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## EDITORIALS

*Editorial opinions expressed are those of the writers.*

### Some Thoughts on the Present Status and Future Prospects of Chemotherapy of Leprosy Based on Experience with Treating Tuberculosis

In few other fields of chemotherapy has our progress toward therapeutic control of an infectious disease been so fast and so rewarding as in human tuberculosis over the last decade. The availability of potent bactericidal drugs, their rational selection and combination, and the identification of the most appropriate parameters for evaluating the effects of treatment are among the major factors which have contributed to the present favorable state of tuberculosis chemotherapy.

The basic principles of modern treatment of this disease were developed within the framework of a study of the quantitative relationships between the nature and doses of the available drugs and the bacillary population on which they were presumed to act. Simplification of the criteria of evaluation, by concentrating on those parameters which generate the maximum of information with a minimum of organizational burden, has also greatly contributed to the progression toward present and future control of the disease both on a limited and on a large scale. As a result of a concerted effort between individual investigators, research groups, the pharmaceutical indus-

try, and international organizations, regimens of high effectiveness and safety and of relatively short duration have been designed, developed, and made available to the medical community. During this process, the special needs of those areas of the world where the problem of tuberculosis is still acute and far from being solved were not disregarded. They were the key factors in influencing the research process. For example, the cost of treatment and the problems of obtaining compliance with the regimens under difficult operating conditions were given very high priority. It is not unrealistic to say that in implementation of mass programs of eradication of tuberculosis the critical step is no longer the solution of basic medical problems but is adequate and selective allocation of financial and manpower resources by the governments of those countries where tuberculosis is still a threat to public health.

Several of these aspects are common to tuberculosis and leprosy. Both are infectious diseases with tendency to become chronic; in both the causative agent is a mycobacterium and in both the bacillary population is very numerous. Application

of a quantitative approach like that described above to leprosy is more difficult than to tuberculosis. The difficulties in controlling the growth of the offending organism, the long times and complex techniques required to define the response of *M. leprae* to the action of a drug or combination of drugs, and the absence of an adequate host immunological response (particularly in the most severe forms of the disease) are some of the major features which make leprosy harder to study than tuberculosis. To some extent, however, the two diseases have basic elements in common and it is possible that critical analysis of the factors involved in the recent developments in tuberculosis chemotherapy can also be of some use for leprosy.

**Rationale for the use of drug combinations in tuberculosis and leprosy.** Treatment of tuberculosis is based on the administration of several drugs in combination. This is done to prevent emergence of resistant strains of *M. tuberculosis* and is the practical application of the concept that bacterial resistance is "selective" rather than "inductive." Experiments carried out in the late forties by M. Pyle<sup>1</sup> had indicated that a large enough, seemingly homogeneous population of mycobacteria contains a variable number of cells which are, as a result of genetic mutation, resistant to the action of a given antibacterial agent prior to any contact between these organisms and the drug. When such a population is exposed to the action of that drug alone, only the sensitive fraction of the bacillary population is killed. As the resistant subpopulation continues to grow actively, within a certain period of time the previously sensitive population will be replaced by an entirely resistant one and the agent employed will have lost its original therapeutic effectiveness. On this basis it would be incorrect to say that the mycobacteria have "developed" resistance to that given agent; rather, the agent has exerted a selective pressure on the bacterial population destroying the sensitive fraction and, by so doing, favoring the overgrowth of the resistant one.

It is hard to understand why this concept and its practical therapeutic implications remained for decades strictly confined to the domain of tuberculosis. It would have been beneficial to medicine if the combined drug approach to the treatment of all severe, high-inoculum bacterial infections had been submitted to extensive experimental and clinical testing in fields other than tuberculosis, for example in leprosy. The frequency with which mutants genetically resistant to the major antituberculosis drugs are encountered in a wild population is now rather well known. It varies from  $1 \times 10^{-3}$  for ethionamide, to  $1 \times 10^{-5}$  for isoniazid, to  $1 \times 10^{-8}$  for rifampin<sup>2</sup>. This means that a population of 100,000,000 tubercle bacilli contains one bacterium resistant to rifampin, 1000 resistant to isoniazid, and 100,000 resistant to ethionamide. Any one of these compounds, if given alone to a patient whose caverns contain, say,  $10^8$  to  $10^9$  bacilli per cavern, will inevitably lead to a selection process of the type described above. The probability that the initial sensitive population will be replaced by an entirely resistant one is roughly estimated by the difference between the size of the bacillary population and the size of a population known to contain at least one colony resistant to the drug we intend to use. We can also calculate the probability that a microorganism will be simultaneously resistant to two drugs. If the probability of resistance to drug A is  $1 \times 10^{-3}$  and that of resistance to drug B is  $1 \times 10^{-5}$  the probability of simultaneous resistance to A and B is  $(1 \times 10^{-3}) \times (1 \times 10^{-5}) = 1 \times 10^{-8}$ . Simultaneous resistance to a third drug C (the mutation rate to resistance being, say,  $1 \times 10^{-8}$ ) is even rarer:  $(1 \times 10^{-3}) \times (1 \times 10^{-5}) \times (1 \times 10^{-8}) = 1 \times 10^{-16}$  which corresponds to one colony resistant to A, B and C being present in 10,000-tera/bacilli. As such huge populations of bacilli are not encountered in practice, we do not expect to find triple resistance.

In leprosy, and particularly in its lepromatous form, the number of bacilli is extremely high. It has been estimated that pa-

<sup>1</sup> Pyle, M. M. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. Proc. Staff Mayo Clinic 22 (1947) 465.

<sup>2</sup> Commission du Traitement de L'U.I.C.T. Considerations sur les medicaments antituberculeux et recommandations sur les regimes de chimiotherapie. Rev. Fr. Mal. Resp. 4 (1976) 157-163.

tients with LL may harbor  $10^9$  to  $10^{11}$  viable *M. leprae*. If the process through which resistant microorganisms are selected in leprosy is the same as that in tuberculosis, then the reason for the increased frequency of dapsone resistance of *M. leprae*<sup>3</sup> is probably the long standing monotherapy with dapsone. We must also recall that dapsone has been used not only by itself but also in discontinuous fashion and most probably at too low a dosage. This latter point is of relevance since when dapsone was administered to mice at doses giving rise to serum concentrations corresponding to those obtained in man after therapeutic doses of the drug, it killed only 75% of the viable bacilli, which resulted in dapsone being classified as a weak bactericidal agent<sup>3</sup>. Although it is always difficult to extrapolate animal data to man (particularly in leprosy), in the absence of direct experimental confirmation, it seems unlikely that a figure of 25% represents the fraction of the bacillary population totally resistant to dapsone, even though the mutation rate of *M. leprae* to dapsone is unknown. If this had been the case, then the phenomenon of dapsone resistance would have been more quickly and more widely observed clinically. The figure of 25% probably corresponds instead to the sum of the totally resistant plus the partially resistant fractions of the population, which is of little relevance from the therapeutic point of view. It is in fact quite clear that even at "full" therapeutic doses of dapsone, a significant proportion of the bacillary population escapes the action of the drug, and it would be interesting to study the possible relationships of this situation to the nature of "persisters" in leprosy.

The situation becomes even more complicated if one assumes that the relative ratio of "fully resistant"/"intermediate sensitive" bacilli can differ in the different subjects. In general, one can only feel that in the past dapsone has been utilized in a way which counteracted its remarkable therapeutic potential particularly in LL patients with an extremely great number of bacilli and practically no immunological defenses.

<sup>3</sup> Ellard, G. Combined treatment for lepromatous leprosy. *Lepr. Rev.* 51 (1980) 199-205.

To a lesser extent, the same considerations apply to the use of rifampin in leprosy. Several studies have indicated that rifampin, administered in a single dose of 1500 mg or in a few lower doses of 600 mg can kill up to 99.99% of the bacilli<sup>4</sup>. This has led to the suggestion of using one single 1500 mg dose of rifampin in every untreated LL patient, then continuing the treatment with dapsone alone or with dapsone and clofazimine<sup>5</sup>. Such an approach should, in my view, be regarded more as a general epidemiological measure than as a serious attempt to cure the disease in an individual patient. The hypothesis that a single administration of 1500 mg is enough to eradicate *M. leprae* in an individual could only be supported first by assuming that the total number of antibiotic molecules is compatible with the total number of bacilli present in the body of that given patient, second that an ideal ratio molecule/bacillus will be achieved wherever bacilli are located in the body in the relatively few hours available for contact to take place, and third that every molecule reaches its target within the bacterium and leads to a lethal event. Following the same reasoning the proposed 2 days per month treatment does not seem any better.

On the basis of what we have said so far, a combination of rifampin plus dapsone at full (or possibly higher) doses than those used or recommended so far and for an adequate period of time can be regarded as a reasonable basis for a regimen suitable for fresh untreated LL cases. As with the regimen of 9 months rifampin plus isoniazid in tuberculosis, the duration of the rifampin-dapsone treatment could involve shorter treatment with dapsone (at increased doses) and longer treatment with rifampin (600 mg daily is probably adequate). The addition of a third, and even a fourth drug, selected according to the principles described

<sup>4</sup> Colston, M. J., Hilson, G. F. R. and Bannerjee, D. J. The "proportional bactericidal test." A method for assessing bactericidal activity of drugs against *Mycobacterium leprae* in mice. *Lepr. Rev.* 49 (1978) 7-15.

<sup>5</sup> Report of the Seventh Meeting of the Steering Committee of the Scientific Working Group on the Chemotherapy of Leprosy. WHO Special Programme for Research and Training in Tropical Diseases. Geneva: 24-25 April 1980.

in the next section could prove to be useful, as in tuberculosis.

The reports of an increasing frequency of dapsone resistance in leprosy patients and the correspondingly increasing risk that other individuals will become infected with mycobacteria already resistant to dapsone strongly suggests that there is need to develop a regimen effective both in the presence of a totally sensitive bacillary population and in the presence of dapsone resistance. In retrospect, one wonders whether the fact that only a relatively minor fraction of leprosy patients was treated in the past with dapsone might not turn out to be a good thing. Here again the experience in tuberculosis chemotherapy can be applied to leprosy. It has been shown that antituberculosis regimens including four bactericidal drugs in the initial intensive phase, followed by two such drugs in the continuation phase, is as effective in the presence of complete initial sensitivity to the four drugs as in the presence of initial isoniazid or isoniazid plus streptomycin resistance<sup>6</sup>. Of great relevance is the fact that similar results have been recently reported for regimens with intermittent administration from the very beginning<sup>7</sup>.

In general, the ultimate objective for treatment of leprosy today is to have one single regimen effective in both situations. In this context it seems reasonable to suggest that such a regimen should also be tested, after an appropriate adjustment of dosage and of time of application, in patients with smaller bacillary loads, as in tuberculoid leprosy, on the basis of the expected rate of breakdown of these patients to multibacillary disease.

**Nature of drugs used for treatment of tuberculosis and possible implications for treatment of leprosy.** The specific role played by each of the drugs in the so-called short-course regimens for tuberculosis is a key for understanding and explaining their remarkable therapeutic effectiveness. Since

we are concerned here with the interrelationships between tuberculosis and leprosy, I will confine myself to those regimens which have been developed for countries where both diseases are highly prevalent. These are the regimens that last 4 to 6 months. These regimens are characterized by an initial intensive phase in which four bactericidal drugs are administered simultaneously over a period of 2 months, followed by a continuation phase in which the best results are achieved with two such drugs administered for an additional 2 to 4 months period<sup>6</sup>. The scope of the initial intensive 4-drug phase is to kill dividing bacilli, the continuation phase to kill persisters<sup>6</sup>. As is well known, a significant proportion of patients undergoing treatment for tuberculosis abscond from treatment as soon as they start feeling better, particularly when faced with the prospect of being treated for 18–24 months, as was the case in the traditional isoniazid-streptomycin-PAS regimen. One of the main advantages of the highly bactericidal initial intensive phase is that even if some patients do abscond from treatment 2–3 months after beginning treatment, they do so at a stage in which the sputum of the great majority of the cases does not contain bacilli any longer and spreading of infection is prevented<sup>6</sup>. This was not the case with traditional regimens, with which sputum conversion occurred at a much later stage.

In this initial intensive phase streptomycin, isoniazid, rifampin and pyrazinamide are given daily. With this regimen, sputum conversion can be expected to occur within 3 months in more than 95% of the patients. The consequences on spreading of infection by those who stop treatment are evident, but one must expect that stopping of treatment after the initial intensive phase will be followed by a higher relapse rate than that observed when the treatment is carried to completion. The doses administered are 1 g for streptomycin i.m. and 5 mg/kg body weight (b.w.), isoniazid, 10 mg/kg b.w. rifampin, 2–2.5 g pyrazinamide according to whether the patient weighs <50 kg or >50 kg, all three orally. The administration of these 4 drugs, one i.m. and three orally, is followed by serum concentrations which increase over the first 2–3 hr when the peak concentrations are achieved.

<sup>6</sup> Fox, W. The current status of short course chemotherapy. Proceedings of the XXIVth World Conference of the I.U.A.T. Bull. Int. Union Tuberc. 53 (1978) 268–280.

<sup>7</sup> Hong Kong Chest Service/British Medical Research Council. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet 1 (1981) 171–174.

During the 12 hr after administration, two quite different pairs of curves are observed, depending on the height of the peak levels. The first pair includes streptomycin and pyrazinamide, whose peak concentrations are of the order of 30  $\mu\text{g/ml}$ ; the second pair includes rifampin and isoniazid, with peaks of the order of 10  $\mu\text{g/ml}$ . Although to different quantitative extents, the kinetics of the four drugs in the blood compartment are compatible and independent of each other since the curves obtained when each drug is given alone are similar to those observed after combined administration<sup>8</sup>. A practical and important consequence is that if the capacities of diffusion of the four drugs from the blood compartment to the tissue compartment are similar, the maximal concentration gradients between blood and tissue (at which diffusion can be expected to be maximal) occur at approximately the same time for all 4 drugs. This results, in turn, in concomitant perfusion of the affected tissue by all four bactericidal drugs. In a typical case, 2 hr after the administration, the serum of a patient contains (on the average) concentration of streptomycin 60 times the minimal concentrations that inhibit the growth of *M. tuberculosis* (MIC = 0.5  $\mu\text{g/ml}$ ), of pyrazinamide 3 to 6 times the MIC (5–10  $\mu\text{g/ml}$ ), of rifampin approximately 100 times the MIC (0.1  $\mu\text{g/ml}$ ), and of isoniazid 50 times the MIC (0.2  $\mu\text{g/ml}$ )<sup>9, 10</sup>. Apart from the effects of simultaneous presence of the four drugs in preventing selection of resistant strains, it is important to analyze the specific role of each drug in terms of its selective action on subfractions of the bacillary population.

Recently, the tubercle bacilli in a lung cavern were classified on the basis of their metabolic activity and anatomical localization and on specific effects of each antituberculosis drug in the combination<sup>11</sup>. The bacillary population can be divided into

four sub-groups: the first (group A) includes actively multiplying bacilli; the second (group B), quantitatively smaller, is composed of bacilli growing intermittently; the third (group C) corresponds to intracellular organisms (within the macrophages), and the fourth (group D) corresponds to the so-called "dormant" bacilli, metabolically inactive, whose role in the disease is unknown.

Streptomycin, isoniazid, and rifampin are thought to be active on the extracellular population of the actively multiplying bacilli (group A). Rifampin, because of the speed with which it starts to be bactericidal, is the only one capable of killing the intermittently growing fraction (group B). Rifampin and pyrazinamide, known to penetrate macrophages and to be active at acid pH, kill the intracellular fraction (group C)<sup>11</sup>. We have here a microbiological explanation of the clinical effects of the short-course regimens: rapid achievement of sputum conversion (killing of extracellular bacilli) and prevention of late relapses (killing of persisters).

An approach of this nature could be usefully applied to leprosy, at least in an attempt to rationalize the selection of drugs to be used since there are several not unimportant elements common to tuberculosis and leprosy. The first is that, in both, the bacillary population can be considered to be essentially homogeneous (*M. tuberculosis* or *M. leprae*); the second is that the microorganisms have different anatomical localizations (exemplified by the intra- and extra-cellular situation); the third is that the bacterial population can be assumed to be in more than one metabolic state (exemplified by the "viable" versus "dormant" bacilli).

Since the principle of combining bactericidal drugs in order to sterilize patients through the killing of mycobacteria wherever located and in whatever metabolic state is effective in tuberculosis, it is not unreasonable to think that it would be successful for leprosy. In its more severe form, LL, leprosy is a disease which is characterized by almost unique dissemination of bacilli in large numbers and into practically all tissues investigated. Bacilli are continuously present in extremely large numbers in blood at a level so high that it would be

<sup>8</sup> Acocella, G. Unpublished data.

<sup>9</sup> Garrod, L. P. and O'Grady, F. *Antibiotic and Chemotherapy*. 2nd ed. Edinburgh and London: E. S. Livingstone, 1968.

<sup>10</sup> Le pyrazinamide 25 ans après. A symposium, Algiers, 1979. Milan: Bracco Ind. Chimica, 1979.

<sup>11</sup> Mitchison, D. A. and Dickinson, J. M. Bactericidal mechanisms in short-course chemotherapy. *Bull. Int. Union Tuberc.* 53 (1978) 254–259.

incompatible with clinical recovery in any other infectious disease but which is not, paradoxically, accompanied by overt signs of septicemia. Bacilli are found in significant numbers in blood vessels, skin, liver, spleen, polymorphonuclear leukocytes, monocytes, histiocytes. Extracellular bacilli have also been found circulating in the blood. In these extremely severe cases, treatment with dapsone alone is followed by a rapid decrease in the bacillary count.<sup>12</sup>

The extraordinary distribution of *M. leprae* in practically all parts of the human organism strongly suggests the need for a combined therapeutic approach. In addition to this "quantitative" approach, a more "qualitative" type of approach may be appropriate, with selection of drugs able to penetrate biological membranes with different structures and nature and able to exert their antimicrobial activities intracellularly. The aim of antibacterial therapy is to expose all the *M. leprae*, in whatever body compartment, to the effects of the drug. The bacteria most available for and therefore susceptible to the bactericidal effects are those in the circulating blood. It is harder to be sure that the bacilli will be killed when the drug must cross complex biological membranes with differing structures. All efforts at screening compounds able to reach therapeutic concentrations in the most diverse compartments of the organism are certainly worthwhile.

Screening should not be limited to rifampin and dapsone, whose good tissue distribution and intracellular activity are known and for which only minor adjustment may be needed but should be extended to compounds with perhaps less exciting overall properties but still able to contribute to the combined therapeutic effect as pyrazinamide does in tuberculosis, taking advantage of relatively minor but nevertheless useful features.

The role of the so-called "persisters" in leprosy remains somewhat obscure. Persisters have been defined as those microorganisms that have temporarily lost their initial sensitivity to one or more drugs as a

result of adaptation to environmental changes<sup>13</sup>. This hypothetical change in sensitivity was proposed to explain the fact that these organisms can be isolated at the end of a treatment which includes a drug to which the persisters are found to be sensitive. On this basis the treatment is defined as microbiologically "adequate"<sup>13</sup>. If the hypothesis of a drastic decrease in the metabolic activity of the persisters is correct, then there are very few chances of isolating active compounds since a minimum level of metabolic activity is prerequisite for detecting possible sites and mechanisms of action of potentially active drugs. In this sense, there is a high degree of similarity between "persisters" in leprosy and "dormant" bacilli in tuberculosis.

If, however, the concept of "adequate" treatment is revised according to our discussion above, then a much simpler interpretation of the nature of persisters can be given—that they are microorganisms which for some reason (of which one could be inaccessibility) were never exposed to the action of the antileprosy drugs. If the second hypothesis is correct, then a possible solution of the problem could be to apply therapeutic procedures able to guarantee the presence of adequate amounts of several antibacterial drugs in the largest possible number of tissues and body fluids. Once again high dose polychemotherapy with compounds able to cross lipid membranes could be a solution to the problem and might also shorten the duration of the leprosy treatment.

**Duration of treatment for tuberculosis and leprosy.** In tuberculosis, as a result of the process described in the introduction of this article, effective regimens of 4–6 to 9 months' duration are available. These represent considerable decreases from the 18–24 months with the classical isoniazid-streptomycin-PAS combination. In 1975, the International Union Against Tuberculosis, at its Mexico City Congress, defined any treatment lasting less than 12 months as "short course."

Unfortunately, in the field of leprosy

<sup>12</sup> Drutz, D. J., Chen, J. S. N. and Lu, W.-H. The continuous bacteremia of lepromatous leprosy. *New Engl. J. Med.* **287** (1972) 159.

<sup>13</sup> Toman, K. Bacterial persistence in leprosy. *Int. J. Lepr.* **49** (1981) 205–217.

there is still uncertainty about the most appropriate duration of chemotherapy, since the process of defining an optimal regimen (or group of regimens) for the various forms of leprosy is still going on. This status is reflected, for example, in the fact that in some of the regimens being evaluated by THELEP, lifelong dapsone is recommended at one extreme and a single administration of rifampin at the other extreme. In between, a large variety of regimens with various combinations of drugs and durations of treatment are being evaluated. The "persistence" of the principle of life-long treatment seems to reflect some sort of reluctance on the part of leprologists to take the decisive step of stopping chemotherapy. There are good reasons to think that the time for this can be established now.

Recent studies<sup>14</sup> have indicated that treatment of patients with lepromatous leprosy for 6 months with dapsone and rifampin was successful even in the presence of initial dapsone resistance. In this study, persisting viable bacteria were detected after completion of treatment. However, even when persisters are detected after treatment, this can be regarded as a minor problem because the number is very small indeed and because the problem can be solved in the same way as the few bacteriological relapses after short-course treatment in tuberculosis, so long as sensitivity to the drugs originally employed is retained, as it is in tuberculosis. Under these circumstances, treatment can in fact be restarted with the same combination of drugs.

The difficulty some leprologists have in abandoning the principle of lifelong treatment of leprosy has a strong ethical connotation and derives from the lack of a reliable reference point in terms of treatment. In retrospect, however, the situation was the same during the development of the whole concept of short-course treatment of tuberculosis. The experimental and clinical evidence available at that time was not sufficient to guarantee that the concept would necessarily be successful. Shortening the

time of application of the new regimens from the officially accepted ones was not an obvious or natural consequence of the nature and number of the drugs included in the regimens. The duration of treatment was one of the main parameters submitted to study to the extent that the "time" concept and not the number or type of drug used was eventually used to identify the new approach to tuberculosis chemotherapy.

Certainly, some evidence was available for evaluating regimens at the lower end of a theoretical scale of duration of treatment. A triple combination of streptomycin, isoniazid, and pyrazinamide had been found to be associated with a 15% relapse rate<sup>15</sup>, an unacceptable figure in view of the therapeutic potentials of those drugs, as confirmed by the later results obtained with the short course regimens. The results provided, however, a good reference point and an ideal starting line for further changes in the number of drugs, their nature and doses as a function of a variable time factor. At the other extreme of the time scale, double combinations of rifampin and isoniazid were tested for 6–9 or 12 months<sup>16, 17</sup>. In these regimens, supplement of streptomycin or ethambutol was given for the first 2–3 months, but the contribution of those two drugs to the overall effectiveness of the regimens has been questioned<sup>18</sup>. Since no major differences were found between the 9- and 12-month regimens and a few cases of relapses were observed after the 6-month regimen, the 9 month regimen was selected for treatment of tuberculosis in Europe<sup>19</sup> and recently in the USA<sup>20</sup>.

<sup>14</sup> Waters, M. F. R., Rees, R. J. W., Pearson, J. M. H., Laing, A. B. G., Helmy, H. S. and Gelber, R. H. Rifampicin for lepromatous leprosy: nine years' experience. *Br. Med. J.* 1 (1978) 133–136.

<sup>15</sup> Kreis, B. Two–three months' regimens for pulmonary tuberculosis. *Bull. Int. Union Tuberc.* 51 (1976) 71.

<sup>16</sup> British Thoracic and Tuberculosis Association. Short-course chemotherapy in pulmonary tuberculosis. *Lancet* 2 (1976) 1102.

<sup>17</sup> Brouet, G. Etude cooperative de traitements antibacillaires de court durée dans 14 centres français. *Bull. Int. Union Tuberc.* 49 (1974) 398–410.

<sup>18</sup> Fox, W. The chemotherapy of pulmonary tuberculosis: a review. *Chest* 76 (1979) 785–796.

<sup>19</sup> Fox, W. and Mitchison, D. A. Short chemotherapy for tuberculosis. *Lancet* 2 (1976) 1349.

<sup>20</sup> Guidelines for short-course tuberculosis chemotherapy. *Morbidity and Mortality Weekly Report* 29 (1980) 97–105.

In the short course regimens of 4–6 months, additional factors in the interrelationships between the time of application of drugs and specific therapeutic needs could be applied, for example:

1. rifampin should be administered throughout treatment if the regimen is to be equally effective in presence of bacilli initially sensitive or in case of resistance to isoniazid or streptomycin;
2. there is no apparent advantage in prolonging administration of pyrazinamide beyond the initial intensive 4-drug phase<sup>18</sup>.

A good, reasonably large scale example of antileprosy treatment with combinations of several drugs administered over a definite period of time is the Malta project for eradication of leprosy<sup>21</sup>. In this particular trial, rifampin was administered in combination with prothionamide, isoniazid, and dapsone to patients with various forms of leprosy. The duration of treatment ranged from 6 to 9 months but in the majority of cases from 6 to 24 months. There was no pre-established duration of the treatment. It was terminated after evaluation of the clinical and bacteriological status of each individual patient. After chemotherapy was stopped, the patients were kept under observation for several years, and no relapses have occurred in a substantial proportion of the treated cases after 5 years.

Although it is quite clear that a too rigid definition of the duration of a regimen involves the risk of treating patients who, for some reason, react more slowly to the regimen (e.g., late converters in tuberculosis) for too short a time; nevertheless, it would be of practical advantage to develop regimens with overall effectiveness well-defined in terms of time. This would also be useful when comparing different regimens. On the whole, it does not seem unrealistic to expect that intensive combined treatment of leprosy could be for length of time of the same order of magnitude as those used in tuberculosis.

**The problem of compliance.** Tuberculosis is a disease affecting the poor sector of the population and leprosy affects the even poorer. There is also a consensus that in the majority of the developing countries low social status is usually associated with a poor understanding of sanitation (as the number of those who stop tuberculosis treatment too soon indirectly indicates). This assumption has led to considering the patients as a passive component in the system of drug delivery within a treatment scheme. As the overall standard of living increases, so does the capacity of the subject to take a more active and rational attitude toward his disease. This process cannot be expected to be very quick; however, until such an ideal situation becomes a reality, sound and realistic regimens should demand as little active participation of the patients as possible. In tuberculosis and leprosy, the final goal should be to stimulate the patient to be an active component in the system which means, in practical terms, self-administration. This would have the obvious advantages of reducing the involvement of the medical and paramedical staff in the administration of the drugs to the patients, particularly in mass eradication campaigns.

Simplification of the therapeutic regimens is the key to success of any large scale treatment program. A few comments in this respect seem to be appropriate. When dealing with diseases like tuberculosis or leprosy, which affect millions of patients, the development of a therapeutic regimen can be divided into two steps. The first involves testing the various regimens under strictly controlled experimental conditions in a relatively small number of patients, in order to detect differences between treatments. The second is large scale application of the selected regimen(s) under field conditions. Experience indicates that, at least for tuberculosis, the overall efficiency of a regimen deteriorates in the second phase. The degree of deterioration depends on several obvious factors, of which the complexity of the regimen, usually well-controlled in the experimental phase, is one of the more important.

It is inevitable that during the experimental phase, the problems related to the prac-

<sup>21</sup> Freerksen, E. and Rosenfeld, M. Leprosy eradication project of Malta. *Chemotherapy* 23 (1977) 356–386.



tical application of a regimen are secondary to those of assessment of effectiveness and safety. The emphasis reverses in the second phase, when the practical problems become primary, to an extent that can even jeopardize the overall value of regimen. Understanding of these factors derives from practical experience in tuberculosis chemotherapy and it is important that they be carefully considered by those who are designing antileprosy regimens. With the drugs available for both tuberculosis and leprosy, simplicity of administration can easily be achieved.

Entirely oral regimens can be developed if there is appropriate arrangement and selection of compounds. Technical solutions can also be found for the main problem of tuberculosis and leprosy treatment, avoiding accidental monotherapy by combining several drugs in the same pharmaceutical preparation. Complex regimens should be avoided. In this respect, daily regimens make far fewer demands on the organizational infrastructure than intermittent regimens.

It is hard to predict whether or not intermittent regimens will ever prove to be suitable for large scale eradication programs. To a certain extent intermittent regimens appear to be more appropriate for treating patients living in urban areas than for those living in rural areas or where long distances need to be covered either to get the patients to the medicines or the medicines to the patients. Undoubtedly, an intermittent regimen would be less costly than a daily regimen, provided that the same clinical results can be obtained with a smaller number of doses. In leprosy, however, the value and role of intermittent regimens, as opposed to daily, are far more for the future than they are for tuberculosis since evidence currently available or being collected is limited to the effects of intermittent administration of one or more of the components of the regimen, rather than to regimen itself. The ultimate goal, the ideal regimen, seems to us to be one whose application on a large scale does not require the presence of doctors for its implementation and whose para-medical staff can be reduced to a minimum, which will also lead to large savings in the overall cost of treatment.

**The cost of treatment in tuberculosis and leprosy.** An analysis of the past and present situations in leprosy chemotherapy leads to the unfortunate but realistic conclusion that one can no longer think of leprosy as a disease which might be cured with a drug no more expensive than aspirin. Research in leprosy, as in any other field of medicine, becomes more and more expensive, a consequence of its being conducted mainly in the technically advanced countries, with the obvious negative reflections on the cost of therapy. The economical impact in the developing countries would be even more pronounced if it were not for the invaluable contribution of the outstanding motivation of the people involved, at all levels, in leprosy research and therapy.

The experience with dapsone showed it to have two favorable aspects: the first that leprosy can be a curable disease, the second that it could be cured with a very cheap drug. Paradoxically this second aspect also had a negative effect, since it induced a false sense of security about the future of the disease, which probably limited the efforts to improve leprosy chemotherapy. This has become dramatically evident in the ever-increasing dapsone resistance observed. Every effort should be made to maximize the benefits to be obtained with the existing drugs and from minimizing the overall cost of the antileprosy regimens. This will certainly not be an easy task, but it is an objective which can be achieved, as it has been in tuberculosis.

On the basis of what we have said above, economic considerations should never prevail over the medical ones or disease might be perpetuated and even made artificially worse, causing a need to increase the allocation of financial resources. Simultaneous and parallel campaigns should be started to make governments, national and international organizations, more aware of the dimensions of the problem of leprosy and of the possibilities of limiting its disastrous social effects with comparatively minor economical commitments. The authority, the knowledge, the experience, and motivation are certainly not lacking in the field of leprosy research. On this basis, there is no reason to doubt that the whole operation will eventually be successful and that the days

when leprosy will be entirely under control  
are not so distant.

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