Can leprosy be eradicated with chemotherapy?
An evaluation of the Malta Leprosy Eradication Project

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Summary The Malta Leprosy Eradication Project (MLEP) was proposed in 1971 by Freerksen with the aim of eradicating leprosy in Malta. The project involved re-treatment of all known cases in Malta as of 1972 and all new cases thereafter with a regimen consisting of Isoprodian (a combination of dapsone, prothionamide and isoniazid) and rifampicin for varying intervals depending on the severity of their disease and their response to treatment. Overall the response to therapy was excellent with an extremely low relapse rate.

During the 30 years of the project the incidence of leprosy steadily decreased continuing a decline that had started at least two decades earlier and Freerksen declared the disease eradicated from Malta in 2001. Although given the long incubation period of leprosy cases may still be occasionally detected in the future, the disease has been basically eradicated at this time and there are no patients currently receiving treatment.

This work was done at the leprosy clinic, Boffa Hospital, Floriana, Malta.

Introduction

The country of Malta consists of three islands with a total population of about 400,000 located 90 km south of Sicily. Most of the population resides on the main island of Malta and the remainder on Gozo. Leprosy has been present in Malta at least since 1630 when the first case was recorded but it may have been introduced from the east and south Mediterranean as early as the 9th century AD or more likely from Rhodes by the Knights of St John of Jerusalem in 1530.

Chemotherapy for leprosy has been available since the 1940s but early hopes that the sulphones would control and perhaps eventually eradicate leprosy proved in vain.1 The arrival of new and highly bactericidal drugs for leprosy beginning with rifampicin however brought about renewed hope that the disease could be controlled and might eventually be eradicated and in 1971 Freerksen proposed such an effort in Malta.2 It was titled The Malta Leprosy Eradication Project (MLEP) and was approved by the government of Malta and supported by the German Leprosy Relief Association (DAHW) and the Sovereign Military
Order of Malta. Based on his research using *Mycobacterium marinum* as a substitute for *M. leprae* he had developed a regimen for the treatment of leprosy utilising Isoprodian (a combination of prothionamide, dapsone and isoniazid) and rifampicin. Isoniazid was included because in spite of Shepard’s earlier findings ‘it shows some anti-leprosy activity in experimental and clinical use and also serves as a valuable synergistic component in drug combinations’. The length of treatment required for leprosy depended upon the bacterial index (BI) on skin smears and biopsy, the type of leprosy, the extent of the disease and the response to therapy. This project thus represents the first major effort to treat all leprosy patients for a limited period of time similar to what the World Health Organization (WHO) would recommend more than a decade later.

In a Report published in 2001 Freerkens stated that the MLEP was complete and that leprosy had been eradicated from Malta. An independent evaluation of the project was commissioned and conducted in Malta during October 20–28, 2002 and is the subject of this report. Previous evaluations of this project had been done by Leiker in 1986, Jopling in 1984 and 1986 and Jacobson in 1992. These evaluations found no clinical evidence of disease activity in the patients who had completed therapy.

**Materials and Methods**

**Patients**

Initially the 201 known patients in Malta as of 1971 were recruited into the project and started on the treatment in 1972; many had been previously treated with dapsone monotherapy. All 63 new patients detected in Malta from 1971 onwards were recruited for the project; two had died before starting therapy and one left the country before starting therapy. A further case was diagnosed in a person entering the country illegally who was deported to continue therapy in his homeland. By the year 2000 the number of patients treated was 260 including 59 new patients (33 LL, 15 BL, 1 BB, 4 BT and 6 TT) and there have been no new patients detected since then.

This review focused on the 133 patients seen or reviewed in the 1992 evaluation plus the three diagnosed since then. The 136 patients included 103 from the original group of 201 old cases and 33 from among the 59 newly diagnosed cases.

**Therapy**

Therapy for all patients initially consisted of two tablets of Isoprodian (175 mg of prothionamide + 50 mg of dapsone + 175 mg of isoniazid) daily with 600 mg of rifampicin for adults. Later Isoprodian-RMP (87.5 mg of prothionamide + 25 mg of dapsone + 87.5 mg of isoniazid + 150 mg of rifampicin) became available and was given as four tablets daily for adults. The dose for those weighing less than 50 kg was reduced based on weight. Treatment was given for 5 months to those with inactive disease at the start of the trial. Overall therapy was given for about 24 months with a range of 5 to 88 months, BI positive cases received longer treatment. Those from the original group of 201 patients averaged 30 months of treatment and those diagnosed after 1/72, 35 months. Also some of the patients in the group of 201 previously treated patients received Isoprodian + rifampicin for only 5 months followed by Isoprodian alone. This does not seem to have made any difference in the overall results but one of the two patients who relapsed was from this group. Since neither Isoprodian nor
prothionamide is now readily available the last patient (diagnosed in 2000) has mostly been treated with the standard WHO MB regimen.

Results

Patients

Case detection in Malta has generally been and remains passive and when leprosy is suspected they are referred to the leprosy clinic for further evaluation. The newly diagnosed patients entering the project had a complete physical exam, skin smears from at least six sites and a biopsy. They were seen every month while on therapy or more often if they had problems such as reactions. Skin smears were taken from at least two of the original six sites each time so that all six sites were regularly evaluated. When their disease became skin smear negative the follow up interval was usually extended to yearly. At the time of this evaluation, 239 patients of the 260 in the project had completed therapy, one was still on therapy (diagnosed in 2000), three had died while on therapy, and the remainder had been lost to follow up before completing therapy.

One hundred and seven of the 260 had died as of 2002, 83 remained under surveillance, 20 were lost to follow up. The 83 still under surveillance were scheduled for review as were 14 others who could still be contacted. Sixty-seven of these came as scheduled and the charts of the other 30 together with the 39 other patients seen in 1992 were reviewed. None of the patients seen had skin lesions suggestive of relapsed disease or progressive motor or sensory loss. All patients seen or reviewed had had skin smears within the previous 1–3 years and all were negative except for the patient still on therapy.

Classification of the 136 patients reviewed seemed accurate based on our evaluation and/or the record. One hundred and nineteen were MB and 17 PB. The Ridley-Jopling classification of the 119 MB was 89 LL, 23 BL, 7 BB. The 17 PB were all BT but there had been 6 TT cases between 1972 and 1975 and none since. Among the 136 patients reviewed 58% were male and 42% female with an overall average age of 37 (range 8 to 78 years) at diagnosis. However the 33 started on therapy since 1972 had an average age of 51 with a range of 16 to 78 at diagnosis. Only 62 of the 119 MB patients had originally been skin smear positive with a BI ranging from 1+ to 6+ with an average of 2.3+. The average BI for the 33 from the original group of 201 patients was 1.9+ while that for the 29 diagnosed since 1/72 was 3.0+.

Relapses

The first of the two relapses occurred in an 85 year old female with LL disease who had originally been diagnosed in 1949. She had been on dapsone but was still BI 5+ when starting Isoprodian-rifampicin (I + R) therapy in 1972 and she took it for 21 months. She became smear negative in 1975 but relapsed both clinically and on smears in 1988. She was restarted on therapy but died of congestive heart failure before completing it. The second relapse occurred in a 38 year old male who was diagnosed in 1967 and treated with dapsone until 1972 when he started a 21 month course of I + R. Although he received the rifampicin for only the first 5 months he was smear negative when he completed therapy. He relapsed in 1991 with a BI of up to 3+. He was given an additional 21 months of therapy whence he became smear negative and has remained so since then. Freerksen2 described two other patients who earlier (1976) in the project developed what may have been new lesions shortly
after therapy was discontinued. They were given an additional 12 and 18 months of therapy respectively and became skin smear negative. Both of them were reviewed in 2002 and neither had any evidence of relapse now 25 years after treatment was discontinued.

Toxicity of the regimen has generally been very low in all patients. Eight patients developed abnormal liver function tests during therapy. The problem was transient in six of them but persisted in two until their treatment was discontinued. About 25% also had various gastrointestinal complaints but these generally were also transient.

**REACTIONS**

Among the 136 cases reviewed, 45% of the 62 cases who were skin smear positive at the start of therapy had erythema nodosum leprosum (ENL, type 2 reactions) and 3% had both ENL and reversal (type 1) reactions. Ten percent of the PB cases also had reversal reactions. The majority of the reactions seemed to be of moderate severity and were generally well managed with prednisone and/or thalidomide without any major complications.

**DISABILITIES**

Fifty-five per cent of the pre 1972 cases reviewed had no significant disabilities though some had areas of decreased or absent sensation. Nineteen percent had areas of decreased or absent sensation and a few also had one or two areas of decreased motor function but none were disabled in terms of self care or employment. Twenty-six percent had motor and/or sensory loss and in a few cases vision impairment all of which were disabling to varying degrees.

**EPIDEMIOLOGY**

Most cases detected in Malta came from a small number of villages, notably Zejtun and Mgarr in Malta, and Sannat in Gozo, and particular families within those villages. This has not markedly changed over the years but the number of cases detected has decreased steadily. Figure 1 shows the pattern of new cases detected since 1953.

![Figure 1. Fall in the incidence of Leprosy in Malta between 1953 and 2002.](image-url)
Discussion

The Freerksen regimen appears to have been effective with relatively little toxicity and satisfactory acceptance. The relapse rate as noted has been low with only two to date and none as yet among those diagnosed and treated since 1972. Granting then that the regimen has been adequate, has leprosy now been eradicated from Malta? The last case was detected in January of 2000 and there are no known patients in Malta requiring treatment at this time but it is perhaps somewhat premature to say the disease has been totally eradicated. An occasional case may still occur in the ‘leprosy endemic’ areas of the islands, relapses might still occur and there is always the possibility of an occasional case entering Malta from other endemic countries.

The next question then is was the MLEP the only reason leprosy appears to have been eradicated? The disease was declining in the country during the two decades before the MLEP was started and this process perhaps further aided by the widespread use of BCG in the country might have continued as it did in Norway until leprosy disappeared from Malta. The treatment of all previous cases along with the newly diagnosed may have contributed to the diminished transmission.

Finally, do the results of this trial mean that a similar effort might be equally successful in more highly endemic countries? First of all retreating all the patients who previously had not been treated with MDT would be very expensive though less so if one focused only on the MB patients. Secondly, such a programme is much more easily managed within the confines of two relatively small islands than in large countries often with difficult access to many areas. Lastly, although an intensive chemotherapy programme theoretically might eventually eradicate leprosy in any country, in those still detecting very large numbers of new cases annually this would probably take much longer than two or three decades. Clearly as noted by others eradication may be aided by increases in the standard of living. Thus for the present the continued application of WHO MDT via high quality control programmes in all leprosy endemic areas is probably the best approach perhaps ultimately using one of the vaccines now under study selectively in some of the most highly endemic areas.

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References