NEW DEVELOPMENT IN LEPROSY CONTROL AND THE ISSUES OF INTEGRATION

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ABSTRACT

Control of leprosy has up till now depended on active case finding, early diagnosu, and lon.&r-term treatment with dapsone monotherapy of all cases, but especially of infectious (lepro matous and bordprline-lepromatousJ patients. Thu strategy u failing because of poor compliance, microbial persistence which causes relapse in patients prematurely stopping dapsone therapy, and relapses associated with a world-wide epidemic of secondary dapsone resutance. Primary dapsone resutance, occurring in any type of leprosy, u increasingly being detected. WHO now recommends that all multibacillary lepro.,.y patients should be treated ulith a three-drug regimen of rifampicin, dapsone, and pither clofazimine or ethionamide prothionamide, in a rhythm especially suitable for field superoision, for a minimal duration of two years and preferably until the patient becomes'smear ne~tive. Paucibacillary patients may be treated with short course therapy consuting of rifampicin monthly for six doses plus six months of daily dapsone. These regimens will cause a steep increase in work load, not least to the skin-smear laboratory. But after about three years, the work load should begin to reduce substantially. Then after about 10 years, it should reach well below the present level. It is suggested that integration with the TB seroices might be possible about three years after the setting-up of multidrug therapy in any area. Full integration into PHC could be possible after about 10 .years. But intewation is likely to fail unless massive health education is undertaken to lessen the stigma of leprosy.

INTRODUCTION

Leprosy is the most chronic and most complicated of all bacterial diseases. Yet, from lack of tools, control methods are far more restricted than those for tuberculosis. There is no proven vaccine comparable to BCG for immunoprophylaxis in children, and the several candidate vaccines now available will take at least a decade to evaluate. There is no simple skin test comparable to the Mantoux test which reliably indicates contact with Mycobacterium leprae. ELISA methods currently being developed for detection of antibodies to the specific phenolic glycolipid antigen are more complicated to perform, and are not invariably positive even in known cases of leprosy (1). In most areas, it is difficult to spare scarce resources for chemoprophylaxis. In addition, both BCG vaccination for leprosy, apparently effective in Uganda but almost ineffective in Burma (2, 3), ICRC vaccination (Bapat, personal communication) and dapsone chemoprophylaxis may precipitate the appearance of indeterminate and early tuberculoid leprosy when given to patients already infected with M. leprae and presumably incubating the disease.

Therefore control of leprosy has hitherto depended on the third method of TB control, namely, active case finding, early diagnosis and good treatment of all patients but especially of infectious, that is, lepromatous (LL) and borderline-lepromatous (BL) leprosy, cases. Dapsone monotherapy, both cheap and safe, was used as standard treatment from 1950

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until 1982, being applied in vertical programmes over most of the Third World with considerable success. But there were two major limitations: The all-too-persistent social stigma inhibited both early self-presentation and regular attendance for treatment, and the difficulty experienced in recognising many early yet already highly infectious LL patients results in their having infected almost all their immediate as well as many casual contacts before they develop sufficient symptoms and signs for the diagnosis to be made.

CURRENT PROBLEMS

But dapsone monotherapy is now failing everywhere for three main reasons.

Poor Compliance.
Dapsone monotherapy was a long-term therapy -much longer than in tuberculosis. WHO (4) recommended that tuberculoid patients should be treated until they become quiescent, and for a further 18 months there after. As the end-point (of quiescence) was very difficult to identify, most workers treated tuberculoid (TT) and borderline-tuberculoid (BT) patients for five years, even though little change occurred after 18 months to two years in almost all patients. Lepromatous patients (5) were adviced to stay on dapsone for a full 10 years after achieving skin-smear negativity, which implied a total of about 15 years in BL and 20 years in LL leprosy although most LL patients were, in fact, left on treatment for life.

Yet little improvement could be seen by the patient himself after 3-5 years of treatment.
Futhermore, in many control schemes, patients were expected to attend monthly to collect their dapsone, yet most soon found that no ill-effects quickly developed if treatment was interrupted through their failure to collect the medication. Therefore there was little incentive to take treatment regularly. In adclition, many patients on treatment developed reactions whether ENL or reversal (upgrading or type I) which often resulted in a deterioration in their clinical condition -as far as the patient was concert's, he had bt.com worse on treatment. This belief was reinforced by the now discredited practice during reactions of reducing the dosage of, or of stop pill altogether for a period, the dapsone therapy; the doctor apparently blamed dapsone for that reaction, and an iatrogellic fear of dapsone was induced. Faith in dapsone was further decreased by that number of relapses which were seen in increasing numbers occurring in long-term patients both on and off treatment. Table I lists a representative series of compliance tests performed ill different countries. Not only was compliance poor, evell among some of the patients who attended regularly to collect their monthly quota of dapsolle, but many patients abounded from treatment., Collier (6) in a computerised study from 14 "better centers " in Asia run by a voluntary agency, found that >500/0 of patients had disappeared within four years of commencing treatment; surprisingly, thcre was no significant difference in their disappearance rates between tuberculoid, borderline or lepromatous patients.

Dapsone Resistance (DR)
This is now the major problem in leprosy control. There is a world-wide epidemic of
secondary D R among treated LL and BL patients. Yet, unlike drug resistance in tuberculosis, which appeared within a few months of the introduction of streptomycin, relapse due to the emergence of sulphone resistance was not seen for a decade (7). Dapsone was introduced in Malaysia, as in many other countries, around 1948; relapses due to what was subsequently shown to be DR began to be detected in 1960/1961. When Pettit and Rees, applying Shepard's mouse footpad infection, first proved DR in 1964, they estimated (8, 9) the prevalence to be about 2/1000 and the incidence about 1/1000 LL and BL cases per annum. By 1973 (10) the prevalence had risen to 2.5% of those who had commenced treatment

Table 1: Dapsone Compliance on outpatient daily self administration

Center		No of patients	Doses Taken (%)	Grossly Irregular Patients (%)
Malawi	(1974)	164	53	30
Addis Ababa	(1974)	89	42	11
Gudiyatham	(19!6)	100	87	11
Gudiyatham	(1981)	125	60	37
Mandalay and		170	74	24
Rangoon	(1979)	455	24	56
Dichpalli	(1981)	55	34	47
Addis Ababa	(1981)	308	78	11

(Data from numerous sources, collected by Dr. G. A. Ellard)

with dapsone, and 7.8% of those who had commenced treatment with solapsone (in effect, low dose dapsone), the incidence being respectively 0.3% and 0.8% per year. In 1981, 10.1% of all LL and BL patients registered in West Malaysia were diagnosed as DR, over half having been proven by dapsone-sensitivity testing in mice, although this figure also included very few cases of primary dapsone resistance (Lim, personal communication).

DR surveys based on sensitivity testing of M. leprae in mice have now bcen performed in at least 11 areas and nine countries (11). The minimal prevalence (Table 2) has varied between 29 and 100 per thousand lepromatous patients. The worst prevalence so far reported, based on relapse rates on treatment (prima facie resistance) and not yet confirmed by clinical or mouse testing, was 400 per thousand (9) from a remote area of Central Burma. In Malaysia, most patients had received dapsone in full dosage (1-2 mg per kg body weight per day) for many years, and the majority of relapses were due to high-resistant mutants of M. leprae. In Ethiopia, low dose dapsone was widely used from around 1960 to 1973. reaction et al. (12) studied all LL and BL patients in the Addis Ababa area with prima facie evidence of dapsone-resistant leprosy during the period 1973 to 1977. From about 1500 patients at risk, 254 relapse cases were seen, and 41 others had been diagnosed before the start of the study. By its end, 154 patients had been proven by sensitivity testing in mice and/or by clinical trial to have dapsone-resistant leprosy giving a minimal prevalence of about 100 per 1000. Most stJ:ains of M. leprae had low or intermediate levels of resistance. Relapses had occurred two to more than 20 years after commencing treatment, compared to 5-24 years in Malaysia (13). The incidence was about 3% per annum. If the situation had been left unchanged, it was estimated that 300/0 of all LL and BL patients in Addis Ababa would have developed a dapsone-resistant relapse by 1980. However, full-dose dapsone therapy was reintroduced, following which the incidence of DR fell (at least temporarily) to around 1% per annum (Warndorff, personal communication).

As it may take several years for the tiny subpopulation of high resistant mutants to be selected out by full dose dapsone therapy from a bacterial population largely composed of low resistant mutants, and for it to multiply sufficiently to cause a second relapse, the present, fall in incidence is entirely as anticipated. But the problem would appear only to be defferred, not to he solved, by the single measure of raising the dapsone dosage. The reason for the late emergence of dapsone-resistant M. leprae as compared with drug-resistant M. tuberculosis is explained by the former's prolonged generation time of 12- 14 J days, and by the fact that 100 mg dapsone) gives a peak blood level 500 -600 times the minimal inhibitory concenb'ation for fully sensitive strains. Yet it is doubtful how often dapsone monotherapy will cure (sterilise of all living M. leprae) LL patients. I have very recently seen a patient relapse with presumed DR 37 years after commeneing treatment with solapsone in England in 1947! To overcome re sistance, multidrug therapy is as essential in the treatment of multihacillary (LL, BL and Borderline (BB» leprosy (MBL), as it is in tuberculosis.

Furthermore, when LL and BL patients relapse with secondary DR, they eventually he-come infectious once again. Their contacts are infected with resistant bacilli, and those who are unable to overcome the infection sub-clinically will develop primary dapsone resistant leprosy of any type Pearson and his colleagues (14) were the first to make a systematic study of dapsone-sensitivity testing in mice of strains of M. leprae :4 from serially-admitted, newly-diagnosed, multibacillary leprosy patients in Ethiopia; five of eight (subsequently 16 of 29) patients were found to suffer from primary DR. Similar series have been reported from a number of other countries, with prevalences of 4 -40% primary DR (11). In the WHO THELEP ;:

Table 2. Results of Surveys of Secondary Dapsone Resistance

Country	Number at risk	Minimal Prevalence (per 1000)	Incidence (% per year)	Degree of resistance
Burundi	925	67	-	Majority high
Costa Rica	200	68	1.0	Majority high
China				

(Jiangsu)	236	51	-	Majority high or intermediate
(Shanghai)	777	86	-	Majority high
Ethiopia	1500	100+	3.0	Majority intermediate or low
India				
(Karigiri)	1580	95	-	Majority high
(chingleput)	660	29	-	Majority high
Isreal	100	37	-	intermediate
Malaysia				
(1964-66)	5000	2	0.1	high
(1973)	5000	25	0.3	Majority high
(1981)	5000	100++	-	Majority high
Mali	105	57	3.0	intermediate or high
Upper Volta	355	70	-	Majority high

Table adapted from Ji Caohong (11)
+ About one third of resistance
.++ About one half of resistance
Confirmed by mouse footpad tests.

(15) controlled clinical trials in Bamako, 14 of 40 (35%) previously untreated LL and BL patients serially admitted to the trial were found to have dapsone-resistant M. leprae, and in Chingleput, South fudia, 21 0f 56 (37.5%) similar patients were resistant. Therefore, primary DR is already widespread. Although to date most patients (except in Malaysia) show only 10w-Ievel resistance, the level is likely to rise steadily. It must be assumed that primary DR occurs in at least as high a proportion of indeterminate, tuberculoid (TT) and borderline tuberculoid (ET) as in multihacillary patients, even though the former cannot he surveyed using the mouse footpad technique as they lack a bacterial population sufficient to infect mice. Therefore primary DR cannot be detected in paucihacillary leprosy (PBL) save by the failure of patients to respond to standard dapsone therapy, during which time serious deterioration, especially nerve damage, may result. Pearson (16) now working in fudia, has just presented the first series of proven cases. Therefore multidrug therapy is as essential in PBL as in MBL.

Persistence of M. leprae

Bacterial persistence is as important in leprosy as it is in tuberculosis, but as leprosy bacilli are intracellular and as studies have failed to reveal any evidence of site persistence, microbial persistence in leprosy is thought to he due to physiologically dormant bacilli.

Waters et al (17) were able to isolate dapsone sensitive strains 0£ M. leprae from three of 12 LL patients treated for 10-12 years with standard dapsone therapy under good conditions and whose inactive disease status corresponded to the duration of treatment.

The same group Studied 362 LL and BL in- patients treated in Malaysia £or 18.5-22 years up to 1970 with supervised dapsone rnono-therapy and who then stopped chemotherapy (Waters et al., in preparation). It was found that 25 patients (8.8%) relapsed over the next 8-9 years. The dapsone sensitivity of their strains of M. leprae was studied in a third of the relapse patients; half were fully dapsone sensitive and half showed various levels of resistance. There was no evidence of reinfection after stopping therapy. This study showed that in a small proportion of patients treated very well with dapsone monotherapy, persistence might survive for as long as 20 years.

MODERN TREATMENT OF LEPROSY

Leprosy control is still based on good treatment But because of the increasing prevalence and incidence of both secondary and primary DR, dapsone monotherapy is now inadequate and is fast becoming unethical. Multidrug therapy (MDT), comparable to the treatment of tuberculosis, is essential. Unfortunately, there are only four drugs bacterial for M. leproe: rifampicin, very rapidly bactericidal so that 99.9% 0£ bacilli are killed within a week, but which, when given as monotherapy may produce resistance within 4 to 7 years (18, 19); clofazimine, slowly bactericidal but to which only one proven case of resistance has so far been reported (20); ethionamide (and the completely interchangeable prothionamide which acts in the same way, and gives cross resistance), to which resistance may develop in about 8 years (21), but which is moderately rapidly bactericidal; and dapsone.

Rifampicin is expensive. Nevertheless, a single dose of 600 mg is nearly as rapidly bactericidal as a single dose of 1200 mg, or as 600 mg given daily (22,23). Because of the long generation time of M. leproe, monthly doses are effective, and no major toxic effects have been noted in patients receiving either 1200 mg monthly over six months (24) or 600 mg in two consecutive days every four weeks for up to five years. Moreover, the latter dosage has been found to be as effective bacteriologically over 3-5 years as daily dosage (25), thus permitting the drug to be given cheaply and in a rhythm easily supervised under field conditions. But rifampicin resistance must be prevented by the giving of a second bactericidal drug (in addition to dapsone to which many may be resistant) to all patients with a significant bacterial load. Taking into account bactericidal effectiveness, cost, toxicity, compliance, and the need for treatment of limited duration, a WHO Study Group Meeting in 1981 (26) has recommended two basic regimens.

Regimen for MBL

MBL is defined as all LL, BL and BB patients, and also those BT patients who have one or more smear sites with a bacterial index (BI) or Ridley's scale of 2+ or greater (2+= l or more AFB seen in 10 oil immersion fields).

The recommended regimen was:
1. Rifampicin 600 mg once-monthly supervised.
2. Clofazimine 300 mg once-monthly, supervised, plus 50 mg daily, self-administered.
3. Dapsone 100 mg daily, self-administered.

The monthly (or four-weekly) doses of rifampicin and clofazimine are swallowed in front of the doctor or a reliable paramedical worker. Dosage depends on age and body weight. The dose of dapsone is 1-2 mg per kg body weight per day. The dose of rifampicin is 450 mg monthly in patients weighing 35 kg or less and pro rata in children. If the 50 mg clofazimine cap8Ules are unavailable, 100 mg is given every second day, a much more difficult rhythm to remember .

If clofazimine is totally unacceptable because of its effect on skin colour, the alternative drug is ethionamide (or prothionamide). The dosage in adults is 250-375 mg daily, self-administered. Gastrointestinal side effects are less if the dose is taken after meals. Jaundice is a problem in some parts of the world, for example China (27), France (28) and Singapore (29), but not in others, for example Malta (30) and Paraguay. In the latter, Alvarcnga et at (31) observed only 16 cases of jaundice among 754 patients treated with rifampicin and isoprodian (dapsone 100 mg, prothionamide 350 mg and isoniazid 350 mg daily).

The triple-drug regimen should be given always for a minimum of two years and pre ferably, in our present state of knowledge, until the patient becomes smear-negative, when the anti-Ieprosy treatment may be stopped. Thus, unbeaten LL patients may require 5-11 years, untreated BL perhaps 3-6 years, and untreated BB 2-3 years of treatment. Treated inactive smear-negative LL and BL patients (who may or may not be incubating secondary OR) should receive two years of the regimen before stopping anti-leprosy chemotherapy. Relapsed, smear-positive patients, who mayor may not have OR, should be treated until they become smear negative (minimum two years). Smears should be taken serially from the sites of the relapse lesions.

The advice to continue therapy until the patient becomes smear-negative was not given .in the belief that the achievement of smear negativity was any test of cure; there is ample evidence to disprove this concept. But in general, the higher the bacterial load (that is, the more severe the infection) and the lower the patient's resistance (that is, the closer he or he is to polar LL), the longer it will take to achieve smear-negativity under effective treatment. In general, in any bacterial disease, it appears reasonable to relate the total duration of chemotherapy to the severity of the initial infection and to the patient's resistance or lack of it.

The MBL regimen will successfully treat new patients, whether or not they suffer from primary OR, relapsed patients whether or not they have developed sccondary OR, and old patients, apparently successfully b-eated with dapsone monotherapy, but who may be incubating secondary OR. The only variable is the length of treatment. Should a patient relapse after stopping therapy, then no new (lrng resistance will have been acquired. The one uncertainty is the effect on. per sisters. Combined daily dapsone and rifampicin therapy has been shown to produce fewer per sisters at six months than dapsone mono. therapy (32). In a trial in Malta, combined chemotherapy with daily rifampicin and isoprodian (dapsone, prothionamide and isoniazid) was administered to a very mixed group of more than 200 patients. The tuberculoid patients in general received about six months, treatment, and the MBL patients 18-24 months' treatment, although there was considerable individual variation. Joplin and his colleagues (30) reviewed 116 MBL patients; most of them had been followed for 6-9 years since stopping all anti-leprosy chemotherapy. None had relapsed clinically. Smears were weakly positive in 34 (29.3%), but in only nine were scanty "solid staining" AFB found. Therefore the risk of relapse due to persisters may take a decade or more to assess, but is not expected to be unacceptably high,

although relapses should be closely monitored by leprosy physicians. In 1982, WHO THELEP commenced two large-scale trials of the regimen in South India, so that results after stopping therapy may be continuously assessed on a long-term basis.

Regimen for PBL

PBL is defined as all indeterminate, TT and BT patients who, when untreated, have no smear site with a BI greater than 1 + on Ridley's scale (1+ = < 10 AFB seen in 100 oil immersion fields).

The recommended regimen is-

1. Rifampicin 600 mg once-monthly, supervised for 6 doses.
2. Dapsone 100 mg daily, self-administered for 6 months.

Should a paticnt be receiving steroids for a reversal reaction at the end of the six months of treatment, the dapsone is continued until the steroids are stopped.

Rifampicin was recommended because alternative therapy is essential to overcome the increasing incidence of primary DR and because short-course therapy with rifampicin had been shown to be very effective in two separate trials. fu one (33), rifampicin was given as monotherapy, 900 mg weekly for eight doses; no relapses were reported in a 3-year follow-up period. fu the other (34), rifampicin was given for 14 days to TT patients and for 21 days to BT patients, and all patients received two injections of acedapsone; no relapses occurred up to two years of follow-up.

It is still too early for the WHO PBL regimento have been evaluated in terhls of relapse rates on large numbers of patients, although to date the results are excellent. Careful monitoring for 4-5 years after stopping treatment remains essential, and relapse, if diagnosed, should be treated by a second full course of the regimen.

There appear, however, to be a number of problems in assessing the PBL regimen, and this should be considered as an essential research project in every control scheme. First, many patients may still have erythematous lesions at six months, not because of bacterial activity, but because of the host's immunological (DMI and/or PTH) reactions to residual bacterial material. Second, relapse may be difficult to distinguish from a late reversal reaction. I have recently been studying a smear-negative BT patient, w ho on pretreatment nerve biopsy was found to have fragmented M. leprae present in nerve; he had neuritis not only at six months but also at 36 months despite continued MDT throughout that time Late reversal reactions are rare, but can occur. Third, a few patients may appear clinically to be neural BT, yet have already downgraded to BB or BL (Waters, in preparation). Therefore, patients who "relapse " after completing the PBL regimen require full investigation, including histological examination and lepromin testing.

THE ISSUES OF INTEGRATION

Following the WHO recommendations, the chemotherapy of leprosy is now much more standardised and is based on the same principles as those determining the chemotherapy of tuberculosis. The immediate implementation of the regimens is essential to overcome the epidemic of DR and to prevent the threatened emergence of rifampicin resistance, although, because of the long time scale of the disease, full evaluation will take at least a decade.

The implementation of MDT, even in pilot project areas, initially imposes a very heavy extra burden of work on the leprosy control staff, including the laboratory staff who have many extra skin smears to take and to read (Figure 1). In-service training to upgrade the competence of all levels of staff is required, and all patients require evaluation and correct location into the two categories of PBL and MBL. Once MDT has commenced, monthly supervision of drug intake is mandatory.

Short-course chemotherapy with rifampicin has already been found to encourage much

better compliance, enabling the majority of PBL patients to complete an effective course of chemotherapy, At the same time as easing the burden of treatment on the individual patient, once the bulk of PBL patients have completed their course of MDT, the workload of the leprosy control scheme personnel is considerably reduced. This enables them to devote more time to the triple drug therapy of MBL patients, to the detection of new cases (both MBL and PBL), and to the treatment of reactions and of ulcers. Indeed, patients with anaesthetic hands and/or feet will require prolonged care to prevent ulceration or infection in the anaesthetic areas long after they have completed their course of anti leprosy chemotherapy.

Once all PBL patients save the newly diagnosed ones and all the old smear-negative MBL patients have completed their courses of MDT, the workloads will have fallen enough in the project area for some form of integration to be considered. Some staff, however, may be posted out to help implementation of MOT in other areas, therefore the gain in staff availability may be less than at first sight would appear probable.

Because of the near universal stigma against disabled leprosy patients, and the problem that PHC and general health and medical staff have in caring fully for their heavy load of acute medicine, it would appear that early complete integration of leprosy will not prove possible. It is suggested that, after about three years of MDT, it should however prove possible for the leprosy staff to make on one additional duty while still caring for new PBL and MBL patients, as well as the deformed patients off treatment. The obvious additional duty is integration with the tuberculosis services.

From the experience of Hansen in Norway, following institution of isolation of leprosy patients (35), as well as that in many countries, especially China and Malaysia, following the introduction of dapsone monotherapy, it may well take about a decade of MOT before the endemic of leprosy shows a significant decline in incidence in the project area. It should then be possible to decide whether complete integration of leprosy personnel will then be possible, or whether, for example, they should be continued for a further period as a "vertical" service, employed in giving the anti-leprosy vaccine which hopefully may then be available.

Leprosy is such a complex and chronic disease, and the leprosy bacillus such a successful "parasite ", that it would be unwise to press for a rigid time limit in which to achieve the long term aim of complete integration of the leprosy service. At the same time, no integration scheme will prove successful, but will onlyresult in the neglect of leprosy patients and the subsequent worsening of the leprosy endemic, unless the underlying problem of stigma against leprosy (the original cause of the creation of a vertical leprosy service) is greatly reduced by adequate and long-term health education on leprosy, both of the general public and of the health professionals at all staff levels.

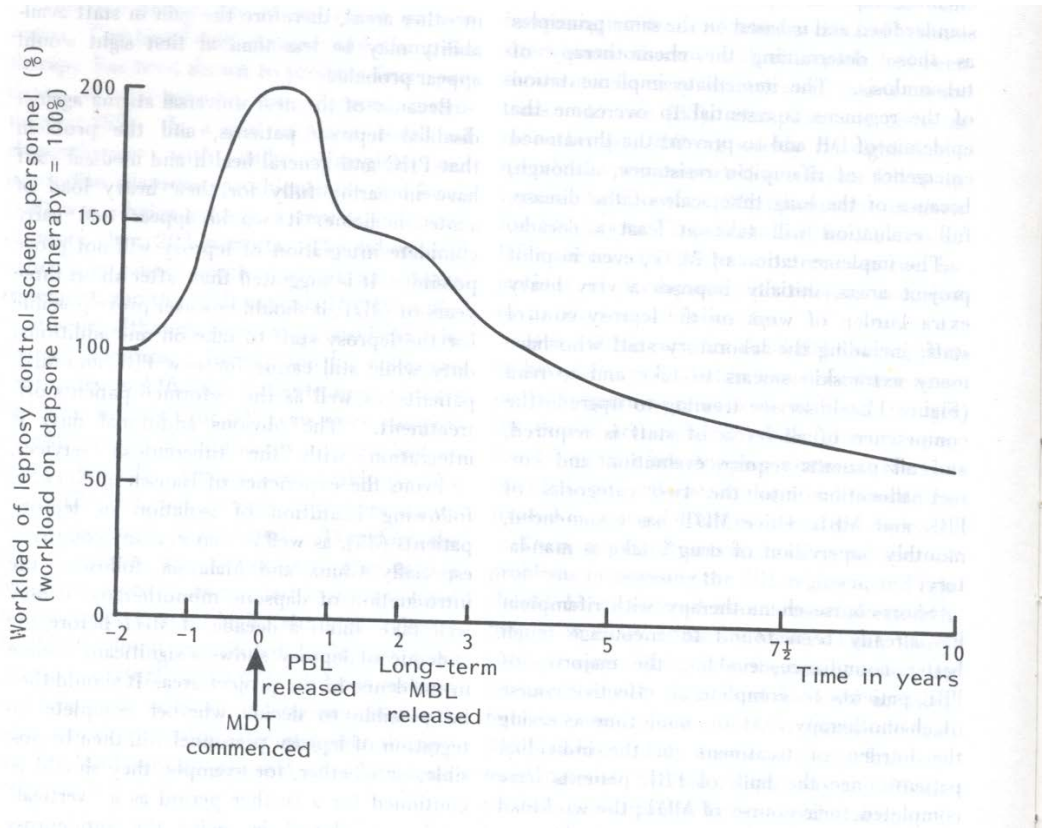

Figure 1. Anticipated «Workload» for an area leprosy control scheme during the first decade of well-instituted MDT .

Initially, there is a steep rise in the planning stage due to patient assessment, reclassification and smearing. The rllst sharp fall around one year is due to release from treatment (RFT) of the PBL patients, with a second smaller fall around 2Y2 to 3 years due to RFT of the dapsone-treated smear negative MBL patients. Therefore a much slower fall may occur resulting from the progressive release of MBL patients as they achieve smear negativity, plus an anticipated gradual decline in incidence during the second 5 years, hopefully associated with an increase in the PBL:

MBL ratio due to earlier diagnosis, but with continuing responsibility for long-term patient follow-up, including treatment of any relapses, care of deformities, especially of ulcers, provision of foot-wear, reconstructive surgery and rehabilitation.

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