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A Case of Relapse with Drug-susceptible *M. leprae* After Multidrug Therapy[1]

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It is already known that following multidrug therapy (MDT) regimens which are relatively "short" and "light," such as those recommended by the World Health Organization (WHO) for leprosy control programs ([5, 6]), relapses occur very exceptionally (if at all) during the first 3 years following completion of treatment. However, since the periods of observation following MDT have not yet gone beyond 3 years, the frequency of relapse at a later stage is still unknown.

Another aspect of MDT which further requires clarification is the relationship between the dosages and the rhythms of administration of the drugs used and the frequency of post-therapeutic relapses.

Lastly, when MDT regimens were proposed for leprosy, it was thought that if post-therapeutic relapses should occur they would be related to the renewed multiplication of persisting *Mycobacterium leprae* which would remain susceptible to the drugs used. However, this essential issue remained to be confirmed.

In Martinique, French West Indies, a lepromatous patient who had been subjected to a course of intensive MDT from 1981 to 1983 relapsed in 1987. The story of this relapse is discussed in this paper because it provides interesting information in relation to the questions raised above, especially the last one.

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METHODS

Therapeutic regimens. Until 1979, leprosy treatment in Martinique was based on dapsone, sometimes supplemented with long-acting sulfonamides. In November 1979, two standard regimens based on drug combinations were decided upon, one for paucibacillary (PB) and one for multibacillary (MB) patients. These regimens were based on daily doses of rifampin (RMP), dapsone (DDS), and prothionamide (PTH) administered without supervision except for an initial phase of a few weeks during which time the patients were hospitalized. The regimen for MB patients included the daily administration of RMP (600 mg), DDS (100 mg), and PTH (500 mg) for 3 months, followed by daily doses of RMP (600 mg) and DDS (100 mg) for 21 months. The regimen for PB patients included daily doses of RMP (600 mg) and DDS (100 mg) for 12 months.

Follow-up of patients. Routine surveillance, during and after MDT, is carried out at the Montestruc Dispensary in Fort-de-France, where patients are attended to as outpatients by specialized doctors. Whenever necessary, patients are hospitalized in the Dermatology Service of the Centre Hospitalier Regional Universitaire of Fort-de-France. In addition to a clinical examination, all patients are subjected to the Mitsuda test and repeated bacteriological smears of skin and nasal mucus. Liver function tests are carried out periodically on all patients who are under MDT.

Before starting MDT, a skin biopsy is taken from each patient and is shipped, by air at +4°C, to the Laboratory of Bacteriology at the Centre Hospitalier Universitaire Pitié-Salpêtrière in Paris, France. That biopsy is used to count the number of acid-fast bacilli (AFB) per mg of tissue, to measure the morphological index (MI), and to be inoculated into mice (within 48 hr of

THE TABLE. *Bacteriological data on serial skin biopsies from the patient.*

Skin biopsy			Drug susceptibility testing[a]					
			No. positive mice/No. harvested mice					
Date	No. AFB per mg	MI (%)	Control	% DDS in the diet			10 mg/kg RMP once a week	50 mg/kg PTH 5 days a week
				0.0001	0.001	0.01		
Oct. 27, 1980	5×10^5	30	2/3	0/2	0/5	0/5	0/4	ND[b]
Dec. 9, 1985	$< 2 \times 10^3$	—	—	—	—	—	—	—
Oct. 5, 1987	2×10^6	30	6/6	0/8	ND	ND	0/5	0/5
Mar. 1, 1988	7×10^5	3	—	—	—	—	—	—

[a] Inoculum 5×10^3 AFB per foot pad; growth means $\geq 10^5$ AFB per foot pad. DDS = dapsone, RMP = rifampin; PTH = prothionamide.
[b] ND = Not done.

taking the biopsy) to measure the susceptibility of the *M. leprae* isolate to DDS and RMP. This mouse foot pad study may be repeated in case of unexpected events, as was the case in the observation reported here.

Patients are carefully instructed on how to take their drugs and are requested to report to the dispensary once a month to pick up their next month's supply. Social workers visit and interview patients regularly at their homes so as to maintain patient compliance at the best possible level.

CASE HISTORY

MB leprosy treated with DDS and SMP (1972-1980). In September 1971, M.A., a male born on 28 February 1930 in Martinique, was recognized as having leprosy of the borderline form. He had a few nodules on his earlobes, and on his trunk and arms patches of about 3 cm in diameter, with ill-defined edges, hypopigmented in their periphery and hyperpigmented in their central part, with normal sensitivity. There was hypoesthesia in the ulnar distribution of the left hand and on the external edges of both feet. Bacteriological examinations of the skin on the chest and arms were positive and negative in earlobes and nasal mucus. These clinical and bacteriological findings were used to classify the patient, and a histopathological examination was not made.

From January 1972 to September 1980, the specific treatment given to the patient included DDS and sulfamethoxypyridazine (SMP) at standard doses (DDS + SMP from January 1972 to May 1973, SMP alone from November 1973 to March 1976, DDS alone from May 1976 to September 1980). During the same period of time, with the exception of a reactional episode (type not specified in the patient's record) of 4 weeks' duration treated with corticosteroids in December 1974, the skin lesions gradually improved. Once-yearly bacteriological examinations, which at that time were of doubtful reliability, were positive in February 1972, March 1976, and April 1980, and negative in 1973, 1974, 1977, and 1978.

In general, the information available gives evidence that this case was really a case of borderline leprosy whose lesions had subsided over a period of about 8½ years. However, on 20 August 1980, new lesions had appeared in the form of nodules on the lumbar areas and sides. Skin smears were strongly positive for AFB on earlobes and arms. The Mitsuda reaction was negative.

A skin biopsy made on 27 October 1980 showed (The Table) a bacillary count of 5×10^5 AFB per mg of tissue and a MI of 30%. These findings suggest that the patient had downgraded to a lepromatous form, probably LL in the Ridley/Jopling spectrum.

The drug susceptibility tests with DDS and RMP (the results of which were known in February 1982) showed that the *M. leprae* strain isolated was susceptible to both drugs.

MDT (May 1981 to May 1983) and subsequent evolution. The patient was hospitalized from 4 May to 2 July 1981, during which period MDT was administered in accordance with the regimen for MB patients described above. Subsequently, MDT was continued on an outpatient basis. The whole treatment can be described in two stages, as

follows: a) from 20 May to 20 August 1981 (i.e., 3 months, with supervised doses during the first 2 months and unsupervised doses during the third month): RMP, 600 mg daily; PTH, 500 mg daily; DDS, 100 mg daily; b) from 21 August 1981 to 14 May 1983 (i.e., 21 months of unsupervised intake): RMP, 600 mg daily and DDS, 100 mg daily.

Based on the level of coincidence between the dates on which the patient was requested to collect his drugs at the dispensary and the dates on which he actually came, and also from his interviews with the medical and social personnel, it seems that his compliance to treatment was satisfactory during the first 21 or 22 months of the MDT course, and less satisfactory during the last 3 to 4 months.

During the whole course of MDT, liver function tests were within normal limits. Also during the whole course of MDT, his skin lesions gradually improved and they had virtually disappeared by March 1983. A routine bacteriological examination was positive in May 1983.

After completion of MDT, the patient was put under post-therapeutic surveillance and was medically examined 2 and 3 months later. He was then seen again in May 1984, 1 year after the end of treatment. It seems that, on this latter occasion, what had urged him to seek medical care was an outbreak of erythematous and painless nodules scattered on his trunk and limbs which had started some 10 days earlier and could possibly be a reactional episode of the erythema nodosum leprosum (ENL) type. Corticosteroids were not given to the patient on this occasion, nor at a later stage.

Routine bacteriological examinations were negative in August 1984, July 1985, and July 1986. In December 1985, a skin biopsy sent to the Paris laboratory showed $< 2 \times 10^3$ bacilli per mg of tissue (The Table), which demonstrates the efficacy of the MDT course taken by the patient.

Relapse (September 1987). On 27 September 1987, after 1 year during which time the patient had not been seen, lepromatous nodules and erythematous infiltrated plaques had appeared on his trunk. Routine smears were positive for AFB from the ears, back and nasal mucus. The new lesions were diagnosed as a relapse. Apart from this, there was no evidence of infection by the AIDS virus, nor of a malignancy, nor of any other pathological process.

A skin biopsy taken on 5 October 1987 and shipped to the Paris laboratory showed (The Table) 2×10^6 bacilli per mg of tissue and a MI of 30%, demonstrating an active lepromatous relapse. The *M. leprae* strain isolated from the same biopsy was sensitive to all of the drugs used in this patient's treatment, i.e., RMP, PTH, and DDS, at normal therapeutic concentrations for the first two drugs and at the concentration of 0.0001% in the mouse diet for the DDS.

DISCUSSION

In 1971, this patient was found to have a borderline form of leprosy and for 9 years was treated with dapsone (DDS) and sulfamethoxypyridazine (SMP). However, in 1980 he downgraded, and his disease evolved into the lepromatous form. The *M. leprae* strain that was then isolated was fully susceptible to DDS and RMP. Thus, the most likely explanation for the worsening of the disease in 1980 is that the patient did not ingest all of the drugs that he was collecting periodically from the dispensary.

Subsequent to his lepromatous downgrading in 1980, for 25 months (May 1981 to May 1983) the patient was given intensive MDT with daily doses of RMP, taken without supervision (except during the first 2 months), combined with DDS and PTH or with DDS alone. The MDT course was effective, as was demonstrated by the low bacillary count in a skin biopsy taken in December 1985. In 1987, the patient relapsed again at the time when the *M. leprae* strain isolated from his lesions was fully susceptible to the three drugs which had been used previously. This relapse occurred 76 months after the initiation of an intensive MDT course of 25 months and 52 months after MDT was stopped.

This case raises three main questions which will be discussed successively.

a) Why was the *M. leprae* strain isolated during the relapse still susceptible to the three drugs used during the course of MDT?

Let us assume that the patient did not take all of the drugs he was collecting. He may well have collected his combination of drugs regularly but not have ingested the correct

doses, as he seems not to have done for DDS and SMP from 1971 to 1980. However, the patient ingested enough of these drugs to kill the vast majority of drug-susceptible bacilli in his bacillary population, as evidenced by the substantial decrease in the bacillary count in the biopsy of December 1985. Furthermore, all mutants resistant to RMP, PTH, and DDS were also killed, as evidenced by the susceptibility to these three drugs demonstrated at the time of the relapse. Thus, the only organisms remaining in the bacillary population of the patient when the relapse occurred were persisters.

So far, relapses with drug-susceptible organisms have been observed after long-term treatment of MB patients with DDS alone ([4]), and recently after a course of RMP as monotherapy of sufficient duration (more than 50 doses) to have selected RMP-resistant mutants in other patients ([1]). The most likely explanation proposed for relapse with RMP-susceptible organisms was that RMP-susceptible organisms could not be killed by the drug because they did not experience a burst of multiplication, perhaps because they were present in a dormant or persisting state that rendered them phenotypically resistant to RMP. A similar explanation is proposed in the present case. Here, organisms simultaneously susceptible to RMP, PTH, and DDS could have been insensitive to these drugs because they were also in a dormant phase.

If this is true, one then has to explain why all mutants resistant to RMP, PTH, and DDS could be killed, while some organisms susceptible to the three drugs were protected by their dormant state. This should remain possible in view of the very different sizes of the various subpopulations of the organisms. It could well be that when the elimination of all resistant mutants, which are few in number, was already achieved, the killing of the comparatively large population of drug-susceptible organisms had not yet terminated, hence the possibility of a few of these susceptible bacilli remaining in a persisting state until MDT was completed, and then resuming multiplication.

b) Why could a relapse occur after such an intensive course of MDT?

It now seems interesting to make a comparison between the relapse reported here and observations made in some THELEP supported drug trials ([3]). In two large-scale field trials of MDT for MB leprosy carried out in Karigiri and Polambakkam, India (V. K. Pannikar, personal communication), 503 patients who were bacteriologically positive prior to treatment received either the WHO standard regimen for MB patients ([6]) or a slight modification of it. These two regimens were far less intensive than the one used in the case reported here. These patients have been followed up, on the average, for a period of 3 years following cessation of MDT. No relapse has been observed thus far.

To explain the occurrence of the relapse reported here, there is a possibility that even after using MDT regimens of the highest possible potency, there would still remain a risk that some (drug-susceptible) persisters would cause a relapse. This hypothesis is in the same vein as some observations made in another series of THELEP-supported drug trials. In those trials, it was possible during the course of chemotherapy to demonstrate, through inoculation of thymectomized irradiated mice, that persisting *M. leprae* were detected in approximately 9% of all patients, irrespective of the regimen used and the duration of treatment ([2]).

So far, as indicated above, the administration of the MDT regimens in MB patients investigated in the THELEP drug trials has not been followed by any relapse during post-therapeutic surveillance. However, these periods of post-therapeutic surveillance are, on the average, for 3 years only. It might be that post-MDT relapses with drug-susceptible organisms begin to appear 4 years or more after completing MDT. If this is so, the relapse reported here might be the first of a series which will increase in number with time, as the number of patients subjected to MDT and subsequently followed up for periods of 4 years and more will increase.

Of course, if this latter hypothesis proves to be a reality, it will be necessary to study the dynamics of the phenomenon and the relationship between the various parameters related to the potency of MDT regimens (dosages, rhythms, and duration of administration of the drugs) and the frequency of relapses.

c) How can we explain the incubation time for such a relapse?

In principle, it seems logical, as recently proposed ([1]), to measure the incubation period of relapse with resistant *M. leprae* from the beginning of chemotherapy, because it is from this time that drug-resistant mutants are selected within the patient's bacterial population. Conversely, the incubation period of relapses with drug-susceptible *M. leprae* should logically be measured from the end of an MDT course, since it is at that time that the drugs cease to control persisting organisms and, therefore, cease to be able to prevent relapses. However, in the study on relapses following RMP monotherapy referred to above ([1]), it was observed that the median incubation time of relapse is, in general, much longer than the time required to reconstitute a large bacterial population from either resistant mutants or from persisting organisms. The likely explanation proposed for this phenomenon was that, in both cases, the remaining organisms experience bursts of multiplication followed by long periods of being dormant. There was also a broad range of incubation times, suggesting large variations in the ability to control small populations of *M. leprae* from patient to patient. The incubation time for the relapse reported here, which was 52 months (more than 4 years), could be explained in a similar manner.

In conclusion, the explanation proposed for this relapse is that while all drug-resistant mutants were eliminated by the combination of RMP, PTH, and DDS, some persisters that were sensitive to the same drugs remained dormant until after cessation of chemotherapy when they resumed multiplication.

This appears to be the first documented case of a relapse following a course of intensive MDT in which the organisms were susceptible to the three drugs used. Thus, this observation gives evidence of what was thought when the principles of MDT for leprosy control were established, and that is that if post-MDT relapses were to occur, they should be with drug-sensitive organisms. Still, to make that assumption absolutely unquestionable, in the case of this observation one must eliminate the possibility of a reinfection with drug-sensitive bacilli but the methods available are unable to resolve this point. This observation also falls in line with the hypothesis that some patients subjected to MDT may not relapse until many years after completion of treatment.

SUMMARY

A male born in 1930 was diagnosed as smear-positive borderline leprosy in 1971, and was treated with dapsone and/or sulfamethoxypyridazine from 1972 to 1980 with clinical improvement. However, new skin lesions with smears strongly positive appeared in August 1980, and he was diagnosed as having downgraded to lepromatous (LL) leprosy, but the bacilli recovered from the skin biopsy were fully susceptible to both dapsone and rifampin by mouse foot pad technique. Between 1981 and 1983, the patient was treated with 24 months of rifampin 600 mg and dapsone 100 mg daily, supplemented with prothionamide 500 mg daily during the initial 3 months, and his skin lesions gradually improved during treatment with the combined regimen. Afterward, the patient was kept under surveillance without treatment. From 1984 to 1986, his skin smears were negative, and no bacilli could be found from a skin biopsy taken in 1985. Then in 1987, 52 months after stopping treatment, new skin lesions appeared with a high concentration of *Mycobacterium leprae* (2×10^6/mg tissue). The drug-susceptibility test again demonstrated that the organisms were fully susceptible to both dapsone and rifampin. Apparently the relapse was due to remultiplication of drug-susceptible persisters.

RESUMEN

Un hombre nacido en 1930 fue diagnosticado con frotis positivo de lepra dimorfa en 1971, y fue tratado con dapsona y/o sulfametoxipiridazina desde 1972 hasta 1980 con mejoramiento clínico. Sin embargo, lesiones de la piel nuevas con frotis fuertemente positivos aparecieron en agosto 1980; y fue diagnosticado como haberse bajado a lepra lepromatosa (LL) pero los bacilos recuperados de la biopsia de la piel estaban completamente susceptibles a ambas dapsona y rifampicina por la técnica del pie del ratón. Entre 1981 y 1983, el paciente fue tratado con rifampicina 600 mg por 24 meses y con dapsona 100 mg diarios, suplementado por protionamida 500 mg diaria durante los iniciales 3 meses; y lesiones de la piel gradualmente mejoradas durante el tratamiento con el régimen combinado. Des-

pués, el paciente fue puesto bajo vigilancia sin tratamiento. Desde 1984 a 1986, los frotis de piel estaban negativos, y no se podía encontrar ningún bacilo de una biopsia de la piel tomada en 1985. Entonces en 1987, 52 meses después de parar el tratamiento, nuevas lesiones de la piel aparecieron de nuevo con concentración alta de *Mycobacterium leprae* (2×10^6/mg tejido). El examen de susceptibilidad a drogas demonstró de nuevo que los organismos estaban completamente susceptibles a ambas dapsona y rifampicina. Aparentemente la recaída fue debida a la re-multiplicación de los bacilos persistentes droga-susceptibles.

RÉSUMÉ

Un cas de lèpre borderline à frottis cutané positif a été diagnostiqué en 1971 chez un homme né en 1930. Sous traitement par dapsone et/ou sulfamethoxypyridazine de 1972 à 1990, il s'est cliniquement amélioré. Mais de nouvelles lésions, à frottis positifs, sont apparues en Août 1980 et ont fait considérer que la lèpre avait évolué vers la forme lépromateuse. Les bacilles prélevés par biopsie cutanée et inoculés à la souris se sont montrés totalement sensibles à la rifampicine et à la dapsone. De 1981 à 1983, le malade a reçu quotidiennement pendant 24 mois 600 mg de rifampicine et 100 mg de dapsone, plus 500 mg d'éthionamide pendant les trois premiers mois du traitement. Les lésions cutanées se sont progressivement améliorées durant le traitement. Ensuite le malade a été gardé en observation sans traitement. Entre 1984 et 1986 les frottis cutanés ont été négatifs et une biopsie cutanée faite en 1985 a, elle aussi, été négative. Toutefois en 1987, 52 mois après l'arrêt du traitement, de nouvelles lésions cutanées sont apparues avec une forte teneur en bacilles (2×10^6 bacilles/mg de tissu). L'antibiogramme fait chez la souris a montré que les bacilles étaient restés totalement sensibles à la dapsone et à la rifampicine. Vraisemblablement la rechute a été dûe à la remultiplication de bacilles persistants sensibles.

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