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THE STRATEGY OF LEPROSY TREATMENT : A PERSONAL VIEW

by

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1. Introduction

Mycobacterium leprae and *M. tuberculosis* are the most important human Mycobacterial pathogens. Chemotherapy, with dapsone, was first applied to leprosy in 1942-1945, chemotherapy of tuberculosis started later, in 1950, with streptomycin. But — as opposed to leprosy — enormous progress has been made in the treatment of tuberculosis : many active drugs became available and the application of the discipline of prospective, randomized or controlled clinical trials defined optimal therapeutic regimens, some of them leading to 100 per cent cure within 6-9 months, irrespective of the severity of the disease at the start.

In the meantime treatment of leprosy still relies almost exclusively upon the administration of dapsone monotherapy. Indeed dapsone is stable, cheap and relatively nontoxic at the doses administered. It has however two serious shortcomings : the necessity for long term treatment and the appearance of dapsone resistance.

Dapsone treatment of the tuberculoid forms of the disease requires 2-5 years, borderline cases 5-10 years and lepromatous cases at least 10 years if not a lifetime (3rd and 4th WHO Expert Committee; Wheate and Pearson, 1979). As a result, sanitary educators find themselves in the uncomfortable and frustrating situation to have to tell the patients that leprosy is not at all a dreadful disease, because it is curable, but that they have to take medication for years or for their whole life. In such circumstances it is not at all amazing that patient compliance is very poor, all being irregular and at least 30 per cent very irregular in drug intake (Ellard *et al.*, 1974; Low and Pearson, 1974; Molesworth, 1975).

Due to the possibility of presence of drug resistant mutants to any drug in large bacterial populations, all monotherapy is due to lead to resistance in a proportion of multibacillary, lepromatous patients (Floch, 1966; Pattyn, 1972; Shepard, 1972; Rees, 1975; Ellard, 1974; Pearson *et al.*, 1975). Studies have shown that the prevalence of dapsone resistance among lepromatous patients varies between 5 and 30 per cent (Pettit *et al.*, 1966; Peters *et al.*, 1976; Levy *et al.*, 1977; Pearson *et al.*, 1979; Baquillon *et al.*, 1980 b) and the first cases of primary dapsone resistance have already been observed (Pearson *et al.*, 1977).

Population surveys in Tchad (Nebout, 1974), Haute Volta (Blanc *et al.*, 1978) and Mali (Baquillon *et al.*, 1980 a) revealed that, dapsone monotherapy applied for 20-25 years, has reduced considerably the magnitude of the leprosy problem almost exclusively among paucibacillary patients, of which large numbers are to be released from control, but there remains an irreduced nucleus of multibacillary patients, many of whom are still infectious and an unknown proportion of these dapsone resistant.

Other drugs active on *M. leprae* have been discovered and voluntary and/or national organisations are making them available, particularly clofazimine and rifampicin. It is dramatical that in the absence of the results of controlled clinical trials nobody at present knows how to make the best use of the new drugs. The danger is great that inadequate use of the new drugs, particularly rifampicin, results in rifampicin resistance, where on theoretical grounds and some experimental clinical evidence, there is a possibility to use the new drugs in such a way that the treatment of leprosy can be shortened so much that paucibacillary patients (Pattyn *et al.*, 1979) can be cured in a very high percentage within 2-3 months and multibacillary patients probably in a high percentage within a finite time, together with the certainty that those who relapse will do so with entirely sensitive organisms, and can be retreated with the same drugs and an identical percentage of cure rate. For all practical purposes this is much more advantageous than uncomplied lifelong dapsone monotherapy.

In the meantime however patients have to be treated and the question of the optimal regimens for the different forms of the disease, previously treated or untreated and adapted to local circumstances, remains open. With the greater availability of newer, more potent drugs this question becomes all the more urgent.

Most of those responsible for the treatment of patients are in a situation where the organization of controlled clinical trials is impossible or extremely difficult to organize, either from lack of personnel, lack of a sufficiently large number of new patients or both.

It is the purpose of this paper to suggest more rational treatment regimens to be evaluated in those centers or areas, able to do so through correct supervision and follow-up of patients, so that after some years they might be more generally applied.

2. **Available drugs**

Rifampicin is the most powerful and rapidly bactericidal drug against *M. leprae* and has therefore raised the hope to allow considerable stortening of leprosy treatment. Administration of 600 mg daily or a single dose of 1,500 mg kill at least 99.9 per cent of the organisms in a patient within less than 3 days (Shepard *et al.*, 1974). The sensitivity of the mouse foot pad test limits the monitoring of a reduction in viability to 10^{-3} (Shepard, 1960). After a single dose of 1,500 mg, 99.9 per cent of the bacilli are still dead after 28 days (Shepard *et al.*, 1974). However, this is by no means sufficient to cure a patient. Indeed lepromatous tissue may contain 10^8 and more bacilli per g. A patient with 25 per cent of his skin involved, assuming 5.10^8 organisms per g, carries a bacterial load of $6.25\ 10^{11}$ organisms of which $6.25\ 10^{10}$ may be viable at the start of treatment. When 99.9 per cent of these are killed by a single dose of rifampicin, $6.25\ 10^7$ living bacilli are still present (and less if the killing rate is higher

than 99.9 per cent). The remaining viable bacilli will start to multiply again after some time : a skin biopsy from a lepromatous patient who had received a single dose of 1,200 mg rifampicin a year earlier was fully infectious for mice (Pattyn *et al.*, unpublished observation, 1980) and living bacilli were isolated from a nerve biopsy from one out of 8 patients who had been treated with rifampicin 900 mg once a week during 3 months (Pattyn *et al.*, 1976). Treatment will have to last for longer than 3 months.

Rifampicin can be administered continuously (600 mg per day) or intermittently. Allergic complications during long term high dosage intermittent treatment have been observed mainly in S. E. Asia and the Far East (Poole *et al.*, 1971), but not earlier than after 3 months. The following intermittent regimens have caused no harm :

— 900 mg 1/7 during 3 months (Pattyn *et al.*, 1975 b)
— 1,200 mg 1/30 during 6 months (Languillon *et al.*, 1979)
— 450 mg 2/7 during 12 months (Gomi, 1971)
— 600 mg 2/7 during 6 months (own observation)
— 1,500 mg once every 11 weeks (Shepard *et al.*, 1974)
— 600 mg 7/7 during 4 weeks, followed by twice weekly 600 mg during 8 months (Dutt *et al.*, 1979)
— 600 mg during 2 consecutive days once a month during 1 year (Shepard *et al.*, 1972)
— in general reactions are not observed when dosage below 15 mg/kg body weight are administered intermittendly (Gyselen, 1971).

The second drug with an important bactericidal effect is ethionamide (or prothionamide, these two thioamides differ in the structures of the side chains, but have an identical activity. Prothionamide has fewer side effects). Ethionamide is highly bacteridical (Shepard, 1969; Colston *et al.*, 1975; Pattyn, 1978), but probably less than rifampicin. Precise measurements in man remain to be done. Ethionamide is notorious for gastric side effects at doses of 1 g or more per day in the treatment of tuberculosis. *M. leprae* however is more sensitive to these drugs, allowing the administration of 500 mg per day, avoiding these side effects. One great drawback of ethionamide is that it must be administered daily (Pattyn, 1978).

Dapsone and *clofazimine* are essentially bacteriostatic and slowly bactericidal. The minimal inhibitory concentration of dapsone for *M. leprae* is exceptionally low, but both dapsone and clofazimine have to be administered in full dosage (50-100 mg daily) for 3 to 6 months to kill a minimum of 99.9 per cent of an *M. leprae* population (Shepard, 1973; Collaborative effort, 1976).

This property explains why after years of monotherapy with dapsone, relapses are so frequent (3,22 per cent per year, Noordeen, 1971) and also why dapsone has to be taken for years and/or irregularly before resistance occurs. Because of their essentially bacteriostatic activity, these drugs should no longer be considered as the « basic » drugs in the treatment of leprosy, but as companion drugs of the more bactericidal substances, with as most important function the prevention of the appearance of drug resistance against the latter. The role of dapsone and clofazimine is comparable to that of PAS, streptomycin or ethambutol in the treatment of tuberculosis, where the curative drugs are the combination of rifampicin and INH.

Clofazimine with its disadvantage of induction of skin pigmentation in non-pigmented individuals, offers however also an advantage, in that it can be administered intermittently and has an anti ENL effect (Collaborative effort, 1976).

Dapsone does not lend itself to intermittent treatment (Pattyn & Saerens, 1974; Pattyn, 1977) but the derivative acedapsone does. Acedapsone injections (automatically supervised), given once every 11 or 8 weeks produce steady, low DDS plasmalevels. Its main usefulness is in chemoprophylaxis or in providing basic, continuous low dapsone levels, giving some correction for irregular unsupervised additional oral dapsone intake (Ellard, 1975).

Thiacetazone (Colston *et al.*, 1978) is purely bacteriostatic. Streptomycin is bactericidal for *M. leprae*, but perhaps only on extracellular organism (Pattyn & Saerens, 1978). Its activity in man has practically not been evaluated.

3. **The question of persisters**

In 1974, Waters *et al.* detected in biopsies of patients who had been on regular, supervised dapsone therapy for 10-12 years, small numbers of viable *M. leprae* after inoculation into thymectomized irradiated mice, which are exquisitely sensitive to leprosy bacilli. These bacilli were termed persisters. The hypothesis was made that these are responsible for relapses after stopping treatment. The proportion of 10/12 patients positive for « persisters » should be compared with the relapse rate of 0.8 per cent to 3.2 per cent per year over 10 years (see under section 7).

Persisters have also been found in 7/12 patients treated with rifampicin monotherapy for 5 years, and in 1/5 treated with the combination rifampicin and dapsone for 6 months (Gelber *et al.*, 1977). Many of the persister strains do not grow as well as bacilli taken from untreated patients, which may mean that not all of them should give rise to relapses, while the results of Gelber *et al.* (1977) point to the possibility of killing persisters by combined therapy, and probably even more if the more bactericidal drugs ethio- or prothionamide were added to the treatment.

4. **The objectives of treatment**

A. *Cure of patients*

Treatment of patients in the *tuberculoid spectrum* of the disease could be shortened considerably by the use of rifampicin (Pattyn *et al.*, 1979 and unpublished follow-up study of this trial).

Borderline patients (BB — BL and LLs — the latter resulting from downgrading reactions in the absence of treatment, irregular dapsone treatment, or dapsone resistance) can theoretically be sterilized bacteriologically, since their cell mediated immunity is still competent : as in all infections chemotherapy intends to kill the great majority of bacteria, while the natural host defense mechanisms are supposed to take care of the few persisting organisms.

Based on the above mentioned findings on persisters and the fact that polar *lepromatous patients* (LLp) have a specific deficiency in cell mediated immunity (Godal, 1978) it is always said that it is virtually

impossible to cure these forms of the disease. However these affirmations are based on the relapses occuring after treatment with dapsone monotherapy, there is insufficient information about the prevalence of persisters after combined therapy including 2 bactericidal drugs and it has not been shown that all persisters should necessarily give rise to relapses.

B. *Prevention of development of drug resistance*

If it is now generally accepted that multibacillary patients (those with a bacterial index (BI) > 1) should be treated with a combination of drugs, one regrettable widespread concept is that the main effort should be to prevent the appearance of dapsone resistance, thereby overlooking that the prevention of development of resistance against the bactericidal drugs would be a disaster, because of the difficulty to treat these patients and the danger of spreading such strains. Furthermore if resistance to dapsone is slow to appear, resistance to bactericidal drugs appears more rapidly : 4 years in the case of ethionamide (Pattyn *et al.*, 1975 a) and 3-4 years (43 months) in the case of rifampicin (Jacobson and Hastings, 1976).

C. *Interruption of transmission*

In this respect great expectations have been put on a relatively large single dose of rifampicin (1,500 mg) (Languillon, 1977).

However this cannot be very useful as already pointed out.

Monthly or bi-monthly administration of such doses may be more effective in his respect, but other drugs should certainly be administrated in combination to prevent the selection of rifampicin resistance. As a result of the long incubation time, the effect of treatment on the incidence of leprosy can only become manifest after several years and will depend on the quality of the detection system.

D. *Maximum supervision*

It is generally felt that, to improve patient compliance, the potent bactericidal drugs should be administered under supervision, e.g. the drug delivery system. For this reason the choice is between reinforcement of the drug delivery system allowing intensive, « maximum » short term regimens or no reinforcement of the drug delivery systems and the application of less intensive, less than maximum regimens of (much) longer duration. All practical propositions will always be compromises between these two constraints.

Several possibilities may be considered :

— daily supervised ambulatory treatment, organized in treatment clinics, in out-patient departments or health centers. The existence of a programme for primary health care may be very important in this respect. An alternative is to have treatment given by a socially important responsable person in the community (as was done for tuberculosis among nomads in Algeria);
— hospitalisation or residence near a treatment center;
— application of intermittent regimens, adapting as far as reasonably feasible the intermittency to the frequency of patient contact (weekly, bi-weekly, monthly) or adaptation of the frequency of patient contact to the necessary frequency of drug delivery.

— replacement of supervision by motivation. Efforts can be made to convince patients that in turn for regular drug treatment, the duration of the latter could be considerably shortened. Urine examinations for the presence of drugs or drugmetabolites allow to verify drug intake.

5. **Regimens**

It should be stressed that except for the short course chemotherapy regimen of paucibacillary leprosy, none of the regimens that follow has been evaluated at present but might be considered for evaluation.

A. *Paucibacillary leprosy*

These are Idt, TT and BT patients whose bacteriologic index (BI) is < 2.

New cases

Short course, 2 months, chemotherapy on the basis of one weekly administration of rifampicin seems to be effective (Pattyn *et al.*, 1979 and unpublished, although incomplete, long term follow-up data on this trial).

Variations worthwhile to be tested could be :

— 2-3 months daily therapy;
— association of unsupervised ethionamide 500 mg daily to the weekly doses of RMP, to see if clinical improvement can be accelerated;
— somewhat longer duration of weekly treatment : e.g. 10 or 12 weekly 900 mg administrations for the same reason;
— treatment with longer intervals : e.g. 900 mg once a fortnight or once a month, or 600 mg two consecutive days once a month for an identical total amount of drug;
— 600 mg weekly for 8-10 weeks.

Cases already under treatment

Care should be taken that the original diagnosis was correct, the files should contain arguments in favor of the diagnosis and preferably results of bacteriological examination and/or skin biopsy at the start should be available.

Three possible strategies :

— continue traditional treatment;
— include everyone into the new regimen;
— change those patients to the new regimen who had only 1 or 2 years of dapsone treatment.

B. *Multibacillary patients*

These are BB — BL — LL and LLp patients with a BI $\geqslant 2$.

New cases

The rationale is that there should be an introductory phase of maximum daily therapy comprising 2 bactericidal and 1 bacteriostatic drug during 3 months, followed by a continuation phase with 2 bactericidal drugs during 3 months and 1 bactericidal during another 3 months. In tuberculosis 9 months treatment with analogous regimens are 100 per cent effective, and are not followed by relapse, 6 months treatments are followed by

5 per cent relapses (Fox and Nunn, 1979), but in certain circumstances this may be more advantageous than the existing regimen.

Alternatives to be studied are :

— intermittent rifampicin (once or twice weekly) during the continuation phase;
— shortening of the introductory phase to 2-1 even 1/2 month, followed by intermittent (once or twice weekly) rifampicin, associated for 3-6 months with daily ethionamide, but prolonging the total duration of treatment;
— continuation phase with dapsone monotherapy for several months, eventually terminated by another phase of short course intensive combined treatment;
— in areas with high prevalence of dapsone resistance, dapsone should be replaced by clofazimine.

Such regimens imply the strengthening of the drug delivery systems and the willingness of the medical personnel to accept the idea that to stop treatment in leprosy, patients should not necessarily be bacteriologically negative, since humans eliminate dead leprosy bacilli very slowly.

Without much strengthening of the drug delivery system, treatment may be improved — but will still be of long duration (2 years or more) with the following regimen :

from the start or after an introductory phase of any duration : rifampicin and clofazimine 600 mg on two consecutive days once a month with one monthly injection of acedapsone and unsupervized dapsone.

Cases already under (dapsone) treatment

Three groups can be considered :

— treated for less than 5 years, BI $\geqslant 2$ — treat as new cases;
— treated for less than 5 years, BI < 2 — treat as paucibacillary patients;
— treated for more than 5 years, BI positive : treat as new patients, realizing that this group is probably poorly compliant and at risk for developing resistance;
— treated for more than 5 years BI negative : Treat as paucibacillary patients.

6. Need for National or Regional Programmes

If the increasing availability of multiple drugs for the treatment of leprosy can be of great benefit for the patients and the community in which they live, this greater availability may also be the source of great difficulties in the future, particularly the development of resistance, if the best use is not made of them.

It is therefore mandatory that precise, standardized regimens be applied nationally or regionally, and that it be realized that in the absence of the necessary infrastructure to assure correct use of the new drugs it is preferable to abstain from introducing them to avoid more harm. Treatment of leprosy should be standardized and not « individualized » by the personal appreciation and initiative of doctors or paramedicals. National or Regional

programmes should provide rules for the management of new cases and those already under treatment, while training and equipment must be made available for standardized bacterioscopy, and the diagnosis and management of complications : reversal reactions and erythema nodosum leprosum.

7. *Implementation — Evaluation*

Detailed protocols should be written and discussed with resource persons and responsable personnel.

Clinical examinations should be performed at the start and at 6-12 months intervals with precise recording of lesions, including neurological symptoms. Standardized bacteriological examinations should be performed with the same frequency. When relapse is suspected, efforts should be made to obtain independent assessment, repeat bacteriological examination with measurement of the morphological index by a reference laboratory, a skin biopsy should be taken for foot pad inoculation to confirm the presence of viable bacilli and to perform sensitivity tests.

The greatest difficulty for the evaluation of treatment regimens in leprosy is the duration of follow-up. Whereas in studies on tuberculosis therapy a follow-up of 1-2 years is generally considered sufficient since all relapses occur within this time (Fox & Nunn, 1979), in leprosy this follow-up period should be longer due to the much longer generation time of *M. leprae*.

There are only fragmentary data on relapse rates after stopping treatment in leprosy. Noordeen (1971) found 3.2 per cent per year particularly if treatment was irregularly followed when the bacteriological negative status was attained.

In a recent study in Malaysia (Waters, personal communication), concerning lepromatous patients who had stopped dapsone therapy when they were bacteriologically negative and followed for 10 years thereafter, the relapse rate was 0.8 per cent per year, with 10 relapses appearing within the first 5 years and 13 between the 6th and 10th year.

It may be concluded that follow-up should be for a minimum of 5 years, but that during these first 5 years very important information would be obtained.

National organisations, with the help of voluntary organisations should take up the responsability for this long term follow-up, by assuring the continuous presence of the necessary personnel, the lack of continuity of the latter being corrected by perfect, standardized files and procedures, on all patients, and centralisation of the data.

8. **Cost**

Developing countries can certainly not afford the costs involved in the treatment regimens proposed. However, voluntary organisations provide considerable amounts of money to many areas, to cover the costs of leprosy control programmes including building of centres, and their maintenance, paying for equipment, transportation and salaries. In these programmes, the cost of drugs amounts to only 5 per cent of the total. Increasing the expenditure for drugs considerably signifies only a marginal increase in the total expenditure (Styblo, personal communication). This relatively small increase may be highly profitable in the long run if treatment can be considerably shortened. Besides, clofazimine and rifampicin

are already made available to many areas. To use them in a less than optimal way, with all the dangers attached, or to make the best use of them including evaluation, is the choice.

REFERENCES

Baquillon, G., Bernard, L., Cisse, M., Sow, S., Saint André, P. & Pattyn, S. R. (1980a) : Evaluation of leprosy control activities in Bougouni Zone, Mali. (in press).

Baquillon, G., Ferracci, C., Saint André, P. & Pattyn, S. R. (1980b) : Dapsone resistant leprosy in a population of Bamako (Mali). Lepr. Rev. (in press).

Blanc, M. (1978) : Evaluation de la campagne de masse contre la lèpre en Haute Volta après dix ans d'activité (1966-1976). Acta leprol., **73**, 39-58.

Collaborative effort of the U. S. Leprosy Panel (1976) : Spaced clofazimine therapy of lepromatous leprosy. Am. J. Trop. Med. Hyg., **25**, 437-444.

Colston, M. J., Ellard, G. A. & Gammon, P. T. (1978) : Drugs for combined therapy : experimental studies on the antileprosy activity of ethionamide and prothionamide, and general review. Lepr. Rev., **49**, 115-126.

Dutt, A. K., Jones, L. & Stead, W. W. (1979) : Short course chemotherapy for tuberculosis with largely twice weekly Isoniazid-Rifampicin. Chest, **75**, 441-447.

Ellard, G. A. (1974) : Growing points in leprosy research (4). Recent advances in the chemotherapy of leprosy. Lepr. Rev., **45**, 31-40.

Ellard, G. A., Gammon, P. T. & Harris, J. M. (1974) : The application of urine tests to monitor the regularity of dapsone self-administration. Lepr. Rev., **45**, 224-234.

Ellard, G. A. (1975) : Pharmacological aspects of the chemotherapy of leprosy. Lepr. Rev., **46**, 41-51.

Floch, H. A. (1966) : Sur la chimiorésistance du bacille de Hansen et le traitement de la lèpre par des associations médicamenteuses. Bull. Soc. Path. Exot., **59**, 188-192.

Fox, W. & Nunn, A. J. (1979) : The cost of antituberculous drug regimens. Am. Rev. Resp. Dis., **120**, 503-509.

Gelber, R. H., Waters, M. F. R., Pearson, J. M. H., Rees, R. J. W. & McDougall, A. C. (1977) : Dapsone alone compared with dapsone plus rifampicin in short-term therapy of lepromatous leprosy. Lepr. Rev., **48**, 223-229.

Godal, T. (1978) : Immunological aspects of leprosy. Present Status. Progress in Allergy, **25**, 211-242.

Gomi, J. (1971) : Intermittent rifampicin regimens in treatment of pulmory tuberculosis. Acta Tub. Pneumol. Belg., **62**, 313-314.

Gyselen, A. (1971) : International symposium on intermittent treatment with rifampicin. Acta Tub. Pneumol. Belg., **62**, 336-338.

Jacobson, R. R. & Hastings, R. C. (1976) : Rifampicin resistant leprosy. Lancet, **2**, 1304-1305.

Languillon, J. (1977) : Traitement de la maladie de Hansen par une dose unique de 1.5 g de rifampicine associée à une sulfonothérapie continue. Méd. Trop., **37**, 717-719.

Languillon, J., Yawalkar, S. J. & McDougall, A. C. (1979) : Therapeutic effects of adding Rimactane (Rifampicin) 450 mg daily or 1200 mg once monthly in a single dose to dapsone 50 mg daily in patients with lepromatous leprosy. Int. J. Lepr., **47**, 37-43.

Levy, L., Rubin, G. S. & Sheskin, J. (1977) : The prevalence of dapsone resistant leprosy in Israel. Lepr. Rev., **48**, 107-112.

Low, S. J. M. & Pearson, J. M. H. (1974) : Do leprosy patients take dapsone regularly ? Lepr. Rev., **45**, 218-223.

Molesworth, B. D. (1975) : Results of leprosy control project, Malawi. Lepr. Rev., **46**, 149-152.

Nebout, M. N. (1974) : Bilan de huit ans d'autotraitement des lépreux du secteur 3 de Moundou (Tchad). Bull. Soc. Path. Exot., **67**, 484-494.

Noordeen, S. K. (1971) : Relapse in lepromatous leprosy. Lep. Rev., **42**, 43-48.

Pattyn, S. R. (1972) : Comments on the chemotherapy of leprosy as influenced by the present knowledge on *Mycobacterium leprae*. Lepr. Rev., **43**, 126-136.

Pattyn, S. R. & Saerens, E. J. (1974) : Results of intermittent treatment with dapsone and rifampicin of mice inoculated with *Mycobacterium leprae*. Ann. Soc. belge Méd. Trop., **54**, 35-41.

Pattyn, S. R., Rollier, M. T., Rollier, R. & Verdoolaeghe-Van Loo, G. (1975a) : Sensibilité envers la dapsone, la sulfa methoxypyridazine et l'éthionamide de *Mycobacterium leprae* provenant de malades traités par ces substances. Int. J. Lepr., **43**, 356-363.

Pattyn, S. R., Rollier, M. T., Rollier, R., Saerens, E. J. & Dockx, P. (1975b) : A controlled clinical trial on initial three months continuous and intermittent rifampicin therapy in lepromatous leprosy. Lepr. Rev., **46**, 129-139.

Pattyn, S. R., Dockx, P., Rollier, M. T., Rollier, R. & Saerens, E. J. (1976) : *Mycobacterium leprae* persisters after treatment with dapsone and rifampicin. Int. J. Lepr., **44**, 155-158.

Pattyn, S. R. (1977) : The effect on the multiplication of *Mycobacterium leprae* of irregular administration of dapsone to mice. Ann. Soc. belge Méd. Trop., **57**, 175-179.

Pattyn, S. R. (1978) : Further data on the effect of ethionamide and prothionamide in experimental leprosy. Lepr. Rev., **49**, 199-202.

Pattyn, S. R. & Saerens, E. J. (1978) : Evaluation of the activity of streptomycin on *Mycobacterium leprae* in mice. Lepr. Rev., **49**, 275-281.

Pattyn, S. R., Bourland, J., Warndorff, J., Cap, A. & Saerens, E. J. (1979) : Short course two months treatment of paucibacillary leprosy with rifampicin. Preliminary results. Ann. Soc. belge Méd. Trop., **59**, 79-85.

Pearson, J. M. H., Rees, R. J. W. & Waters, M. F. R. (1975) : Sulfone resistance in leprosy. A review of one hunderd proven clinical cases. Lancet, II, 69-71.

Pearson, J. M. H., Haile, G. S. & Rees, R. J. W. (1977) : Primary dapsone resistant leprosy. Lepr. Rev., **48**, 129-132.

Pearson, J. M. H., Haile, G. S. & Barnetson, R. St. C. (1979) : Dapsone resistant leprosy in Ethiopia. Lepr. Rev., **50**, 183-199.

Peters, J. H., Shepard, C. C., Gordon, G. R., Rojas, A. V. & Elizondo, D. S. (1976) : The incidence of DDS resistance in lepromatous patients in Costa Rica : their metabolic disposition of DDS. Int. J. Lepr., **44**, 143-151.

Pettit, J. H. S., Rees, R. J. W. & Ridley, D. S. (1966) : Studies on sulfone resistance in leprosy. Int. J. Lepr., **34**, 375-390.

Poole, G., Stradling, P. & Worlledge, S. (1971) : Potentially serious side effects of high-dose twice-weekly rifampicin. Brit. Med. J., **3**, 343-347.

Rees, R. J. W. (1975) : Drugs for leprosy. Tropical Doctor, **3**, 92-95.

Shepard, C. C. (1960) : The experimental disease that follows the injection of human leprosy bacilli into foot-pads of mice. J. exp. Med., **112**, 445-454.

Shepard, C. C. (1969) : Minimal effective dosages in mice of clofazimine and of ethionamide against *Mycobacterium leprae*. Proc. Soc. Exp. Biol. Med., **132**, 120-124.

Shepard, C. C. (1972) : Combination of drugs against *Mycobacterium leprae,* studied in mice. Int. J. Lepr., **40**, 33-39.

Shepard, C. C., Levy, L. & Fasal, P. (1972) : Rapid bactericidal effect of rifampin on *Mycobacterium leprae*. Am. J. Trop. Med. Hyg., **21**, 446-449.

Shepard, C. C. (1973) : Experimental chemotherapy in leprosy, then and now. Int. J. Lepr., **41**, 307-319.

Shepard, C. C., Levy, L. & Fasal, P. (1974) : Further experience with the rapid bactericidal effect of rifampin on *Mycobacterium leprae*. Am. J. Trop. Med. Hyg., **23**, 1120-1124.

Waters, M. F. R., Rees, R. J. W., McDougall, A. C. & Weddell, A. G. M. (1974) : Ten years of dapsone in lepromatous leprosy : clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. Lepr. Rev., **45**, 288-298.

Weathe, H. W. & Pearson, J. M. H. (1979) : A practical guide to the diagnosis and treatment of leprosy in basic health unit. Addis Ababa, All Africa Leprosy and Rehabilitation Centre, 2nd edition.

W. H. O. Expert Committee on Leprosy (1966) : Third Report. Geneva, Technical Report Series, 319.

W. H. O. Expert Committee on Leprosy (1970) : Fourth Report. Geneva, Technical Report Series, 459.