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EDITORIAL

Editorial opinions expressed are those of the writers.

The Chemotherapy of Leprosy. Part 2*

Drug resistance

The phenomenon of drug resistance in leprosy has been comprehensively reviewed by Ji.[143] In his review Ji summarized evidence of the increasing prevalence of both secondary (acquired) and primary resistance to dapsone as a result of the use of dapsone monotherapy as standard treatment for over 30 years since its introduction in the early 1950s, and for the selection of strains of *Mycobacterium leprae* resistant to rifampin and the thioamides when these were also used as monotherapy for treating lepromatous patients. Most secondary dapsone-resistant strains display high-grade dapsone resistance, multiplying in mice fed 0.01% dapsone in the diet; whereas most primary-resistant strains currently possess low-grade resistance being inhibited by 0.001% but not 0.0001% dietary dapsone. Ji also outlined the probable bacteriological basis for the selection of such resistant strains from the small numbers of mutants likely to be initially present in the large bacterial populations harbored by previously untreated lepromatous patients, and described methods for determining the susceptibility of strains of *M. leprae* to dapsone and rifampin using the mouse-foot-pad model.

Since there have been no authenticated reports of clofazimine-resistant strains of *M. leprae*,[144] it appears that resistance to this drug is less common than resistence to the other established antileprosy drugs. Further evidence of the exquisite dapsone susceptibility of all strains of *M. leprae* isolated prior to 1977 has been published by Shepard, *et al.*[145] Other points worthy of mention are the stability of dapsone resistance in dapsone-resistant strains of *M. leprae* both in the mouse and in man,[34, 40, 42, 146] and the contrast between the step-wise resistance of *M. leprae* to dapsone and the apparent single-step resistance to other antileprosy drugs, such as rifampin, ethionamide, prothionamide, thiacetazone and thiambutosine.[80, 143, 147–149] Further evidence for the ubiquity of primary dapsone resistance has come from THELEP[150] and Chen, *et al.*[151]

* We are fortunate to have the opportunity of publishing this authoritative review of the chemotherapy of leprosy by Dr. Gordon Ellard. Due to space constraints, it has appeared in two parts, the first part in the December 1990 issue and the second part in this issue.—RCH

[144] Levy, L. Clofazimine-resistant *M. leprae*. Int. J. Lepr. **54** (1986) 137–140.

[145] Shepard, C. C., Rees, R. J. W., Levy, L., Pattyn, S. R., Ji, B. and Dela Cruz, E. C. Susceptibility of strains of *Mycobacterium leprae* isolated prior to 1977 from patients with previously untreated lepromatous leprosy. Int. J. Lepr. **54** (1986) 11–15.

[146] Guelpa-Lauras, C.-C., Grosset, J.-H., Constant-Desportes, M. and Brucker, G. Nine cases of rifampin-resistant leprosy. Int. J. Lepr. **52** (1984) 101–102.

Testing of combinations of drugs in the mouse foot pad

When Shepard, *et al.*[28] first suggested preventing the selection of drug-resistant strains of *M. leprae* during chemotherapy by giving combinations of drugs, they pointed out the importance of first testing the combinations of drugs against *M. leprae* in the mouse to discover whether they could antagonize each other's activity. Such studies were carried out in the mouse, using both the kinetic and proportional bactericidal test methods, and showed that the bactericidal activities of rifampin, dapsone, clofazimine, ethionamide and prothionamide were not antagonized when they were given in a variety of combinations.[55, 109, 127, 129] Similar studies carried out in the neonatally thymectomized Lewis rat showed that the bactericidal activity of rifampin was undiminished when it was given in combination with low dosages of dapsone,[94, 152] thus providing experimental evidence for the potential therapeutic efficacy of combined regimens of supervised intermittent oral rifampin and injectable acedapsone.

Drug compliance

Studies of the regularity of dapsone ingestion have been reviewed by Ellard[153] and Huikeshoven.[154] Although it is self-evident that patients cannot expect to respond satisfactorily if they fail to take their allocated treatment, it is surprising how few physicians are aware of the importance of poor compliance—the major cause of treatment failure in tuberculosis[155, 156] and, in all probability, in leprosy, too. Although all patients treated with the WHO Study Group regimens will show highly satisfactory clinical and bacteriological improvement in the short term due to the ingestion of supervised monthly rifampin doses, if they fail to self-administer their daily dapsone and clofazimine treatment, they inevitably run serious risk of ultimately relapsing with rifampin-resistant leprosy.

The most satisfactory method for monitoring dapsone ingestion is the quantitative urinary dapsone/creatinine (D/C) ratio procedure in which the concentrations of dapsone, plus its diazotizable metabolites, and of creatinine are measured using simple colorimetric methods.[157, 158] It is important to allow for the effects of diuresis by ratioing to creatinine[159] because of the slow rate of elimination of dapsone and its metabolites from the body (half-life about 1 day). Thus, if this is not done and a purely qualitative procedure used, the excretion of natural diazotizable compounds in normal urine may result in concentrated samples from non-compliant patients being classified as positive, whereas dilute samples from compliant patients may be erroneously read as negative.

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[147] Waters, M. F. R., Pearson, J. M. H. and Rees, R. J. W. Drug-resistant leprosy: A comparison between proven dapsone and proven thiambutosine resistance. Int. J. Lepr. **44** (1976) 152–153.

[148] Hastings, R. C. and Jacobson, R. R. Rifampin-resistant leprosy. Health Coop. Papers **1** (1981) 47–54.

[149] Guelpa-Lauras, C.-C., Cartel, J.-L., Constant-Desportes, M., Millan, J., Bobin, P., Guidi, C., Brucker, G., Flageul, B., Guillaume, J. C., Pichet, C., Remey, J. C. and Grosset, J.-H. Primary and secondary dapsone resistance to *M. leprae* in Martinique, Guadeloupe, New Caledonia, Tahiti, Senegal and Paris between 1980 and 1985. Int. J. Lepr. **55** (1987) 672–679.

[150] THELEP: Subcommittee on Clinical Trials of the Chemotherapy of Leprosy Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Primary dapsone resistance in Bamako and Chingleput: final report. Lepr. Rev. **58** (1987) 209–218.

[151] Chen, J. K., Wang, S. Y., Hou, Y. H., Ni, G. X., Zhang, J. L. and Tang, Q. G. Primary dapsone resistance in China. Lepr. Rev. **60** (1989) 263–266.

[152] Fieldsteel, A. H. and Levy, L. Single dose rifampin treatment of *Mycobacterium leprae*-infected neonatally thymectomized Lewis rats. Int. J. Lepr. **44** (1976) 546–547.

[153] Ellard, G. A. Drug compliance in the treatment of leprosy. Lepr. Rev. **52** (1981) 201–213.

[154] Huikeshoven, H. Patient compliance with dapsone administration in leprosy. Int. J. Lepr. **49** (1981) 228–258.

[155] Fox, W. Self-administration of medicaments; a review of published work and a study of the problems. Bull. Int. Union Tuberc. **32** (1962) 307–331.

[156] Fox, W. Compliance of patients and physicians: experience and lessons from tuberculosis—I. and II. Br. Med. J. **287** (1983) 33–35 and 101–105.

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

[158] Ellard, G. A., Gammon, P. T., Helmy, H. S. and Rees, R. J. W. Urine tests to monitor the self-administration of dapsone by leprosy patients. Am. J. Trop. Med. Hyg. **23** (1974) 464–470.

[159] Ellard, G. A. Profile of urinary dapsone/creatinine ratios after oral dosage with dapsone. Lepr. Rev. **51** (1980) 229–236.

An approximate estimate of the proportion of dapsone doses being ingested can be obtained by comparing the mean D/C ratios of test urine samples with those from patients receiving their standard daily dapsone treatment (100 mg) under supervision. Individual D/C ratios of less than 30 usually indicate that some scheduled daily dapsone doses have not been ingested, while apparent D/C ratios of less than 10 suggest that no dose of dapsone has been taken for at least 4 days. Such studies have often shown that only about half of the dapsone tablets handed out to leprosy patients are actually ingested, and that more than a quarter of all patients self-administer their medication very irregularly.

Simple urine tests are not available for monitoring the self-medication of clofazimine, ethionamide or prothionamide. However, studies of their compliance have been undertaken using special formulations containing minute amounts of isoniazid added to drug-containing capsules or tablets to act as an innocuous marker, or the commercially available combined dapsone plus prothionamide plus isoniazid formulation (Isoprodian).[139, 160, 161] Drug ingestion could then be assessed by simple colorimetric methods for the isoniazid metabolites isonicotinic acid and acetylisoniazid.

These studies showed that the compliance of lepromatous patients being treated with the WHO Study Group regimen in the THELEP Field Trial at Karigiri in South India was exceptionally good. Thus, over 75% of the daily dapsone and clofazimine doses were ingested. There was a marked correlation in the taking of the two drugs, with the result that the patients at greatest risk of developing rifampin resistance because of poor dapsone compliance were the very ones least likely to take their daily clofazimine treatment. In the study of Isoprodian ingestion carried out at Hyderabad in India, compliance was much poorer; only about half of the prescribed tablets were ingested. Although enormous variations in individual patient compliance were demonstrated, there was a continuous range of compliance and patients could not be simply grouped into good and poor compliers. It was concluded that only about 40% of the patients ingested therapeutically adequate amounts of their treatment as a result of gastro-intestinal side effects and poor compliance, and that if prothionamide is to be used as an alternative to clofazimine in the MDT of lepromatous leprosy, its compliance should be monitored using a suitable isoniazid-marked formulation.

"Bubble" or "calendar" packs[162–164] have recently been produced commercially for the administration of the WHO Study Group recommended regimens. It is hoped that in addition to simplifying treatment delivery and helping to protect the patients' monthly stocks of drugs from dirt and dampness, they may encourage patient compliance and discourage the potential pilfering of rifampin.

Persisters

Persisters are viable, drug-susceptible, leprosy bacilli that can be recovered from lepromatous patients after many years of apparently successful treatment with dapsone,[31] rifampin or rifampin plus thiambutosine,[41, 165] or clofazimine.[42]

The most comprehensive information regarding persisters comes from the recent THELEP controlled clinical trials in Bamako and Chingleput,[53] which showed that persisters could not be eliminated over a 2-year period by combined regimens of either dapsone plus rifampin, dapsone plus

[160] Stanley, J. N. A., Pearson, J. M. H. and Ellard, G. A. Ethionamide, prothionamide and thiacetazone self-administration; Studies of patient compliance using isoniazid-marked formulations. Lepr. Rev. **57** (1986) 9–18.

[161] Ellard, G. A., Pannikar, V. K., Jesudasan, K. and Christian, M. Clofazimine and dapsone compliance. Lepr. Rev. **59** (1988) 201–213.

[162] Winsley, B. E., McDougall, A. C. and Brown, K. E. Chemotherapy of leprosy: "bubble" or "calendar" packs for the administration of rifampin, dapsone, clofazimine, or prothionamide/ethionamide. Int. J. Lepr. **51** (1983) 592–594.

[163] Georgiev, G. D. and Kielstrup, R. W. Blister calendar packs for the implementation of multiple drug therapy in DANIDA-assisted leprosy control projects in India. Lepr. Rev. **58** (1987) 249–255.

[164] Georgiev, G. D. and McDougall, A. C. Blister calendar packs—potential for improvement in the supply and utilization of multiple drug therapy in leprosy control programs. Int. J. Lepr. **56** (1988) 603–610.

[165] 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.

rifampin plus clofazimine, or dapsone plus rifampin plus prothionamide. These studies also demonstrated that during the first 2 years the proportions of persisting *M. leprae* were typically of the order of 1 in 10^6.

Since inocula of greater than 10^6 *M. leprae* fail to multiply in normal mice, persisters are best detected at these earlier times by inoculating either 10^5 bacilli into thymectomized/irradiated (TR) mice,[53, 166] or 10^6 *M. leprae* into neonatally thymectomized Lewis rats.[167, 168] Model experiments involving the inoculation of mixtures containing very small proportions of viable bacilli suggested that the nude mouse might be more efficient than the TR mouse in detecting very small proportions of viable organisms,[169, 170] and that it may also be possible to detect persisters using normal mice by employing an initial inoculum of up to 10^7 *M. leprae* and then passaging into additional mice after a further 6 or 12 months.[171] However, neither of these models has yet been reported to have been employed in persister studies.

It seems probable that persisting *M. leprae* are not killed by any of the antileprosy drugs or their combinations so far tested, or by the limited bactericidal host mechanisms that operate in lepromatous patients, so that the initial persister populations of the order of 10^4, revealed during the first 2 years of rifampin-containing treatment, may survive almost indefinitely. Drug-susceptible nonpersisters are extremely rapidly killed by rifampin,[30, 172] and the dead organisms then slowly removed by the body. Bacterial indices typically fall by 0.62–0.85 units a year,[24, 53] equivalent to the removal of 75%–85% of the dead organisms each year, with faster rates among patients with borderline lepromatous leprosy.[95] As the dead organisms are cleared, the proportion of persisting *M. leprae* steadily increases.

Although the phenomenon of bacterial persistence is not limited to leprosy,[173, 174] it is clear that there may well be fundamental differences in the nature and origin of persisters in different diseases. Thus, persisting tubercle bacilli are susceptible to killing by rifampin and pyrazinamide and lead to relapse if they are not eliminated;[175] whereas persisting *M. leprae* appear to be totally insusceptible to drug action and to date seem unlikely to lead to relapse after cessation of treatment.

It was previously noted that leprosy bacilli from special sites, such as nerves, dartos muscle and striated muscle, tend to retain their solidly staining characteristics during continued treatment considerably longer than the initially more-numerous bacilli in the skin.[176] As a consequence, it was from such supposedly protected sites, where it was believed that the bacilli might be less liable to attack by the normal defense mechanisms of the body or by drugs and so could preferentially multiply, that many of the biopsies were taken from which persisters were subsequently isolated.[31, 165, 177]

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[166] Rees, R. J. W. Animal models in leprosy. Br. Med. Bull. **44** (1988) 650–664.

[167] Fieldsteel, A. H. and Levy, L. Neonatally thymectomized Lewis rats infected with *Mycobacterium leprae*: response to primary infection, secondary challenge, and large inocula. Infect. Immun. **14** (1976) 736–741.

[168] Gelber, R. H., Humphres, R. C. and Fieldsteel, A. H. Superiority of the neonatally thymectomized Lewis rat (NTLR) to monitor a clinical trial in lepromatous leprosy of two regimens of rifampin and dapsone. Int. J. Lepr. **54** (1986) 273–283.

[169] Colston, M. J. and Kohsaka, K. The nude mouse in studies of leprosy. In: *The Nude Mouse in Experimental and Clinical Research.* New York: Academic Press, 1982, vol. 2, pp. 247–266.

[170] Lancaster, R. D., Hilson, G. R. F., McDougall, A. C. and Colston, M. J. *Mycobacterium leprae* infection in nude mice: bacteriological and histological responses to primary infection and large inocula. Infect. Immun. **39** (1983) 865–872.

[171] Fieldsteel, A. H. and Colston, M. J. The intact mouse as a host for the detection of small numbers of viable *M. leprae* in the presence of large numbers of heat-killed *M. leprae.* Int. J. Lepr. **49** (1981) 499–500.

[172] Grosset, J. Recent developments in the field of multidrug therapy and future research in chemotherapy of leprosy. Lepr. Rev. **57** Suppl. (1986) 223–234.

[173] Toman, K. Bacterial persistence in leprosy. Int. J. Lepr. **49** (1981) 205–217.

[174] Grosset, J., Guelpa-Lauras, C.-C., Lecoeur, H. and Truffot-Pernot, C. Microbial persistence in mycobacterial infections. Health Coop. Papers **1** (1983) 41–49.

[175] Mitchison, D. A. The action of antituberculosis drugs in short-course chemotherapy. Tubercle **68** (1988) 219–225.

[176] Pearson, J. M. H., Rees, R. J. W. and Weddell, A. G. M. *Mycobacterium leprae* in the striated muscle of patients with leprosy. Lepr. Rev. **41** (1970) 155–166.

These investigations showed, however, that viable persisting *M. leprae* could be as readily isolated from the skin as from these supposedly special sites. In retrospect, the rarity of persisters (of the order of 1 in 10^6 in the original population) suggests that the bacilli seen microscopically at these sites were probably drug-killed bacilli whose fragmentation had been retarded as the result of protection in their particular intracellular locations.

It should be noted that "persisting (apparently) viable bacilli" (as judged by their staining properties) were encountered among 5 of 28 multibacillary patients, who had been treated with acedapsone for 5 years in a study in Karimui in Papua New Guinea,[61] which had apparently been uncovered by the faster removal of dead organisms. That these organisms were not "classical" persisters is indicated by their relatively large numbers and the fact that they disappeared after a course of rifampin treatment.[178] Presumably, they arose as a result of the lack of bactericidal activity of the low concentrations of dapsone generated by acedapsone and the extremely limited cell-mediated immunity of lepromatous patients.

In view of the apparent impossibility of eliminating persisters with combinations of any of the known antileprosy drugs,[53] it would seem logical to conclude that in any formal sense lepromatous leprosy cannot be cured. However, the results of the studies in Malta and Sungei Buloh, when termination of treatment was followed by very low relapse rates,[48, 50] indicate that persisters pose less of a threat than was formerly supposed, since all of the patients in these two studies would have been expected to harbor persisters when their treatment was stopped. The current lack of relapses among multibacillary patients treated to smear negativity with the WHO Study Group regimen[51, 52] is even more encouraging.

It is clear that the selective survival of persisters does not stem from their being located in sites not reached by antileprosy drugs. Thus, experimental studies have shown that dapsone and rifampin readily penetrate into the peripheral nerves of the mouse, rat, dog, sheep, and rhesus monkey, as well as into other tissues, and into mouse and rabbit macrophages.[32, 97, 179–184] Furthermore, Peters and his colleagues[181] were able to directly demonstrate the penetration of dapsone into human peripheral nerve.

The excellent absorption of both dapsone and rifampin[70, 97] and their extensive reabsorption from the kidney are entirely in accord with rapid diffusion across virtually all cellular membranes, which is to be expected from their lipophilicity and lack of charge at body pH. Furthermore, dapsone's long half-life (a little over a day), and the fact that standard daily dosages give peak serum concentrations that exceed its estimated minimal inhibitory concentration (MIC) against *M. leprae* by about 500-fold, implies that bactericidal concentrations of the drug have a virtually infinite time to diffuse throughout the whole body.

The penetration of rifampin through cell membranes is probably slower than that of dapsone, as suggested by its slow penetration into the cerebrospinal fluid.[97, 185] It also

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

[178] Russell, D. A., Worth, R. M., Scott, G. C., Vincin, D. R., Jano, B., Fasal, P. and Shepard, C. C. Experience with acedapsone (DADDS) in the therapeutic trial in New Guinea and the chemoprophylactic trial in Micronesia. Int. J. Lepr. **44** (1976) 170–176.

[179] Francis, J. The distribution of sulfone in the tissues of various animals. J. Comp. Pathol. **63** (1953) 1–6.

[180] Allen, B. W., Ellard, G. A., Gammon, P. T., King, R. C., McDougall, A. C., Rees, R. J. W. and Weddell, A. G. M. The penetration of dapsone, rifampicin, isoniazid and pyrazinamide into peripheral nerves. Br. J. Pharmacol. **55** (1975) 151–155.

[181] McDougall, A. C., Rose, J. A. and Grahame-Smith, D. G. Penetration of C^{14}-labelled rifampicin into primate peripheral nerve. Experientia **31** (1975) 1068–1069.

[182] Peters, J. H., Murray, J. F., Gordon, G. R., Gelber, R. H., Levy, L., Lang, A. B. G. and Waters, M. F. R. Tissue levels of dapsone in mice, rats and man. Int. J. Lepr. **44** (1976) 545–546.

[183] Johnson, J. D., Hand, W. L., Francis, J. B., King-Thompson, N. and Corwin, R. W. Antibiotic uptake by alveolar macrophages. J. Lab. Clin. Med. **95** (1980) 429–439.

[184] Acocella, G., Carlone, N. A., Cuffini, A. M. and Cavallo, G. The penetration of rifampicin, pyrazinamide, and pyrazinoic acid into mouse macrophages. Am. Rev. Respir. Dis. **132** (1985) 1268–1273.

[185] Woo, J., Humphries, M., Chan, K., O'Mahony, G. and Teoh, R. Cerebrospinal fluid and serum levels of pyrazinamide and rifampicin in patients with tu-

has a considerably shorter half-life (about 2 hours). Intracellular concentrations of rifampin may, therefore, be significantly lower than the extracellular levels. However, 20-mg doses of rifampin, which give serum concentrations of less than a two-hundredths of those achieved with standard 600 mg doses,[186] still display significant bactericidal activity against *M. leprae*.[102] This must, therefore, imply that there is no site in the body where leprosy bacilli could escape being exposed to potentially bactericidal concentrations of rifampin when standard 600 mg doses are ingested. The extreme lipophilicity and long half-life of clofazimine similarly indicate that potentially bactericidal concentrations of this drug must also permeate every microscopic nook and cranny in the body.

Such conclusions are in accord with the classical experimental studies of persisters in tuberculosis or staphylococcal infections when it was convincingly demonstrated that lack of bacterial killing did not occur because of poor drug penetration.[187] It therefore seems likely that persisters survive in the face of potentially bactericidal drug concentrations because they are essentially physiologically dormant organisms. The persister state may be induced *in vitro* by the exhaustion of nutrients in the growth medium and may occur *in vitro* and *in vivo* as a result of reduced oxygen tension or reduced pH.

The recent THELEP Bamako and Chingleput trials have shown that in lepromatous leprosy persisters comprise only about 1 in 10^6 of the total bacterial population and that they are randomly distributed throughout the body.[53] How the metabolism and multiplication of such a minute fraction of the viable bacillary population might be virtually permanently switched off is a mystery, since it is clear that such persisters survive periods of up to at least two decades of potentially highly effective treatment.

Rationale for introduction of MDT and its initial performance

The evidence presented above indicates that in multibacillary patients there are essentially three populations of leprosy bacilli: a) fully drug-susceptible organisms; b) small, independent populations of drug-resistant mutants; and c) a small population of inherently drug-susceptible, nonmultiplying bacilli (persisters) that are not eliminated by treatment with dapsone, rifampin or clofazimine. In the face of the mounting epidemic of dapsone resistance caused by the former universal use of dapsone monotherapy, it was clearly essential that the treatment for multibacillary patients be changed to a combination of at least two potent drugs, as had proved so successful in combating the problem of drug resistance in the chemotherapy of tuberculosis.[175, 188]

The efficacy of MDT rests on the fact that if combinations of drugs with different targets of action are used, then bacilli resistant to one drug will be susceptible to the other and vice versa. If previously untreated multibacillary patients were initially infected with drug-susceptible *M. leprae*, it is most unlikely that they will harbor any bacilli with double-drug resistance since the chances of this occurring are almost certainly less than 1 in 10^{12}, a number which was thought to be greater than the total population of viable leprosy bacilli in even the most florid lepromatous patient.[189] Recent evidence[172] has in fact shown that the total population of viable *M. leprae* in untreated multibacillary patients is almost always less than 10^{11}. Hence, treatment with two fully potent drugs should be entirely effective.

The clinical and bacteriological evidence presented above strongly suggests that the three most active antileprosy drugs are dapsone, rifampin and clofazimine. Hence, in

berculous meningitis. Curr. Therap. Res. **42** (1987) 235–242.

[186] Dickinson, J. M., Mitchison, D. A., Lees, S. K., Ong, Y. Y., O'Mahony, M. G., Girling, J. D. and Nunn, A. J. Serum rifampicin concentration related to dose size and to the incidence of the "flu" syndrome during intermittent rifampicin administration. J. Antimicrob. Chemother. **3** (1977) 445–452.

[187] McDermott, W. Microbial persistence. Yale J. Biol. Med. **30** (1957) 257–291.

[188] Girling, D. J. The chemotherapy of tuberculosis. In: *The Biology of the Mycobacteria. Vol. 3: Clinical Aspects of Mycobacterial Disease.* Ratledge, C., Stanford, J. and Grange, J. M., eds. New York: Academic Press, 1989, pp. 285–323.

[189] Shepard, C. C. Recent developments in the chemotherapy and chemoprophylaxis of leprosy. Leprologia (Argen.) **19** (1974) 230–236.

view of the increasing prevalence of dapsone-resistant strains, it was clear that a combination of rifampin plus clofazimine should be employed. However, since most primary-resistant strains of *M. leprae* only displayed low-grade dapsone resistance, it was concluded that such a combination would be considerably strengthened by the addition of dapsone. The WHO Study Group[1] therefore recommended that multibacillary patients should be treated with supervised monthly doses of rifampin (600 mg) and clofazimine (300 mg), together with daily doses of dapsone (100 mg) and clofazimine (50 mg) for self-administration.

In view of the spectacular bactericidal activity of single doses of rifampin,[29, 30] it is likely that within a few months such treatment will wipe out the entire population of drug-susceptible (nonpersister) bacilli, together with the much smaller populations of mutants resistant to either dapsone or clofazimine. The key role of the largely self-administered dapsone and clofazimine components is, therefore, to gradually eliminate the small population of rifampin-resistant leprosy bacilli expected to be present at the start of treatment which could well number fewer than a thousand bacilli. In view of the much more modest bactericidal activities of dapsone and clofazimine, it was therefore recommended that MDT should be continued for at least 2 years, and preferably to smear negativity. (For a more detailed discussion of the rationale for MDT, see Ellard,[40] Levy,[190] and Grosset.[172])

Because the maximal bacterial load in paucibacillary patients is only about 10^6, the risks of treatment leading to the selection of drug-resistant mutants are enormously reduced and, in the great majority of cases, the administration of a single effective antileprosy drug would probably be sufficient. However, because of the increasing numbers of new paucibacillary patients who are likely to be infected with dapsone-resistant strains of *M. leprae,* it was recommended that all paucibacillary patients should be treated for just 6 months with supervised monthly doses of 600 mg rifampin plus daily self-administered dapsone (100 mg). Dapsone was included to minimize the risk of rifampin resistance in multibacillary patients who might have been erroneously diagnosed as paucibacillary.

The WHO Study Group originally defined paucibacillary patients as those with indeterminate (I), tuberculoid (TT), or borderline tuberculoid (BT) leprosy in the classification scheme of Ridley and Jopling,[20] whose bacterial index (BI) on Ridley's scale[10] was less than 2 at any site. However, as an additional safeguard, it is now recommended that all smear-positive indeterminate or tuberculoid patients should be treated as if they were multibacillary.

The evidence presented above concerning the antileprosy activities of dapsone, rifampin and clofazimine indicates that if the three drugs are delivered regularly to multibacillary patients, as recommended, and then regularly ingested, no patient, irrespective of past treatment history, should relapse during treatment as a result of the emergence of drug-resistant *M. leprae.* It was also believed that any relapses that might occur after stopping treatment, for example, as a result of the eventual multiplication of surviving persisters, would occur with fully susceptible organisms. This should, therefore, enable relapsed patients to be successfully retreated with the same regimen, as is the case among pulmonary tuberculosis patients who relapse after completing normally effective short-course chemotherapy. It was hoped that relapse rates after terminating treatment would be less than 1% per annum.

Not only have these expectations been fulfilled, they have been considerably surpassed. Among the 2 million patients who have been started on the WHO-recommended regimens, drug acceptability has been excellent. Clofazimine has been well tolerated, even among light-skinned patients, and it has hardly ever been necessary to consider replacing it with an alternative third drug such as ethionamide or prothionamide. There has also been a high level of patient satisfaction with their clinical response, which occurs considerably faster than used to with dapsone monotherapy. Furthermore, there has been a significant reduction in the frequency and severity of erythema nodosum leprosum (ENL) (type 2) reactions among multibacillary patients,

[190] Levy, L. The Kellersberger Memorial Lecture, 1984. Chemotherapy of leprosy—a tool for leprosy control. Ethiop. Med. J. **23** (1985) 31–42.

probably because of the inclusion of clofazimine in the regimen. On the operational side, there has been a marked improvement in patient attendance rates, an increase in the detection of new cases through voluntary reporting, better motivation among health workers, and greater community support resulting from the recognition of the effectiveness of MDT. (For further details concerning the implementation of multidrug treatment see Ellard.[191])

Relapse rates have been negligible. Thus, in the two THELEP-supported field trials carried out in Karigiri and Polombakkam in South India, not a single relapse has occurred among the 2000 multibacillary patients whose treatment has been terminated for at least 4 years after achieving smear negativity. Similarly in a THELEP-supported trial among 457 paucibacillary patients in Malawi, only six showed signs of relapse during a 3-4 year follow-up period.[52]

Chemoprophylaxis

Noordeen[192] has reviewed the chemoprophylactic studies that have been conducted in India and Micronesia, using either oral dapsone or acedapsone injections. Although oral dapsone showed moderate protection, it can hardly be recommended for mass chemoprophylactic use in view of the difficulties of persuading actual patients to take the drug regularly and the fact that most new leprosy cases do not arise among household contacts of known patients.[193] Acedapsone injections given at intervals of approximately 3 months appeared in the past to be an almost ideal method of chemoprophylaxis.[194] Such injections were given for 3 years to almost all of the 1600 people living in three remote villages on the Pacific atoll of Pingelap by Russell and his colleagues from 1967–1970.[178, 195] Although there were no new cases during the 3-year campaign, new cases occurred after 1973, including some among children born after 1968, demonstrating that transmission of the disease was still occurring, perhaps from relapses among the original index cases. In the face of mounting primary resistance to dapsone,[143] it must be assumed that the chemoprophylactic efficacy of acedapsone is likely to be substantially impaired. As a consequence, current chemoprophylaxis trials are investigating the potential efficacy of single doses of 25 mg/kg rifampin in eliminating subclinical leprosy infections that might otherwise eventually progress to active disease.

Promising new drugs: the fluorinated quinolones

The only other major class of drugs with proven activity in the treatment of lepromatous leprosy are the fluoroquinolones. The fluorinated quinolones inhibit bacterial gyrase and have a wide spectrum of antibacterial activity.[196] They are most active against gram-negative organisms, but also display significant antimycobacterial activity. The most active antimycobacterial quinolones *in vitro* were ciprofloxacin and ofloxacin.[197–199] Experimental studies in the mouse foot pad have shown that ciprofloxacin, pefloxacin, and ofloxacin possess antileprosy activity.[200–202] However, of these

[191] Ellard, G. A. Chemotherapy of leprosy. Br. Med. Bull. **44** (1988) 775–790.

[192] Noordeen, S. K. Chemoprophylaxis. Health Coop. Papers **1** (1982) 173–180.

[193] Fine, P. E. M. Leprosy; the epidemiology of a slow bacterium. Epidemiol. Rev. **4** (1982) 161–188.

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[196] Paton, J. H. and Reeves, D. S. Fluoroquinolone antibiotics. Microbiology, pharmacokinetics and clinical use. Drugs **36** (1988) 193–228 (258 refs.).

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[198] Heifets, L. B. and Lindholm-Levy, P. J. Bacteriostatic and bactericidal activity of ciprofloxacin and ofloxacin against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. Tubercle **68** (1987) 267–276.

[199] Leysen, D. C., Haemers, A. and Pattyn, S. R. Mycobacteria and the new quinolones. Antimicrob. Agents Chemother. **33** (1989) 1–5.

[200] Guelpa-Lauras, C.-C., Perani, E. G., Giroir, A. M. and Grosset, J.-H. Activities of pefloxacin and ciprofloxacin against *Mycobacterium leprae* in the mouse. Int. J. Lepr. **55** (1987) 70–77.

[201] Pattyn, S. R. Activity of ofloxacin and pefloxacin against *Mycobacterium leprae* in mice. Antimicrob. Agents Chemother. **31** (1987) 671–672.

three quinolones, ciprofloxacin is the least active against *M. leprae,* only displaying bacteriostatic activity at a daily dosage of 150 mg/kg because of poor absorption in the mouse.[200] Since ciprofloxacin is also incompletely absorbed and rapidly eliminated (half-life about 4 hours) in man,[203, 204] it clearly has no potential clinical future for the treatment of leprosy.

By contrast, all of the other quinolones studied appear to be excellently absorbed both in the mouse and in man. In the mouse, they are rapidly eliminated with a half-life of between 1.5 and 2 hours, but in man their half-lives range from about 6 hours for ofloxacin[205–207] to 11 hours for pefloxacin and fleroxacin.[208] As a consequence, it was anticipated that these quinolones will be far more active in man on a mg/kg basis than in the mouse.[209] This has already been shown to be the case. Thus, whereas daily doses of 150 mg/kg and thrice weekly doses 300 mg/kg pefloxacin had to be given to achieve significant bactericidal activity in the mouse,[200, 201] marked bactericidal activity of the drug was demonstrated in a pilot trial when 10 lepromatous patients were treated with 400 mg pefloxacin twice daily and within 4 months inocula were incapable of infecting either normal or nude mice.[210]

Ofloxacin displayed considerably greater antileprosy activity in the mouse foot pad, daily doses of 150 mg/kg being extremely bactericidal.[201, 202, 211] Its antileprosy activity in man is currently being investigated in a pilot trial in which treatment is started with a single loading dose of 800 mg, followed by 56 days' daily treatment with 400 mg of the drug starting from the 8th day to assess the extent of bactericidal activity of both single and multiple doses of the drug.[52, 210, 212] Such daily doses have already been given to several million European patients, for periods averaging about a week, to treat other bacterial infections and have been found to be excellently tolerated.[206, 213]

Future research

To my mind, future potential research can be broadly divided into two complementary categories: a) research aimed at strengthening the currently recommended treatment for multibacillary patients, and b) operational research aimed at improving case finding, case holding and treatment delivery.

Improving patient compliance. The only important inherent weakness of the regimen appears to be its vulnerability to poor patient compliance. Thus, if patients fail to ingest a substantial proportion of their prescribed daily dapsone and clofazimine treatment, in reality their treatment will tend to become a monthly treatment with 600 mg rifampin and 300 mg clofazimine. The rifampin component will still ensure the rapid elimination of the drug-susceptible popu-

[202] Grosset, J.-H., Guelpa-Lauras, C.-C., Perani, E. G. and Beoletto, C. Activity of ofloxacin against *Mycobacterium leprae* in the mouse. Int. J. Lepr. **56** (1988) 259–264.

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[209] Grosset, J. H. Pharmacokinetics of drug screening. Int. J. Lepr. **55** Suppl. (1987) 852–856.

[210] Grosset, J., Guelpa-Lauras, C.-C., N'Deli, L. and Perani, E. Pefloxacin and ofloxacin in lepromatous leprosy at Adzope (Ivory Coast): II. Biological results. (Abstract) Health Coop. Papers **9** (1988) 69.

[211] Guelpa-Lauras, C.-C., Perani, E. G., Beoletto, C. and Grosset, J.-H. Pefloxacin and ofloxacin activities against *M. leprae* in the mouse. (Abstract) Helath Coop. Papers **9** (1988) 70.

[212] N'Dehli, L., Guelpa-Lauras, C.-C. and Grosset, J. Pefloxacin or ofloxacin in lepromatous leprosy at Adzope (Ivory Coast): I. Clinical results. (Abstract) Health Coop. Papers **9** (1988) 74.

[213] Jungst, G. and Mohr, R. Overview of postmarketing experience with ofloxacin in Germany. J. Antimicrob. Chemother. **22** Suppl. (1988) 167–175.

lation and any small populations of dapsone- or clofazimine-resistant organisms, and an associated rapid amelioration in the patients' symptoms. However, the rate of elimination of the key population of rifampin-resistant mutants will almost certainly be greatly slowed down, since previous trials of clofazimine monotherapy showed reduced activity even when 600 mg doses of clofazimine were given on two consecutive days at monthly intervals.[122] Furthermore, if patients also fail to come regularly for their supervised monthly treatment, the therapeutic contribution of occasionally supervised 300 mg clofazimine doses would be negligible and the patients would, in reality, be receiving rifampin monotherapy. However, recent evidence indicates that even when multibacillary patients are essentially treated with rifampin monotherapy, it will take many years (median duration 9 years) before they will relapse clinically and bacteriologically with rifampin-resistant leprosy.[214]

Thus, even in the best control schemes, unless regular efforts are made to check patient compliance, no one is likely to appreciate the potential disaster that irregular drug taking could lead to, since its consequences are unlikely to be apparent for at least a decade. No one has yet been able to demonstrate how to radically improve patient compliance, whether it be in the treatment of leprosy or any other medical condition. However, I am impressed by the consistently high compliance of patients at the Schieffelin Leprosy Research and Training Centre at Karigiri in South India,[161] where the first THELEP field trial was launched, and the fact that the staff routinely collect urine samples from their patients to test by the dapsone/creatinine ratio method and then inform the patients if these tests indicate irregular drug ingestion.

Clearly, one cannot overemphasize the importance of trying to improve patient compliance and, since there is likely to be a high correlation between the taking of clofazimine and dapsone,[161] urine testing for dapsone with one of the variety of simple methods available should be both informative and valuable. At the simplest level, a deliberate attempt should be made to record skin pigmentation due to clofazimine, since chronic failure to self-administer the drug is likely to be revealed by a lack of skin pigmentation which should usually be apparent within 2–3 months.

Hopefully, delivering treatment in bubble or calendar packs may also aid patient compliance,[164] and a study is currently being mounted in Thailand to discover if this is, indeed, the case. Even a small improvement in patient compliance would completely offset the increased costs of delivering the drugs in this way, especially since at the dosages employed clofazimine is the most expensive component of the triple-drug regimen.[215, 216] However, it should be emphasized that however expensive drugs might be, their cost is never more than a tiny fraction of that required to finance the treatment services needed to identify patients and regularly deliver chemotherapy to them until they can be released from control.

Patient compliance might also be improved by delivering a substantial proportion of the recommended dapsone dose as a slow-release formulation. Promising, well-tolerated, slow-release dapsone formulations have been developed in The Netherlands for monthly intra-adipose injection and have shown satisfactory blood levels in both volunteers and patients.[217, 218] However, potential commercial development of the formulation has probably been impeded by fears surrounding the use of needles, and the risk of transmitting AIDS if their efficient sterilization could not be assured under field conditions.

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[214] Grosset, J.-H., Guelpa-Lauras, C.-C., Bobin, P., Brucker, G., Cartel, J.-L., Constant-Desportes, M., Flageul, B., Frederic, M., Guilaume, J. C. and Millan, J. Study of 39 documented relapses of multibacillary leprosy after treatment with rifampin. Int. J. Lepr. **57** (1989) 607–614.

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[216] Rees, R. J. W. Chemotherapy of leprosy for control programmes: scientific basis and practical application. Lepr. Rev. **54** (1983) 81–88.

[217] Pieters, F. A. J. M., Zuidema, J. and Merkus, F. W. H. M. Sustained release properties of an intra-adiposely administered dapsone depot injection. Int. J. Lepr. **54** (1986) 383–388.

[218] Pieters, F. A. J. M., Woonink, F. and Zuidema, J. A field trial among leprosy patients in Nigeria with depot injections of dapsone and monoacetyldapsone. Int. J. Lepr. **56** (1988) 10–20.

Discovering potential new antileprosy drugs. Formerly, those involved in research into the treatment of leprosy were extremely conscious of the limitations imposed by our inability to cultivate *M. leprae in vitro,* and the consequent need to test compounds for potential antileprosy activity using gram amounts in the time-consuming mouse foot pad system. Such reasons readily explained why research into the chemotherapy of leprosy had for so many years lagged behind that in tuberculosis.[219, 220]

With the astonishing bactericidal activity of single doses of rifampin and the great promise of the fluoroquinolones, the situation has radically changed and the need for discovering other classes of potential antileprosy drugs seems less pressing. Nevertheless, Hastings and Franzblau[221] have recently described a number of essentially *in vitro* methods for testing the potential inhibitory activities of compounds directly against suspensions of leprosy bacilli, while Colston and Lamb[222] have pointed to some of the potential contributions that molecular biology could make to the chemotherapy of leprosy. Thus, enzymes that are prospective targets of drug activity might be cloned from *M. leprae* into appropriate cultivable organisms, which could then generate sufficient amounts of enzyme for testing numerous candidate drugs *in vitro.* Perhaps one of the most suitable enzymes for initially cloning in this way would be dihydrofolate reductase, not only because of its anticipated small size, but also because of the likelihood that inhibitors of the enzyme could act synergistically with dapsone.[90]

Strengthening MDT with fluoroquinolones. Ofloxacin clearly has the potential to significantly strengthen the WHO Study Group regimen for multibacillary patients. Its bactericidal activity when given alone to previously untreated multibacillary patients is manifestly more rapid than that of either dapsone or clofazimine.[107] Thus, it could be added to the triple dapsone/rifampin/clofazimine combination to increase the rate of elimination of the initial population of rifampin-resistant mutants. This would make the regimen far less vulnerable to poor patient compliance, and thereby greatly reduce the chances of patients eventually relapsing with rifampin-resistant leprosy. Furthermore, its efficacy might be such that it could greatly increase the robustness of the regimen (making it essentially "compliance proof"), while at the same time significantly reducing the overall duration of required treatment. Alternatively, it might be used in place of clofazimine.

The two key questions, therefore, that have to be asked are: firstly, how best should it be given and, secondly, how much ofloxacin treatment needs to be added to give a convincingly robust regimen? Preliminary evidence presented by Grosset, at the XIII International Leprosy Congress in The Hague in 1988, suggests that significant bactericidal activity was not achieved by a single 800 mg dose of the drug, and therefore indicates that the most effective way of giving an ofloxacin supplement would be for an initial period of daily treatment rather than as monthly supervised doses.

THELEP is currently using two approaches to attempt to discover how best to use ofloxacin: a) pilot short-term trials using ofloxacin as monotherapy to previously untreated lepromatous patients to discover the rates at which viable *M. leprae* are killed, by inoculating appropriate dilutions of homogenized biopsies into both normal and athymic mice.[62, 223, 224] The sensitivity of this approach is such as to be able to follow the killing of some 99.9% to 99.99% of the initial viable population (a "3 or 4

[219] Ellard, G. A. The treatment of tuberculosis and leprosy. Lepr. Rev. **46** (1975) 149–155.

[220] Mitchison, D. A., Ellard, G. A. and Grosset, J. New antibacterial drugs for the treatment of mycobacterial disease in man. Br. Med. Bull. **44** (1988) 757–774.

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[222] Colston, M. J. and Lamb, F. I. Molecular biology of the mycobacteria. Lepr. Rev. **60** (1989) 89–93.

[223] THELEP: Subcommittee on Clinical Trials of the Chemotherapy of Leprosy Scientific Working Group of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. THELEP controlled clinical trials in lepromatous leprosy. Lepr. Rev. **54** (1983) 167–176.

[224] Grosset, J. and Ji, B. Controlled clinical trials for evaluation of antimicrobial activity against *M. leprae.* Int. J. Lepr. **57** (1989) 529–531.

log kill"). Thus, assuming that the tiny populations of rifampin-resistant mutants are eliminated in essentially the same fashion as the huge populations of drug-susceptible bacilli, one can hope to discover how much ofloxacin treatment might be required to eliminate a population of a few thousand rifampin-resistant mutants. b) THELEP is also trying to obtain direct evidence of ofloxacin's potential contribution to MDT by comparing ofloxacin-containing regimens with the standard WHO Study Group regimen in their ability to permanently cure patients. However, such studies inevitably require huge numbers of patients and many years of follow-up, especially since there has yet not been a single relapse among the 2000 patients treated in the two THELEP field trials with the WHO Study Group regimen 6 years after their treatment was discontinued.[53, 225]

With the rapid advances in molecular biology, particularly those associated with the discovery of the polymerase chain reaction (PCR),[226] one wonders whether such techniques could be applied to help monitor either bacterial killing or relapse. Already two groups have shown how the PCR can be used to specifically detect extremely small numbers of leprosy bacilli.[227, 228] However, to try to detect minute proportions of viable *M. leprae* among a background of dead bacilli would appear to be an order of magnitude more difficult. Furthermore, the "rate determining step" in trials assessing relapse rates is not the time it takes to demonstrate the reappearance of viable *M. leprae* using the mouse foot pad technique, but the time one has to wait for the relapses to appear—which can be anything up to at least 11 years.[214]

Operational research. In their highly pertinent editorial concerning priorities in leprosy control, McDougall and Georgiev[229] aptly commented on how an examination of the abstracts of the papers presented at the XIII International Leprosy Congress at The Hague in 1988 revealed that most contributions were on immunology, molecular biology, or closely related topics; that extremely few dealt directly with operational aspects of leprosy control and that fewer still were of high quality, despite the fact leprosy is a disease for which effective treatment is available. The introduction of MDT has necessitated a major change in the whole technology of leprosy control.[230] Its implementation depends on reliably assessing the bacteriological status of the patients. However, the quality of the taking and staining of skin smears is generally unsatisfactory, since they are often carried out in small, ill-equipped, peripheral laboratories by personnel who have been inadequately trained and are without regular supervision. As a consequence, paucibacillary patients may be misclassified and unnecessarily treated for 2 years or more with three drugs, while, much more seriously, misclassification of multibacillary patients can result in their being given grossly inadequate treatment.[231, 232] Georgiev and McDougall therefore recommended the centralization of laboratory services and the classification of the majority of paucibacillary patients on purely clinical grounds. They also emphasize the importance of treating all multibacillary patients for a minimum of 2 years, and suggest that this could be done without routine recourse to skin smears.

In many countries, leprosy control programs are essentially "vertical," and suffer from important limitations. Thus, their

[225] Noordeen, S. K. A look at world leprosy. Clayton Memorial Lecture, London, 10 January 1990.

[226] Saiki, R. K., Scharf, S., Faloona, F., Mullis, K. B., Horn, G. T., Erlich, H. A. and Arnheim, N. Enzymatic amplification of β-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science **239** (1985) 1350–1354.

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[229] McDougall, A. C. and Georgiev, G. D. Priorities in leprosy control. Lepr. Rev. **60** (1989) 1–7.

[230] Becx-Bleumink, M. Operational aspects of multidrug therapy. Int. J. Lepr. **57** (1989) 540–551.

[231] Georgiev, G. D. and McDougall, A. C. The bacteriological examination of slit-skin smears in leprosy control programmes using multiple drug therapy: a plea for radical changes in current operational methodology. Indian J. Lepr. **59** (1987) 373–385.

[232] Georgiev, G. D. and McDougall, A. C. Skin smears and the bacterial index (BI) in multiple drug therapy leprosy control programs; an unsatisfactory and potentially hazardous state of affairs. Int. J. Lepr. **56** (1988) 101–104.

population coverage is generally rather restricted, since they are only really practical in highly endemic areas with leprosy prevalences of the order of 5 per thousand or more. They often have inadequate contact with the community and are heavily dependent on voluntary agencies. Such vertical programs may also increase the stigma attached to the disease, both in the community and among health personnel.

Once the great majority of paucibacillary patients in highly endemic areas have been released from control, staff freed from vertical programs can either be retrained as general community health workers or transferred to help initiate MDT in areas of lower endemicity. In areas with a leprosy prevalence of 1 per thousand or less, most villages will have so few leprosy patients that delivering monthly supervised treatment by a vertical service would be completely impracticable. In such circumstances, the integration of leprosy into primary health care services is the only feasible method of delivering MDT.

However, for such an approach to be successful, certain preconditions must first be met: good training, systematic supervision, and effective referral possibilities for diagnosis and attending to complications.[233]

[233] Rijleveld, I. In reality: a medical anthropologist's reservations about the viability of leprosy control within primary health care. Lepr. Rev. **53** (1982) 181–192.

There is clearly an urgent need for operational studies being undertaken to find the most effective methods of delivering MDT in a variety of geographical and socioeconomic environments.[106] One of the difficulties always envisaged in embarking on such studies has been that of objectively assessing the efficacy of case finding, case holding, and treatment delivery. Clearly, this cannot be achieved by trying to assess its final outcome—therapeutic progress on a community scale. However, an alternate, more direct approach should be considered, namely, to assess by testing urine samples collected by surprise home visits to a random selection of all registered patients, the actual efficiency of treatment services in delivering chemotherapy to their patients and in persuading them to ingest them regularly.

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