Patient Compliance in Leprosy Control: A Necessity in Old and New Regimens

For two reasons, dapsone monotherapy is considered not to be acceptable any longer in leprosy control programs. Firstly, there is the increasing problem of sulfone-resistant leprosy and, secondly, self-administered dapsone therapy simply cannot be enforced for the long periods of time required. Multidrug therapy (MDT) is now recommended for all leprosy cases with the perspective of release from treatment after a few years at most. Once-monthly supervised rifampin doses form the backbone of the new regimens, supported by daily dapsone self administration for all cases and an additional daily clofazimine component for multibacillary cases only.[1]

Practical management of MDT is built on the completion of 24 monthly clinic visits and supervised doses for multibacillary cases for a maximum period of 36 months, and six monthly clinic visits and supervised doses for paucibacillary cases for a maximum period of nine months.[2] The achievement of therapeutic results by these recommendations remains an open question. Results may or may not be related to compliance with ingestion of the components for daily self administration. Patient compliance is defined as "the extent to which the patient's behavior coincides with the clinical prescription," but what really counts is the achievement or non-achievement of the treatment goal.[3] In the following paragraphs the present knowledge on leprosy patient compliance will be reviewed.

Magnitude of noncompliance in leprosy. Few authors have published extensive data about defaulting in major leprosy control schemes. Hertroijs[4] defined defaulters as "patients who have not attended a treatment center in our area [Mwanza Region, Tanzania] for a period of one year or more unless information has been received as to their receiving treatment elsewhere." Eight years after the beginning of the control scheme, 8665 patients had been diagnosed, of which 32% had since defaulted. The yearly defaulter rate ranged from 10–20%. Of those who had defaulted so far, only 15% had attended more than a year.

Recently, Collier[5] studied leprosy case holding in 55,000 patients seen in 14 different centers in Asia during 1976–1980. At the end of the five-year period, about 75% of all patients had been lost and in the first year after commencing treatment, the percentage was already nearly 50%. Koticha and Nair[6] analyzed attendance data from the patient registers of the Acworth Leprosy Hospital (ALH) in Bombay for a period of 25 years. Of 48,345 active resident cases, only 6345 (13%) were taking treatment regularly "on the basis of taking treatment for nine months a year for a minimum period of three years."

Hertroijs[4] defined irregular attenders as "patients who have attended one of our treatment centres less than 9 times out of the 13 possible yearly visits," distinguishing them from defaulters defined above. In the period studied, 30–50% of patients each year had to be classified as irregular attendees according to this definition. In a cross-sectional study of leprosy patients attending six clinics of a mobile treatment unit of Chengalpattu in South India (random sample of 319 patients), only 36% were found to at-

[1] World Health Organization. Chemotherapy of Leprosy for Control Programmes. Report of a WHO Study Group. Geneva: World Health Organization, Tech. Rep. Ser. No. 675, 1982.

[2] ILEP Medical Commission. *The Introduction of Multidrug Therapy for Leprosy.* Rev. ed., 1984.

[3] Sackett, D. L. Introduction. The magnitude of compliance and noncompliance. In: *Compliance with Therapeutic Regimens.* Sackett, D. L. and Haynes, R. B., eds. Baltimore: Johns Hopkins University Press, 1976.

[4] Hertroijs, A. R. A study of some factors affecting the attendance of patients in a leprosy control scheme. Int. J. Lepr. **42** (1974) 419–427.

[5] Collier, P. J. A study of case-holding in leprosy patients in Asia, based on duration of treatment, 1976–80. Lepr. Rev. **54** (1983) 89–94.

[6] Koticha, K. K. and Nair, P. R. R. Treatment defaulters in leprosy. A retrospective study of 42,000 cases. Int. J. Lepr. **47** (1979) 50–55.

THE TABLE. *Risk groups for defaulting and irregular clinic attendance.*

Characteristics	Mwanga region						Bombay ALH		
	Defaulters			Irregular attendees			Dropouts		
	Group	p	RR[a]	Group	p	RR	Group	p	RR
Sex/age	M, 5–19 yr[b]	<0.01	1.75	M, 10–19 yr	<0.01	?	<29 & >60 yr	<0.01	1.02
Marital status[c]	Single	<0.01	1.58	NS[d]	>0.05		NS	>0.05	
Education[b]	Some	<0.01	2.34	NS	>0.05		ND[e]		
Occupation	ND			ND			No job[f]	<0.001	1.06
Classification	PB[g]	<0.01	3.39	PB	<0.05	1.26	PB	<0.001	1.03
Deformities	None	<0.01	2.28	None	<0.01	1.56	Deformities	<0.01	1.01
Home-clinic distance	NS	>0.05		>2 miles	<0.02	1.32	ND		
Registered via	Survey	<0.01	1.44	NS	>0.05		Not referred	<0.001	1.03

[a] RR = relative risk.
[b] School chidren excluded.
[c] Above age 19 years.
[d] NS = not statistically significant.
[e] ND = not done.
[f] No industrial work or white collar job, and no student.
[g] PB = paucibacillary.

tend more than 75% of the appointments and 22% missed more than half of them.[7]

The magnitude of the irregularity in dapsone ingestion became apparent only when, in the last decade, dapsone/creatinine (D/C) ratios in the urine of patients were being analyzed in many leprosy control centers. In nine investigations in which patients were distinguished according to their measure of regularity in dapsone ingestion, the percentage of "regular" patients averaged around 50%.[8] The D/C method has now affirmed for leprosy control what Fox[9] wrote as early as 1958 about anti-tuberculosis campaigns: "Surprisingly, mere attendance at the clinic in no way means regularity in taking medicine."

Determinants of patient compliance in leprosy. In The Table, I have compared the risk groups for non-compliance as identified in two of the retrospective studies mentioned in the preceding section, one situated in East Africa[4] and the other in India.[6] As defined in the report, the "drop-outs" of Acworth Leprosy Hospital (ALH) are comparable with the groups of defaulters and irregular attenders taken together in the Mwanza study. Relative risks (RR) are not mentioned in either of the two studies, but they could be calculated from the vast amounts of raw data presented in both reports. It is noteworthy that in both regions defaulting and irregularity appear to be highly significantly related with most of the demographic and clinical factors enlisted, whereas only in the Mwanza study are relative risks of any importance. This underscores the need for caution before basing strategies on significance in associations only; actually, defaulter rates are very high in all groups and subgroups of patients registered at ALH, and any strategy for improving the situation will have to start from that basic fact.

The associations of defaulting with young men under 20, with not being married, and with having had some education, may all be related both to the stigma of leprosy and to the very high mobility of the population of the Mwanza Region. Very likely, all of these characteristics reinforce each other. Most defaulting in the Mwanza Region takes place during the first year of a patient's treatment and during the peak months of mobility, July–November, during which the agricultural activity is lowest. The combi-

[7] Kumar, A. and Balakrishnan, S. Operational study to monitor the regularity of dapsone intake by leprosy out-patients. Lepr. India **55** (1983) 521–527.

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

[9] Fox, W. The problem of self-administration of drugs. With particular reference to pulmonary tuberculosis. Tubercle **39** (1958) 269–274.

nation of these two factors forms the highest risk factor in that region. As for Bombay, Koticha and Nair add that "more of the patients who are beggars and deformed are irregular than any other class of patients," which might be the sociocultural and economic explanation for the inverse relationship between deformity and regularity in Bombay in contrast to Mwanza.

The reasons for defaulting and irregularity mentioned most in interviews in Mwanza are migration and temporary safaris, sickness and disability, forgetfulness, and no confidence in modern treatment. In the available literature, I found four studies conducted in India, in which the reasons for defaulting and irregularity were systematically explored by interviews.[10–13] Economic reasons appear to be most prominent in the four studies taken together; clinic visits take time and money. Next comes the temporary going to one's native place. A third important set of factors is in the realm of value expectancy and health belief; patients are indifferent, frustrated, ignorant, think they are already cured, have no faith in possible cure, or do not believe they have leprosy. Obviously, the long time needed for successful dapsone monotherapy is a major factor in this frustration. Quite contrary to the findings of Varkevisser[14] and Bijleveld[15, 16] in Tanzania, Kenya, and Nigeria, the four Indian studies do not even mention dissatisfaction with the health service and servants as one of the major reasons for noncompliance. Varkevisser notes that "failure of a person who hands out DDS to turn up at a tree clinic for some months in succession may so thoroughly dishearten patients that some never return." The missing of similar statements in the Indian studies may be related to sociocultural and behavioral differences, and to a truly better health service in India. However, it should be noted that interviews conducted by the health service itself may not easily reveal the reality of dissatisfaction among patients.

Important criticism to the medical approach of the compliance problem was raised some years ago by Becker and Maiman.[17] They see three major deficiencies in the usual approach: a) Characteristics of the patients, the regimen, and the illness are relatively enduring and unalterable. b) Findings in these areas are not able to account for the large numbers of persons who, despite the presence of many "adverse" characteristics associated with a high probability of defaulting still follow the recommended therapy. c) The medical model relies on selecting items for study, rather than upon the prior development of a unified conceptual approach to, or hypothesis about, compliance as a starting point.

From an extensive study of the literature in the realm of value-expectancy models used in compliance, Becker and Maiman found strong indications of generally reliable and interpretable relationships between compliance and perceptions of susceptibility, severity, benefits, and costs, modified by patient-practitioner relationships and by some demographic and personality variables. Building upon an earlier formulation, they hypothesized a Health Belief Model (HBM) for explaining and predicting compliance with health and medical care recommendations (The Figure).

Ways for improving compliance in leprosy control. Interventions for improving compliance generally take one of two major directions: either health education to mod-

[10] Karat, A. B. A., Job, C. K., Karat, S., Sadananda Rao, G. and Rao, P. S. S. Domiciliary treatment programme absentee survey. Lepr. India **39** (1967) 180–189.

[11] Naik, S. S. Irregularity of dapsone intake in infectious leprosy patients attending an urban treatment centre—its magnitude and causes. Lepr. India **50** (1978) 45–53.

[12] Nigam, P., Siddique, M. I. A., Pandey, N. R., Awasthi, K. N. and Sriwastava, R. N. Irregularity of treatment in leprosy patients: Its magnitude and causes. Lepr. India **51** (1979) 521–532.

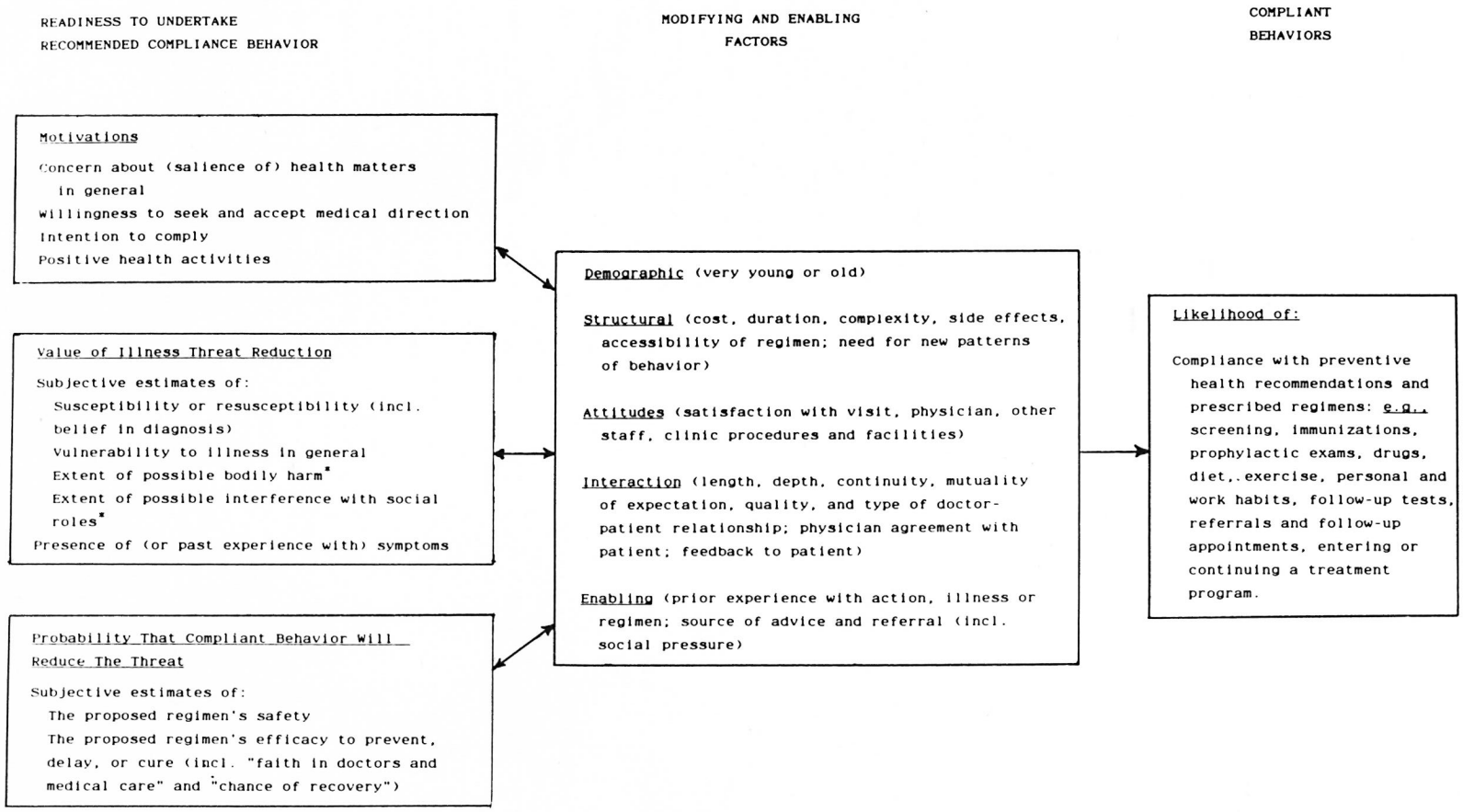
[13] Vellut, C., Van Der Veid, D., Supplisson, C. and Decazes, J. M. L'absentéisme au cours du traitement de la lèpre. Analyse des causes révélées par une enquête en Inde du Sud. Acta Leprol. (Genève) **89** (1982) 27–38.

[14] Varkevisser, C. M. Integration of combined leprosy and tuberculosis services within the general health care delivery system Western Province, Kenya. Amsterdam: Royal Tropical Institute, 1977.

[15] Bijleveld, I. Leprosy care: Patients' expectations and experiences. A case study in Western Province, Kenya. Amsterdam: Royal Tropical Institute, 1977.

[16] Bijleveld, I. An appraisal of diverse actual and potential public health activities in Kaduna State, Northern Nigeria. A report on fieldwork May–July 1977. Amsterdam: Royal Tropical Institute, 1977.

[17] Becker, M. H. and Maiman, L. A. Sociobehavioral determinants of compliance with health and medical care recommendations. Med. Care **13** (1975) 10–24.



THE FIGURE. Health Belief Model for explaining and predicting compliance behavior. (*From:* Becker, M. H. and Maiman, L. A. Sociobehavioral determinants of compliance with health and medical care recommendations. Medical Care **13** (1975) 10–14. Reproduced with permission of the publishers.)

ify beliefs, feelings and action, or reformulation of the health care delivery program. Emphasis on health education is advocated by several leprologists who studied the subject of improving compliance[13, 18] and, most importantly so, in the first contact with new patients.[4] Education and instruction however are of no use if the first strategy for retaining a patient on treatment is not followed, namely, "to provide him with dapsone on a regular basis, holding clinics as announced at the appointed time and place."[14] Care for the patient's disabilities and reactional states is another important requirement for continued compliance.

An important, new, though controversial, approach to leprosy control in recent years is primary health care (PHC). Over a period of five years, Hogerzeil and Reddy[19] noted that case holding in a PHC approach to leprosy among 186 registered patients increased to 90% of patients receiving regular treatment (75% or more), while in a conventional approach among 799 patients the corresponding figure was 64%. Antia,[20] using the same criteria, reported an increase in regularity of treatment from less than 50% before the PHC approach to more than 90% after its introduction. Clearly, PHC has the potential to satisfy many of the HBM factors. If operational in leprosy control on the village level, PHC could imply the understanding support of the "family" (read "village") for the patient and his treatment, another most important determinant of compliance.[21] Bijleveld,[22] however, strongly argues that in most societies essential preconditions for attempting leprosy control by PHC are not met, and that under the present circumstances PHC may even be disastrous for leprosy control programs.

No doubt the most prominent attack on noncompliance in recent years is the introduction of MDT. The XII International Leprosy Congress held in New Delhi in 1984[23] saw several leprologists reporting a regularity of attendance and compliance with drug intake of over 90%. I will cite just one of them (Casabianca): "Contrary to our fear at the beginning, the programme went on so well that it is exciting. The patients took so much interest that each day they were waiting with tumblers of water to swallow the drugs. . . . 95% of the patients are taking pulse therapy on the scheduled day." Similar reports are now reaching the scientific journals. In the experience of Rose in Guyana,[24] "patients definitely prefer the new regimen."

It is not difficult to see these successes in the framework of the HBM. After years of frustration with never-changing and never-ending dapsone monotherapy, both patients and staff of the leprosy control schemes are newly motivated and excited. Intensive health education programs, directed to patients, their families, and village members alike, often accompany this change of therapy. Patients whose therapeutic progress has been extremely slow or nonexistent for years lose their symptoms within a few months, and they are told that very likely they may be released from treatment within a foreseeable period of time.

This new hope is, at the same time, both the strength and the weakness of the new therapy. If a majority of patients will be cured within the prescribed period of treatment, and if only few relapses will occur, the HBM predicts that hope and compliance will be reinforced and success will be prolonged. If, however, eventually the results will be disappointing, hope will be lost and noncompliance among patients and staff alike will be reinforced which, in turn, will reinforce continued failures. It is in this context that compliance is more important now than ever before. We have no experimental

[18] Matthews, C. M. E., Selvapandian, A. J. and Jesudasan, M. Health education and leprosy. Lepr. Rev. **51** (1980) 167–171.

[19] Hogerzeil, L. M. and Reddy, P. K. General health education as the main approach to leprosy control, Dichpalli, India. Lepr. Rev. **53** (1982) 195–199.

[20] Antia, N. H. Leprosy and primary health care. The Mandwa Project, India. Lepr. Rev. **53** (1982) 205–209.

[21] Hayes, R. B. A critical review of the "determinants" of patient compliance with therapeutic regimens. In: *Compliance with Therapeutic Regimens.* Sackett, D. L. and Haynes, R. B., eds. Baltimore: Johns Hopkins University Press, 1976.

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

[23] Abstracts of the XII International Leprosy Congress. Indian J. Lepr. **56** Suppl. (1984).

[24] Rose, P. Short-course multi-drug therapy for paucibacillary patients in Guyana. Preliminary communication. Lepr. Rev. **55** (1984) 143–147.

basis to predict that 100% compliance will produce 100% therapeutic results, nor can we predict the minimum percentage of compliance below which MDT is certainly due to fail. This means that we have no experimental basis for gearing our efforts in watching and improving compliance to the treatment goal. We may only hope that we are safe with the pragmatic recommendations mentioned before[2] which allow for maxima of 33% irregularity in clinic attendance.

Monitoring patient compliance. Monitoring of clinic attendance and the intake of the components for self administration at home will be necessary where compliance is so crucial. The results of such continuous monitoring, moreover, will be indispensable for the evaluation of the regimens and programs themselves. There will be no way for interpreting relapses without systematic data on compliance.

Attendance at clinic appointments and distribution of tablets should be monitored by scrupulous registration. For monitoring drug intake at home, interviewing the patients has proved to be inadequate.[7, 25] According to the comparative data of Gordis,[26] pill counts may also overestimate compliance, especially so "when the medication prescribed is one that might be used by other members of the family," as is certainly the case with the popular dapsone.[15, 16] It might be worthwhile to experiment with "bubble" or "calendar" packs to improve the self administration of MDT components, as was proposed by Winsley and colleagues.[27] Such packs might both increase compliance and help to monitor it, although the family question raised above will still be valid. A urine test is probably the best option for monitoring drug intake. Essential for such a test in large leprosy control schemes is that it is easy and quick, and yet valid.

Urine tests have been developed for dapsone.[28–30] Similar tests for clofazimine are less satisfactory, since only very little is excreted in the urine.[31] We may hope that, in most cases, dapsone intake means clofazimine intake as well where required. Naik and co-workers (personal communication, Leprosy Scientific Memorandum, 1984) suggest "incorporation of 100 mg dapsone in 50 mg of clofazimine capsule so that a simple urine spot test for dapsone which can be performed right in the field would also indicate clofazimine consumption indirectly, in addition to dapsone." Apart from this, it might improve compliance with dapsone intake because, in their experience, many leprosy patients "have lost faith in dapsone and show a tendency to consume capsules and omit dapsone." Note that this latter observation would suggest that a positive urine test for dapsone would make it very probable that clofazimine was also taken according to schedule even when not incorporated with dapsone in one capsule.

Feedback of the urine test results to the patients may be important in improving compliance, as was shown in Chicago, Illinois, U.S.A.,[23] and in Bombay, India.[32] However, my impression from personal communications is that feedback is often neglected. This should be a point of attention.

For the past ten years I have worked on urine and blood tests for dapsone. In our laboratory, we developed an enzyme-linked immunosorbent assay (ELISA) which detects dapsone down to the minimal inhibitory blood concentration for preventing the

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[25] Norell, S. E. Accuracy of patient interviews and estimates by clinical staff in determining medication compliance. Soc. Sci. Med. **15** (1981) 57–61.

[26] Gordis, L. Methodologic issues in the measurement of patient compliance. In: *Compliance with Therapeutic Regimens.* Sackett, D. L. and Haynes, R. B., eds. Baltimore: Johns Hopkins University Press, 1976.

[27] 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.

[28] De Castro, I., De Almeida, S. M. and Nogueira de Castro, N. J. Contrôle da absorção de anti-lépricos nas campanhas de saúde pública. Bol. Serv. Nac. Lepra (Rio de J.) **24** (1965) 13–24.

[29] Peters, J. H., Lin, S. C. and Levy, L. A rapid qualitative spot test for the detection of dapsone in urine. Int. J. Lepr. **37** (1969) 46–51.

[30] 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.

[31] Levy, L. Pharmacologic studies of clofazimine. Am. J. Trop. Med. Hyg. **23** (1974) 1097–1109.

[32] Ganapati, R., Revankar, C. R. and Naik, S. S. Field application of combined therapy for infectious leprosy cases. Lepr. India **55** (1983) 485–489.

growth of *Mycobacterium leprae*,[33, 34] and a hemagglutination inhibition technique (HI) which is simpler but less sensitive.[35] These refined and modern tests certainly are attractive in many respects. However, the required biochemicals are not cheap and the methods, although relatively simple, do not go down to the level of a field test. Instead, for the monitoring of daily dapsone intake in the field, I would advise the simple spot test of De Castro and colleagues[28] which, after some slight modifications, appears to fulfill all of the requirements for simplicity and validity (Huikeshoven and Madarang, submitted for publication 1985). I have reported on this test and its improvements to the XII International Leprosy Congress.[23]

As argued above, treatment compliance in leprosy is more important now than ever before and, therefore, the monitoring of dapsone self administration has retained all of its value. Effectively, the neglect of dapsone intake would reduce MDT to a two-drug therapy for multibacillary patients and to rifampin monotherapy for paucibacillary cases. The selection of *M. leprae* strains that are resistant to rifampin or clofazimine, or both, would be greatly enhanced, and the end of the "MDT era" would be worse than its beginning.

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[33] Huikeshoven, H., De Wit, M., Soeters, A., Landheer, J. E. and Leiker, D. L. ELISA inhibition technique for the demonstration of sulphones in body fluids. II. A new method to monitor leprosy patient compliance under field conditions. Lepr. Rev. **52** (1981) 11–18.

[34] De Wit, M., Huikeshoven, H., Soeters, A., Eggelte, T. A., Landheer, J. E. and Leiker, D. L. ELISA inhibition technique for the demonstration of sulfones in body fluids. Comparison of two ELISA methods. Lepr. Rev. **52** (1981) 215–220.

[35] Huikeshoven, H., De Wit, M., Eggelte, T. A., Landheer, J. E. and Leiker, D. L. Haemagglutination inhibition technique for the demonstration of sulphones in urine. Lepr. Rev. **52** (1981) 229–235.