PART III CLINICAL TRIALS

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III.1. Choice of Patients

Dr Browne
We think now in particular of clinical trials in leprosy and the choice of patients. We have had some observations about the need for patients with lepromatous leprosy, high MI, and high BI, previously untreated. Dr Pearson said that there also should be trials using non-lepromatous leprosy. Would anybody like to pursue these questions?

Dr Pearson
When planning a trial we have to decide what we want to know. If it is whether a drug works in killing bacilli, then one chooses patients with lepromatous leprosy. If it is for other things, such as comparing the incidence of complications, or of reactions on different regimes, you have to decide what response you want to study and choose the appropriate group of patients. The only really important thing is whether a drug cures the disease. The only way to establish this is by giving treatment for a period and then stopping it, and seeing whether the disease is cured. For this type of trial I think that non-lepromatous leprosy is the most suitable type of disease to choose, because such trials can be undertaken and results obtained in a reasonably short time.

Dr Ridley
This is an interesting idea. I think that more information is wanted about the incidence of relapse in tuberculoid patients without treatment.

Prof. Azulay
It might be an interesting idea, but I really don't think it will be worthwhile pursuing because the rate of relapse in tuberculoid cases is very, very low. You will spend too much time, maybe 20 years, in deciding if a therapy is good or not on that basis. I have been working in leprosy for more than 30 years and I can tell you that in tuberculoid leprosy relapse is very rare.

Dr Pearson
Maybe we should not choose polar tuberculoid but rather a type of disease that gives a measurable relapse rate in a reasonable period. Let us look at it from that point of view.

Dr Walter
Dr Pearson's idea to include tuberculoid cases in a trial for testing new drugs is a good one. However it is not only Dr Pearson's idea. Others have put forward this idea too. Dr Languillon has published several papers on the use of long-acting sulphonamides in tuberculoid leprosy. The question is by which criteria of

measure in the early stages without waiting for three or four years until we can histologically confirm a more or less definite cure.

Can we measure in the early stages the effect of the drug? If somebody could find out this, I think we would have some worthwhile result. Possibly we could use another drug, even for a very short time in tuberculoid leprosy; but how can we measure it?

Dr Davey
I was just going to refer to the point that Dr Azulay made earlier. In the presulphone days, we had very large numbers of TT and BT patients on treatment in Nigeria who did very well indeed on chaulmoogra oil treatment, and relapses were very rare among them. The disease just disappeared. The very first paper I ever published was one in the International Journal round about 1939 reporting on a group of about 70 isolated patients across the whole spectrum of leprosy who for reasons outside our control, had to be left to their own devices for two years with no treatment whatever. These were people whose leprosy was sufficiently marked for them to be well known objects in the community and therefore were isolated. After two years the interesting point was that though they had no therapy of any description there were several of these people who had resolved completely, and others had very much improved. So we do have very serious problems when we try to use tuberculoid and near-tuberculoid patients in any form of drug trial.

Dr Browne
There is shortly to be published in *Leprosy Review* a report of 2700 cases of self-resolving leprosy.

Dr. Languillon
I have treated many hundreds of patients with leprosy of tuberculoid form for 17 years with sulphonamides. I have never seen relapses among these patients. They were also treated with dapsone, and relapse was very, very rare. I agree with Dr Azulay, the relapse of the polar tuberculoid form is also very rare in Dakar.

Dr Ramanujam
We have followed up cases of tuberculoid leprosy from 1939 till 1956 when sulphone treatment was available to all patients. This is a special reference to all kinds of tuberculoid leprosy in children and the follow-up study shows that in the vast majority this disease resolves spontaneously. The children were followed for seven years afterwards and there was not even one instance of relapse. I am not able to give you figures of relapses in other patients with tuberculoid leprosy because in our experience classical tuberculoid leprosy is becoming very infrequent in that part of the country where I am working. Dr Pearson made a modification in his suggestion for trials especially to study the incidence of relapses. He said that instead of TT we would like BT cases to be under surveillance for a long period of time. Here I would like to mention that since 1965 we have had a longitudinal trial in borderline cases using very small doses of dapsone ranging from 1.25 to 2.5 mg per day, that is 240 cases in a 20 years' follow-up study. Recent assessment of these cases revealed a relapse rate of 8.8%. We presented these results in one of the seminars held at our institute. At that time the question was posed to me whether this relapse was possibly due to the

small doses of dapsone. From the literature I learned that Dr Davey reported a relapse rate of 29% in the Tokyo Congress in inadequately treated borderline and indeterminate cases. We have information with regard to the relapse rate in the unstable forms of leprosy. Relapse is a very serious problem in lepromatous cases with which we are all concerned, and if you propose to concentrate on the less serious forms of leprosy, we could possibly lose the main issue.

Dr Krenzien
Concerning the selection of patients for control trials, I had out of 67 patients, 48 who were pretreated while 19 were new cases. I found up to now no difference between the previously treated cases and the new cases as to the fall of the BI, even if the counting method was used. This would be an argument to start control trials with a mixture of previously treated and new cases, because we get the same situation in both.

Dr Browne
I too would add a point that already has been made today, namely that we should be most careful in our classification of patients. If we include those with borderline elements and call them lepromatous, then our results are dubious to a very serious degree.

III.2. Duration of Trials

Dr Browne
I think we should say a word or two about the duration of trials we would recommend, and concentrate on lepromatous leprosy in pilot trials. For how long should an initial trial be undertaken? Then for the definitive trial on a wider scale, multi-centre if possible, what should be our recommendations? Some people have suggested that it is possible to obtain definite indications within a few weeks or months.

Prof. Azulay
I had a group of cases, treated with clofazimine over five years, all BI negative and clinically very well. Do you believe that we can withdraw treatment under these circumstances?

Prof. Pattyn
As Dr Pearson said earlier, much depends on the purpose of the trial in question. At the Bergen Congress the Panel on experimental chemotherapy divided trials into three or four groups, very short ones, short ones, long-term ones and very long-term ones. A very short trial can fulfil the purpose of determining the activity of a compound that has previously been tested in the laboratory, a short-term trial can determine short term toxicity effects and things like that, while a very long-term trial will provide information about what is happening in terms of relapses and resistance. Everything depends upon the question, what is the precise purpose of the trial.

Dr Karat
The duration of a trial will depend on the purpose we have in mind, for instance to determine whether a given compound shown to exert some effect in animal

experiments, is active in man. From my own personal experience I know that trials lasting less than six months are not very valuable, because of sampling errors, the techniques, all the various things I have mentioned this morning.

Prof. Freerksen
I think we must differentiate between the time necessary for the treatment of a single case and the duration of a trial. These are two entirely different matters. The duration of a trial depends on the objective we have in mind. Short-term trials can be carried out with a view to studying the activity of a substance during treatment, but in this case the subsequent period without therapy obviously also belongs to the trial, because no trial is complete without the consideration of relapses. In fact, we do not know how long we have to treat a patient and which medication should be applied in order to obtain complete healing. The decisive criterion is the absence of relapses, which can only be studied over a long period during which the patient remains untreated.

Therapeutic methods exhibiting relapses during treatment are obviously of no value. But here we require a clear definition of what is meant by the term "relapse".

It is relatively simple to organize trials providing answers to precise questions. Their interpretation, however, is quite a different matter. Nobody knows exactly how long a patient should be treated, since this has never been sufficiently studied because nobody wants to incur the risk of withdrawing treatment. Dr Azulay has therefore raised a decisive question.

Dr Languillon
If we administer combined therapy with rifampicin and Isoprodian, the trial can be stopped after three to five months, when the Morphological Index is negative, because all bacilli are destroyed and no solid or granular forms are to be seen. Then it would be enough to continue treatment with dapsone *per os,* or better by injection of DADDS every two months. But for the treatment in lepromatous cases it is absolutely necessary to continue treatment for life, because I have seen many patients with lepromatous leprosy which was inactive but when treatment was stopped, after one, two, five years, relapses have appeared

III.3. Duration of Therapy

Dr Browne
Dr Walter, can you be so kind as to summarize briefly the recommendations of the WHO regarding duration of treatment.

Dr Walter
These recommendations are more or less known; namely, five years of regular treatment after negativity has been achieved. However, in lepromatous cases it is recommended that treatment be continued for life. In our discussion we seem to have gone a bit in a vicious circle regarding the alternatives. We have not found any alternatives so far as mass treatment is concerned. The term "mass treatment" is a bit unfortunate, since we are not really doing mass treatment, which implies

treatment of a whole population. We have to distinguish this procedure from the one for cases which do not tolerate easily the generally recommended treatment with dapsone.

Dr Browne

When one looks hard one can always find fragmented bacilli and the only way of defining complete bacteriological negativity is to kill the patient and section all his tissues, when you would certainly find some bacilli in the bone marrow, the liver, the spleen, the lymphatic nodes and between nerve fibres. From the public health point of view this person is no longer a menace. From the individual point of view he may relapse. The group at Sungei Buloh is discussing the possibility and the ethical desirability of ceasing treatment after bacteriological negativity has been achieved. Would that be justifiable?

Dr Rees

Since I am of the British Medical Research Council and responsible for the Leprosy Research Unit you referred to at Sungei Buloh, I would like to comment and justify the point you have challenged. Let me first recapitulate what Dr Browne has said, which clearly relates to his vast experience and that of other leprologists, that some lepromatous patients treated with dapsone for many years, and in spite of negative skin smears, may relapse with active disease when taken off treatment. Excluding the possibility that such patients might have been reinfected it must be concluded that their relapse arises from a residue of living bacilli somewhere in their body tissues. While I am well aware that among clinicians this subject has led to heated controversy and the presentation of somewhat mystical alternative hypotheses, I will present evidence in support of basic bacteriological principles. In other bacterial, and particularly mycobacterial infections, it has been well established that small populations of living and drug-sensitive organisms can persist in the tissues in spite of adequate chemotherapy. Therefore, there is nothing unique about relapses occurring in lepromatous patients after stopping treatment, in spite of many years of therapy. In leprosy the routine bacteriological assessment is made from skin scrapes and therefore on a quantitative basis, based on the assessment of stained skin smears, there could be a small number of organisms present even when a skin smear assessment by routine examination is negative. This is simply a question of numbers of acid-fast bacilli present related to the volume of smears examined and the time allocated. The same discrepancy applies to the examination of smears of sputum from patients with pulmonary tuberculosis. Cultures are more sensitive. In leprosy the examination of skin scrapes would particularly apply if viable persisters existed in sites other than the skin, and likewise would apply if the small number of such persisters were concentrated specifically within the cells of nerves or plain muscle in the skin, rather than uniformally throughout the skin tissue. There is good histological evidence, and mouse footpad infectivity evidence, to suggest that the latter situation is relevant. Namely, that well-stained bacilli in small numbers may particularly be seen only in dermal nerves and arrector pili muscle fibres or in peripheral nerves and striated and smooth muscle fibres in parts of the body other than the skin. Clearly therefore negative skin scrapes could well be only a

question of small numbers of persister bacilli, below the number detectable by routine microscopy. There is good evidence using the mouse footpad infection to support this explanation. Thus it has been established that skin sites negative on microscopy as skin smears, when biopsied and homogenized and injected into mice produce positive infections. Likewise, similar patients with skin smear negativity have been shown to harbour living *Myco. lepr*ae capable of multiplying in the mouse, when biopsies are taken from muscle or peripheral nerve or scrotal skin (including dartos smooth muscle). In fact, our own studies at Sungei Buloh have shown that 7 of 12 lepromatous patients maintained on full dapsone therapy for 10 years have from one or other of these biopsy sites produced infection in mice. This evidence is of paramount importance since it clearly shows, as in tuberculosis, the presence of a few viable persister bacilli in patients treated with chemotherapy for many years, and establishes the mouse infection technique as being more sensitive than routine stained skin smear techniques.

Thus our experimental studies are in line with the experience of leprologists who are familiar with relapse occurring when skin negative patients are taken off dapsone. Unfortunately, the routine application of the mouse infection is not generally available. Our own special studies fully justify continued dapsone therapy long after, if not indefinitely, skin negativity is reached in patients with lepromatous leprosy.

However, having presented evidence that the mouse footpad infection is more sensitive than stained skin scrapes for identifying persisting viable bacilli within the skin or other tissues, it is surely justifiable to use the mouse to monitor and compare the efficacy of other antileprosy drugs. Therefore, if a new antileprosy drug is monitored in the mouse, and inoculation of homogenates from the skin or other tissue sites fails to reveal the presence of living bacilli, it would be reasonable to conclude that the new drug was more beneficial than dapsone. On this basis we consider that if a new drug monitored this way in mice gave completely negative results, it would then be justifiable to withdraw treatment as long as the patient could be regularly monitored using the mouse test. On the basis of our present knowledge we consider this justifiable and moreover the only way that a new drug could be shown in patients to be more effective than dapsone.

Dr Browne

There are two points I should like to make from the chair. One is that in the mouse we have a wonderful model, but it may not pick up every living organism. Chang and other workers suggested that organisms that we would call non-viable on morphological examination, would not grow in the mouse, but in the human they might grow. The other observation is a very practical one. In a developing country with 40 pence per head per year to spend on all medical services, including leprosy, can rifampicin be used for a shorter period to reduce drastically the bacillary load and render the patient non-contagious? Is it a practical possibility then to use rifampicin, say, for a fortnight and then to switch to dapsone? This is perhaps not the ideal, but is this a practical possibility for a developing country with 40 pence per annum per head to spend on all medical services?

Dr Ellard, would you consider it advisable to give one dose of rifampicin, perhaps 1 g, or 1.5 g, and then dapsone to patients in a rural situation who can be visited only once in three months by an itinerating medical officer?

Dr Ellard
My answer would be yes.

Prof. Pattyn
I think we have now started talking about optimal things to do in reality. If you pose the question in terms of what do we do in a situation where we can reach the patients only once every three months, then definitely it would be worthwhile to add a dose of rifampicin at the start. Whether this is the absolute level optimum, we do not know at the moment. But choosing between DADDS alone from the start in the multibacillary patients, or DADDS plus one dose of rifampicin, I think that the latter possibility is certainly the best one.

Dr Walter
It is definitely most desirable, and there is no doubt about it from the public health point of view, to have a drug which reduces or terminates infectivity in a very short time. On the other hand we cannot possibly base our recommendations on the experience gained in 50 cases. We need more trials to be carried out in a proper way by independent workers for longer periods with greater numbers of patients, before we can make practical recommendations on this particular subject.

Prof. Freerksen
Being physicians we should not let economic questions interfere too early with scientific or medical ones. Our duty is to find out the best method for the patient. The administrative authorities should then examine whether our suggestions can be put into practice. May I raise here a concrete question regarding this situation: Should we prefer bactericidal or bacteriostatic substances in leprosy treatment? All of you seem to hold the opinion that preference should by all means be given to bactericidal substances. Since we know, however, that bactericidal substances are not automatically bactericidal medicaments, yet that we can approach the bactericidal effect by using the right combinations (not any and every combination), should we not consequently give preferance to combined therapy instead of single substances?

It is easy to demonstrate that single substances do not induce any bactericidal effect whereas combinations do, at least *in vitro*. In my opinion we have no other alternative to practising combined therapy. It is not difficult to show that combinations with rifampicin are more effective than rifampicin alone as has been demonstrated in Figs 10, 11, 13 and 14 of my first Paper (p. 25). Of course this can neither be examined nor proved at hospital on the basis of a few cases differing moreover in anamnesis and method of treatment. Such studies which unfortunately are rather common nowadays have no informative value.

Prof. Saerens
I don't think that we all are convinced that combined therapy is more bactericidal than one drug alone. On this point I don't agree.

Prof. Freerksen
The question whether we should choose combined therapy or single substances is no longer a matter of conviction, since in our time there is no doubt that combinations prove to be more effective than single substances. I am not aware of any exception as far as mycobacterial infections are concerned.

Prof. Saerens
It is a question of interpreting facts.

Dr Ellard
I should like to remind the audience that many workers, including my colleagues Dr Dickinson and Prof. Mitchison, have shown that single drugs such as isoniazid, rifampicin or streptomycin have a marked bactericidal effect against logarithmic cultures of *Myco. tuberculosis.* Continued exposure to concentrations of these drugs attained in the body with normal therapeutic doses can result in the killing of from 90 to 99.9% of the viable organisms.

Dr Browne
We have not yet answered your question, Prof. Azulay. Shall we advise to stop treatment?

Dr Karat
I should like to make a suggestion: to study the bone marrow of all your 20 patients, keep the negative ones under surveillance and stop the treatment. In all other cases continue treatment. Then you have at least two groups with certain known facts whom you can compare twice a year.

Dr Jopling
I would suggest that this is the stage to introduce acedapsone therapy into this group of patients described by Prof. Azulay.

III.4. Criteria for Non-infectivity

Dr Browne
We should deal briefly now with the criteria for non-infectivity, the criteria for freedom from risk of relapse and the criteria for stopping treatment.

The criteria for non-infectivity: are there any clinical criteria that would help? Do we rely on laboratory data, in particular the presence of morphologically normal, presumably viable organisms, in the discharge from open ulceration or from the nasal mucosa? These are very practical and very important questions. When can we say that a patient is no longer contagious, when can he work in school, or in a restaurant, etc.? These are practical problems. When, as in Hong Kong, can we say a patient may be admitted to a factory and to a high-rise apartment? Freedom from risk of relapse is rather more important and rather more difficult to define.

Dr Pearson
The only way to find out is to do it, carefully classifying the patients so that one can obtain relapse rates after different periods of treatment in different types of leprosy. There may be enough data for us to get some reasonable guesses already available in the world. It would be nice if this could be assembled in one place.

Dr Walter
The point I would like to make is that when such studies are undertaken we should keep in mind that a certain percentage of so-called relapses may in fact be reinfections which are difficult to separate.

Dr Browne
Dr Davey wrote years ago in a paper from Eastern Nigeria that the danger of relapse was particularly great in patients with intermediate types of leprosy. Would you like to add to that?

Dr Davey
I have still firmly that opinion, but I have nothing further to add. I have not been in India long enough to have any firm judgement there.

III.5. Intermittent v. Continuous Therapy: Toxicity and Side-effects

Prof. Saerens
As far as safety of intermittent therapy is concerned, I should like to remind you that the data which we have on tuberculosis have dealt with intervals of administration of one week, as the longest interval. I mentioned yesterday that the intervals seem to be an important factor in the incidence of side-effects. Now for micro-biological reasons one could think of leprosy in terms of a monthly interval or a bi-weekly interval. We don't know if this would not increase the risk of side-effects.

We should be very cautious. There are more side-effects when the interval is one week versus twice weekly. We don't know anything if we would increase the interval to two weeks, three weeks or four weeks. This needs investigation.

Dr Browne
Would you like to comment on the possibility of toxic symptoms arising if a single dose of rifampicin is given at three monthly intervals?

Prof. Saerens
We don't know anything about it. Such an investigation has never been done. If we extrapolate from what we know we should be cautious.

Dr Rees
I entirely agree with Dr Saerens answer. However, from our knowledge in the chemotherapy of tuberculosis it has been well established that the manifestations of rifampicin toxicity are directly related to the length of time between intermittent treatment up to a period of seven days *and* dosage. Namely, the higher the dose in intermittent therapy with rifampicin the greater the incidence of toxicity. Doses of 600 mg were least toxic. Because in leprosy we are hopeful that doses of rifampicin at intervals of one month may be beneficial, intervals of such magnitude and their predisposition to toxicity is completely unknown. At present we are undertaking trials in leprosy using a dose of 600 mg on two consecutive days at intervals of one month, and currently we have no evidence of clinical toxicity or the presence of rifampicin antibodies.

Prof. Saerens
We know that within the first three to four months of any intermittent therapy the incidence of side-effects is small. Most appear after five or six months of intermittent therapy. Dr Rees, how long do you intend to go on with monthly administration?

Dr Rees
This is initially six months.

I think it is justified to be cautious. On the other hand we have also to take into consideration not only the periodicity of the administration but also possibly the number of administrations. What we know is that side-effects appear after a given number of administrations and maybe, if this number is spread over a very prolonged period of time, we will not see anything for several years. We just don't know, it is very difficult to make any guess on this matter.

Dr Hogerzeil
This touches on a practical question. If we give 1500 mg rifampicin in one dose to a patient, should we warn him against taking a further dose of rifampicin later on? At present, in our circumstances, it is not very likely that he would soon be treated with another dose of it, but what I want to ask Prof. Saerens is, do you think that after a single dose of 1500 mg rifampicin the patient ought to watch out against a second dose?

Prof. Saerens
I am afraid, we have no answer. We are naturally afraid of possible severe and maybe fatal accidents, but these have occurred under two different types of circumstances; one under very well monitored intermittent therapy, where different factors have been shown to be implicated, as I mentioned yesterday; and the other one in patients who had been on continuous therapy for a very long time and then accidentally stopped their therapy and started it again without warning anybody, or else their doctor started the therapy again. In the previous period very considerable doses of rifampicin had been taken in all cases. We don't know if one dose could be enough to provoke complications.

Prof. Freerksen
We have experience with about 200 patients many of whom have been treated with rifampicin combination over a period of two years without any toxic symptoms.

Dr Pearson
I have about ten patients treated for about a year with rifampicin 600 mg on two consecutive days once a month. So far no evidence of immunological toxicity has been reported.

Dr Terencio de las Aguas
In my experience over three years with rifampicin I have seen no side-effects. In contrast, with clofazimine in common with other leprologists I very often observed phenomena in the skin. I should like to know the etiology of these phenomena.

Prof. Azulay
During a five years' treatment programme, all our patients had ichthyosis-like lesions. They treated their lesions with oil, and that is all. This is not due to a regression of oedema as was thought at one time.

Dr Jopling
I commonly see this complication in London with my patients who have been on treatment with clofazimine, and therefore I don't think we can postulate any question of silicone or grasses or any such adventitious agents.

Dr Browne
It is very common in the African, from Ethiopia to Sierra Leone.

Dr Karat
One hundred per cent of patients in our country develop the same skin problems. We did wonder whether there was some relationship to the level of unsaturated fatty acid in the human body because of the affinity of clofazimine for fatty tissue. I had put forward this suggestion to Geigy's who tell me that it is very expensive to investigate patients for levels of unsaturated fatty acid before and after treatment with clofazimine.

Dr Ramanujam
Also in our series of cases whom we had treated with clofazimine, we have very often encountered recurrent lepra-reactions. It is true that an ichthyotic skin condition becomes exaggerated in patients on clofazimine. We found that when the dose of clofazimine was reduced and finally stopped, this condition tended to disappear.

Dr Browne
A good treatment is rehydration in simple bowls of water, for then the liquid will be retained in the epidermis by means of a thin layer of lanolin.

Dr Leiker
I am a little bit worried about the combination of rifampicin and ethionamide. With both drugs liver complications are seen. Among the four patients in this second triple trial I mentioned, one patient developed a severe toxic hepatitis; he survived, but this is a warning to be careful, and we have to keep in mind that the possibility exists that by combining these two drugs, the risk becomes greater than in using one drug.

Dr Pearson
I think it was Dr Karat who mentioned two cases of ilio-ulceration mimicking Crohn's disease in patients treated with Lamprene. In retrospect I have seen one case that could also have this. I think it would be worth keeping an eye open for that in our patients treated with clofazimine.

Dr Molesworth
We had one patient on clofazimine, not actually one of mine, but in a neighbouring leprosarium, who produced a violent and fatal gastric haemorrhage

following his second or third dose. We did a post mortem and except for the very engorged gastric mucosa there was no obvious lesion which could have caused it. I merely report it, I have not seen it again.