin’s so-called bactericidal activity in mice was important clinically and that combinations of drugs should be administered in order to prevent the emergence of rifampin-resistant mutants during treatment.

Let us begin by reviewing the bacterial load in a new, untreated lepromatous patient with a bacterial index of 5+ and a morphological index of 2%. Such a patient has a total bacterial load of approximately one trillion organisms (1 raised to the power of 12, or 11²). If 2% of this total are viable, then the patient has 2²⁻¹ or 20 billion live bacilli and is carrying 980 billion (9.81¹¹) dead organisms. Among the 20 billion live bacilli about one in every 100,000 to one in every 10,000,000 are naturally resistant to each available single drug, with the exception noted earlier that there are no preexisting mutants naturally resistant to either dapsone or clofazimine. Multiplying the frequencies of resistant mutants times the total number of viable organisms gives a total load of naturally resistant mutants to any single drug in a new lepromatous patient of 2,000 to 200,000.

In addition to this population of resistant mutants, there is another population of organisms that are viable, but dormant and are not susceptible to the action of any of the drugs we have available in leprosy. The estimated frequency of these persisters is in the range of one in every 100,000 to 10,000,000 viable organisms for a total load of persisters in a new lepromatous patient of 2,000 to 200,000.

Using the mid-point estimates, a new patient with 20 billion viable organisms harbors about 20,000 which are naturally resistant to any single drug, except dapsone and clofazimine, and another 20,000 bacilli which are persisters and not susceptible to any currently available drug. This leaves a total of 19.99996 billion organisms that can be killed by any active single drug or any active drug combination. This drug-susceptible population is the 4 to 6 logs of antibacterial activity or the 99.999% killing commonly reported in mouse foot pad experiments. It should be emphasized that any single active drug kills this population and if all available drugs were used in combination they would kill only this same population of drug susceptible bacilli. Confusion on this point is common and the implication is commonly made that each drug added in a combination kills a different, new 4 to 6 logs of bacilli, when, in fact, all drugs are acting predominantly on exactly the same population. The advantage of combination drug regimens is that each drug acts independently on the population of naturally occurring mutants resistant to any single drug. Multi-drug regimens act to prevent the emergence of secondary resistance to drugs such as rifampin, ethionamide, streptomycin, etc. They do not act any differently than monotherapy in killing the 19.99996 billion organisms that can be killed by any active single drug or any active drug combination.

I would like now to examine the so-called bactericidal activity of once monthly rifampin in a multibacillary model of leprosy, nude mice (Hastings & Chehl, Indian J. Lepr. 63:350, 1991). Nude mice were inoculated in the foot pads with one million (1⁹) viable M. leprae. Ten months later the animals had 2 billion (2⁵) organisms per foot pad with a morphological
index of approximately 10%. Considering the difference in size between mice and humans, these animals were clearly multibacillary (lepromatous). For the next 13 months different groups of these infected nude mice were left untreated as controls, treated with daily dapsone in the diet (0.01%), daily clofazimine in the diet (0.01%), daily rifampin in the diet (0.01%), a combination of dapsone, clofazimine, and rifampin in the diet, and rifampin once monthly by gavage (10 mg/kg). Thirty days after the last monthly dose of rifampin all the animals were sacrificed, the bacilli counted, the bacilli passaged in serial dilution to determine viabilities, and passaged for drug sensitivities.

The untreated mice had $42.6^{9}$ (42.6 billion) bacilli per foot pad. Mice treated with daily monotherapy with dapsone, clofazimine, rifampin, or a combination of all three had bacterial loads of 1.3 to 5.0 billion bacilli, or about the load they had when treatment was started. On the other hand, the mice receiving rifampin once monthly had $36.3^{9}$ bacilli per foot pad. The dilution experiments were capable of detecting approximately one viable organism in 10 million total bacilli. We found no viable organisms in the mice treated with monotherapy with dapsone, monotherapy with clofazimine, monotherapy with daily rifampin, or the combination of all three drugs daily. The untreated controls had approximately 1 billion viables of the total of 42.6 billion bacilli. In the animals receiving rifampin once monthly by gavage we found approximately 100 million of the total of 36.3 billion to be viable. Thirteen monthly doses of rifampin killed one log of bacilli, not the 4 logs per dose that is commonly accepted as a fact, and upon which recommendations are made in the treatment of lepromatous leprosy. In drug sensitivity passages from each group all showed full susceptibility to each of the three drugs, i.e. no resistance developed during the experiment.

We interpreted this experiment to show that once monthly rifampin in a multibacillary model is markedly less active when given once monthly than when it is given daily. Each monthly dose clearly did not kill 99.99% of the organisms. Because the bacilli were still sensitive to rifampin on passage, once monthly rifampin was not even active enough to select for rifampin-resistant mutants. I believe that if recommendations are to be made about the treatment of multibacillary patients they should be made based on models of lepromatous leprosy, not standard mouse foot pad experiments.

Let us now examine the importance of the so-called bactericidal drugs compared to the so-called bacteriostatic drugs. Does it matter? Based on mouse foot pad experiments the bacteriostatic drugs are said to be dapsone and clofazimine. Rifampin, ofloxacin, clarithromycin, and minocycline are said to be bactericidal against *M. leprae*. Bacteriostatic drugs do not work if given in intermittent doses. As we have seen, at least rifampin, which is said to be bactericidal, does not work optimally if given in intermittent doses.

What new tools are available to study the effects of drugs on *M. leprae*? One, which was developed by Franzblau at Carville, is radiorespirometry. In this system bacilli are harvested from the foot pads of infected nude mice at the time the organisms are at optimal viability. Bacillary suspensions are then put into a Budemeer apparatus or a Bactec system and exposed to 14-C radiolabeled palmitate. The palmitate is rapidly taken up by viable leprosy bacilli and is then used as an energy source generating 14-C labeled carbon dioxide. This can be trapped in an alkaline solution and the radioactivity measured. The amount of 14-C labeled carbon dioxide emitted reflects bacillary respiration and therefore, indirectly, viability. The system is stable for several weeks and is sensitive to drug effects within 4 days.

What has been learned with radiorespirometry? All drugs known to be active against *M. leprae* are active in this in vitro system at concentrations achievable in vivo in humans. If the bacilli are lightly centrifuged so they are brought into direct contact with each other in a pellet, none of the anti-leprosy drugs work well in vitro. I interpret this to mean that viable *M. leprae*, when in a pellet in vitro, or when in a globus in vivo, can, at least temporarily, circumvent drug-induced metabolic blockades, probably through scavenging metabolic intermediates from adjacent dead bacilli.

To better understand the issue of bactericidal vs. bacteriostatic drugs against *M. leprae*, let us briefly review the mechanisms of action of the major drugs. We will then look at what is involved in a typical mouse foot pad experiment designed to look at whether an anti-
leprosy drug is bacteriostatic or bactericidal.

Dapsone is thought to act as a competitive antagonist of p-amino benzoic acid and inhibit the dihydropteroate synthetase of the bacillus. After 3-4 generations the drug’s effect is to deprive the bacillus of folate by preventing new synthesis. During the first 3-4 generations after the drug is present, bacillary stores of pre-formed folate function normally. Folate is essential for several metabolic steps involving single carbon transfers, including the de novo synthesis of purines, the intercon-version of serine and glycine, and the interconversion of methionine and homocysteine. The most important is the transformation of uridine into thymidine. After 3-4 generations the lack of folate results in a lack of thymidine, and thus, a lack of new DNA synthesis. This blocks DNA replication and the bacillus cannot multiply. As far as I know, dapsone has no effect on protein synthesis whatsoever. It should be noted at this point that *M. leprae* has an avid system to scavenge purines, and to a lesser extent pyrimidines from its environment. In a globus in vivo the bacillus probably scavenges many of the metabolic intermediates from dead organisms in its vicinity and the ultimate blockade of DNA replication would be complete only when these sources become exhausted of usable thymidine.

I do not know how clofazimine works against *M. leprae*, but I am certain from what I will discuss later, that it does not effect protein synthesis.

Rifampin blocks the DNA-dependent RNA polymerase of *M. leprae*. The lack of new RNA, in turn, prevents the synthesis of new proteins.

Ofloxacin blocks the DNA gyrase of the bacillus. This prevents the uncoiling of DNA which prevents DNA replication and which also prevents DNA transcription into RNA. Like rifampin, the lack of new RNA caused by the action of ofloxacin, prevents the synthesis of new proteins.

Ethionamide is thought to interfere with the synthesis of mycolic acids. The others, including minocycline, clarithromycin, and the aminoglycosides, act to prevent the translation of RNA into new proteins at the level of the ribosome.

It would appear then, that all the anti-leprosy drugs which are thought to be bactericidal in mouse foot pad experiments, act in some fashion or other to prevent the synthesis of new proteins. The two drugs which are thought to be bacteriostatic based on mouse foot pad experiments, dapsone and clofazimine, do not prevent the synthesis of new proteins.

Let us look at what is involved in a typical mouse foot pad experiment from the point of view of the bacillus. I believe the natural environment of *M. leprae* is a globus. I believe much of the biology of the bacillus can best be understood by thinking in terms of a biofilm or colony of bacilli rather than a collection of single organisms. What happens when a biopsy is taken for a mouse foot pad experiment? For one thing the circulation of the host is disrupted so that any on-going supply of nutrients or removal of wastes from the bacillus abruptly ceases. What happens next could be likened to a train wreck. After being stored for varying periods of time, the biopsy is finely minced and then thoroughly disrupted by homogenization or “Mickling” by rapidly shaking the tissue mechanically with glass beads. The home of the bacillus, the globus, is disrupted and a single cell suspension prepared and diluted so that 30 ul contains about 5000 organisms. If the morphologic index is an average of 2%, then the entire inoculum contains a total of 100 viable organisms. These 100 viables are injected into the whole volume of the foot pad of the mouse. Chances are that each viable bacillus finds itself all alone in a strange new environment. In order to survive in this new host it obviously has to make many adaptations. At least several dozen new proteins must be made and made quickly if it is to survive.

What does “bactericidal” mean in terms of mouse foot pad experiments? Certainly if the bacilli grow in the mouse foot pad then we can all agree that they are viable. On the other hand, if the bacilli fail to grow in the mouse foot pad were they dead when they were taken out of their former host by the biopsy or were they incapable of making the massive adjustments needed to survive in the foot pad of the mouse? Drugs, which block the adaptation of the bacilli to the new environment of the mouse foot pad, will appear as “bactericidal.” All of the drugs that are termed “bactericidal” inhibit protein synthesis and, therefore, block this adaptation. The two drugs that are termed “bacteriostatic” do not block protein synthesis and do not block this adaptation.
The present system of terming drugs "bactericidal" or "bacteriostatic" are likely to be artifacts of the mouse foot pad system. Until such time as M. leprae can be cultivated, or until such time as some other quantitative system can be developed to directly measure viability, I do not think we should make statements as to the "bactericidal" or "bacteriostatic" characteristics of anti-leprosy drugs. As currently used these terms are not related to conventional definitions of bactericidal or bacteriostatic mechanisms.

**Current status of the WHO elimination campaign:**

Overall the efficacy of the WHO regimens have been excellent. I believe that this is mainly because of the daily dapsone and the daily clofazimine in multibacillary cases together with some degree of cell mediated immunity in all of the multibacillary patients who do not have lepromatous leprosy. I believe the once monthly dose of rifampin is worth little and the once monthly clofazimine is worth even less. If the patient is compliant with the daily clofazimine for two years there is a substantial depot of clofazimine in the body that remains therapeutically effective for many months after the last dose. I believe this is responsible for the relative lack of relapses in those multibacillary patients with lepromatous leprosy who are treated with a fixed duration of 24 months, and now 12 months.

Obviously, if any treatment is to reduce transmission, case-finding must be efficient enough to identify the patients before they have already infected most of their contacts and virtually all transmission must be from active leprosy patients. I know of no evidence that case-finding has become more efficient since the initiation of MDT. There is also the possibility that M. leprae may exist in an environmental reservoir in soil or moss (Mustafa, et al. Int. J. Lepr. 63:97, 1995). I can only point out that in the Western Hemisphere there are many thousands if not millions of nine-banded armadillos with naturally acquired leprosy. These animals are most likely contracting their disease in the wild from puncture wounds in a moist soil environment. I do not know if armadillos can be a direct source of bacilli to infect humans. On the other hand. I can see no reason why a human living in the same area as infected armadillos cannot acquire leprosy by the same mechanism as the armadillos do so, i.e. from a puncture wound contaminated with environmental organisms. Obviously, MDT of known human leprosy cases will not affect this reservoir of M. leprae or prevent infections from such a mechanism of transmission.

**Future directions of the WHO elimination campaign:**

Let us now discuss the future directions of the campaign. Let us begin by reviewing on-going clinical trials and projected future clinical trials sponsored by WHO.

An ofloxacin multi-center trial involves 1651 MB and 1817 PB patients. The MB patients will receive 1 of 4 regimens: WHO/MDT for 24 months, WHO/MDT for 12 months, WHO/MDT for 12 months plus daily ofloxacin for the first 4 weeks, or rifampin 600 mg daily plus ofloxacin 400 mg daily for a total of 4 weeks. PB patients will receive either standard WHO/MDT for 6 months or rifampin 600 mg daily plus ofloxacin 400 mg daily for a total of 4 weeks. It seems clear to me that the intent of these trials is to further shorten the duration of WHO recommended treatment. It also seems clear to me that any lepromatous patients included among the MB patients receiving 4 weeks of daily rifampin plus daily ofloxacin will relapse after treatment is discontinued.

A total of 1483 PB patients with a single lesion will be treated with either standard WHO/MDT for 6 months or rifampin 600 mg plus ofloxacin 400 mg plus minocycline 100 mg as a single dose. A considerable proportion of these patients will self-heal. With no placebo controls it is impossible to determine how many will self-heal and how many will benefit from the single dose of the 3 drugs. The interesting part of this trial is that if the WHO recommended treatment regimen is shortened to a single dose of 3 drugs, none of these patients will be counted in leprosy "prevalence" as currently defined by WHO. This will obviously increase the likelihood of the "elimination" target being achieved on time.

In newer clinical trials begun in January 1986, 1500 MB and 1800 PB patients are involved. Both groups will receive monthly doses of rifampin 600 mg plus ofloxacin 400 mg
plus minocycline 100 mg. MB treatment will either be for 12 months or 24 months. PB treatment will be for either 3 months or 6 months. The intent of these trials seems to be to make treatment totally supervised as well as shorten recommended treatment durations. Those MB patients with lepromatous leprosy will relapse. The monthly doses of rifampin, ofloxacin, and minocycline will affect the same 4 logs of bacilli that can be killed with any one of the three. The 3 drugs do not act each on a different 4 logs of organisms. Without a placebo control group it will be impossible to say what proportions of the PB patients will self-heal or benefit from the treatment regimens.

Are these clinical trials a good idea? A total of 8251 human subjects are being put at risk. The end points of these trials are lack of efficacy or relapse, either of which carries the danger of irreversible nerve damage. I cannot see how these subjects could give informed consent to participate in these trials. Could the answers to the questions being sought in these massive clinical trials not come from animal or in vitro experiments?

These clinical trials seem aimed at providing support for future recommended regimens becoming shorter and shorter. Shorter regimens will decrease "prevalence" as it is currently defined by WHO which will enhance the likelihood of the "elimination" goal being achieved by the year 2000. Many of these experimental regimens do not contain the two most valuable anti-leprosy drugs we have available, dapsone and clofazimine. To me the rationale for the choices of drugs is based on artifacts of the standard mouse foot pad system, a technology that dates back to 1960. I do not believe the conclusions reached from standard mouse foot pad experiments suggesting bactericidal activity from drugs that in other systems and with other microorganisms are bacteriostatic by virtue of inhibiting protein synthesis.

There are three, purely administrative ways to guarantee "elimination", as defined by WHO, by the year 2000. The first is to shorten the WHO recommended treatment regimens even further. A classic example is the approach of a single treatment with three drugs for single lesion PB cases. If this becomes WHO recommended treatment this eliminates them from being counted in the WHO defined "prevalence." The second approach is to further redefine "leprosy." For example, "leprosy" could be defined as only those patients who had a bacterial index of more than 5+. A third approach, which unfortunately may be occurring, is to create the impression that leprosy is being eliminated. The consequence of this impression is that donors and decision-makers will divert support from leprosy to other health priorities. This will result in less effort to detect new cases and, in turn, a fall in new cases being reported. As a final example of the confusion caused by WHO terminology, by current WHO definitions complete global "eradication" could be accomplished if the WHO officially recommended that leprosy should not be treated at all. I think it is time for plain speaking.

What are the prospects for the future of the WHO elimination campaign? I believe that WHO will announce the elimination of leprosy by the year 2000. Will WHO be interested in a disease they have declared as eliminated after the year 2000? I believe that there will continue to be new leprosy patients after the year 2000 and that they will continue to occur in about the same numbers as currently. Who will care for these patients after the year 2000? Was this whole elimination campaign really a good idea? If it continues on its present course through the year 2000, I believe it will mainly serve only to deny much needed resources to the present, and to the next generation of leprosy workers and leprosy patients.