Centenary Review Article

Indian J Med Res 137, January 2013, pp 15-35

Leprosy - evolution of the path to eradication

Sunil Dogra, Tarun Narang & Bhushan Kumar*

Department of Dermatology, Venereology & Leprology, Postgraduate Institute of Medical Education & Research, Chandigarh, India

Received December 3, 2012

Leprosy is among the world's oldest and most dreaded diseases and it has been synonymous with stigma and discrimination due to the hideous deformities it produced, mystery around its aetiology and transmission and lack of any effective remedy till recently. Leprosy control started with the use of chaulmoogra oil and for the last three decades, multi drug therapy (MDT) has been our main tool against leprosy. In the last two decades, the reported global prevalence of active leprosy infection has dropped by almost 90 per cent by the combined efforts of the World Health Organization (WHO), local governments, health professionals, and non-governmental organizations (NGOs), however, a parallel drop in the incidence or new case detection rate (NCDR) has not occurred. From 1994 through 2011, more than 100,000 new cases are being detected annually, of whom maximum case load is from India. There is need for research on tools for early diagnosis, short and effective treatment, and prevention of deformities and disabilities. Evaluating the role of immunotherapy and immunoprophylaxis will also lead us to better understanding of their mode of action. Further molecular analysis of *Mycobacterium leprae* genome may provide the requisite basis for all this. The current reality is that there is a need to sustain and provide quality leprosy services to all persons through general health services, including good referral system. All these provisions in the integrated health care approach will go a long way in further reducing the stigma. Efforts need to be made to reduce deformity through early detection, self care, physiotherapy and reconstructive surgery and developing sound surveillance systems. With all the remarkable achievements in the fight against leprosy, the stage is now set for the final assault. It is hoped that with the efforts of all the stake holders and strong political will, the disease will be eradicated in the near future.

Key words Deformity - Hansen's disease - leprosy - MDT - multibacillary - *Mycobacterium leprae* - paucibacillary - reconstructive surgery

Leprosy is one of the world's oldest and most dreaded diseases that has tormented humans throughout history, leaving lasting impressions on religion, literature and art. It has been synonymous with stigma and discrimination due to the hideous deformities it produced, mystery around its transmission and lack of any effective remedy till recently. Al-Bukhari's Muslim Hadith (volume 1, 2.443) documented

**Present address*: H. No. 81, Sector 16, Chandigarh 160 015, India

Prophet Mohammed's apparent dread of leprosy in his statement: "*Escape from the leprous the way you escape from a lion"*. In addition to the physical effects of the disease's, patients have also suffered severe social stigma and ostracism from their families, communities, and even health professionals to such an extent that leprosy has been known since ancient times as "the death before death". Armauer Hansen, the discoverer of *Mycobacterium leprae* once commented *"There is hardly anything on earth, or between it and heaven, which has not been regarded as the cause of leprosy; and this is but natural, since the less one knows, the more actively does his imagination work*"[1]. We have indeed come a long way from the era when there was scanty or little information bordering on ignorance about the disease, on magnitude of the problem, intense negative image which led to prevention by segregation of patients and lack of organised services. At the First International Congress in Berlin in 1897 it was agreed that "Leprosy was incurable". However, discovery of *M. leprae* by Armauer Hansen, use of chaulmoogra oil in treatment of leprosy generated hope that leprosy is treatable. Discovery of dapsone in 1941 and later implementation of multi drug treatment (MDT) in 1981 changed the entire scenario. Although much remains unknown about the disease transmission and pathogenesis, tremendous advances have occurred in understanding the pathogenesis and treatment of the disease. In the past two decades, marked success of combined efforts from the World Health Organization (WHO), local governments, health professionals, and non-governmental organizations (NGOs) in identifying patients with leprosy and providing effective treatment to them has resulted in near elimination of leprosy[2-6]. MDT has been the main weapon against leprosy since its inception in 1981 and by 2005, the prevalence in India was less than 1/10000. This was a landmark achievement in the history of leprosy in India. By the end of 2010, the prevalence had come down to 0.69/10000[7]. In this context, it must be pointed out that cases of leprosy are not uniformly distributed but tend to cluster in certain localities, villages or *taluks*. Hence, while the country as a whole has eliminated leprosy, two States, Bihar and Chattisgharh are yet to achieve elimination (with a prevalence rate of 1.12 and 1.94, respectively). Of the total of 640 districts, 110 districts still have prevalence rates between 1 and 2/10000, while in 530 districts, elimination has been achieved[7] (Fig. 1).

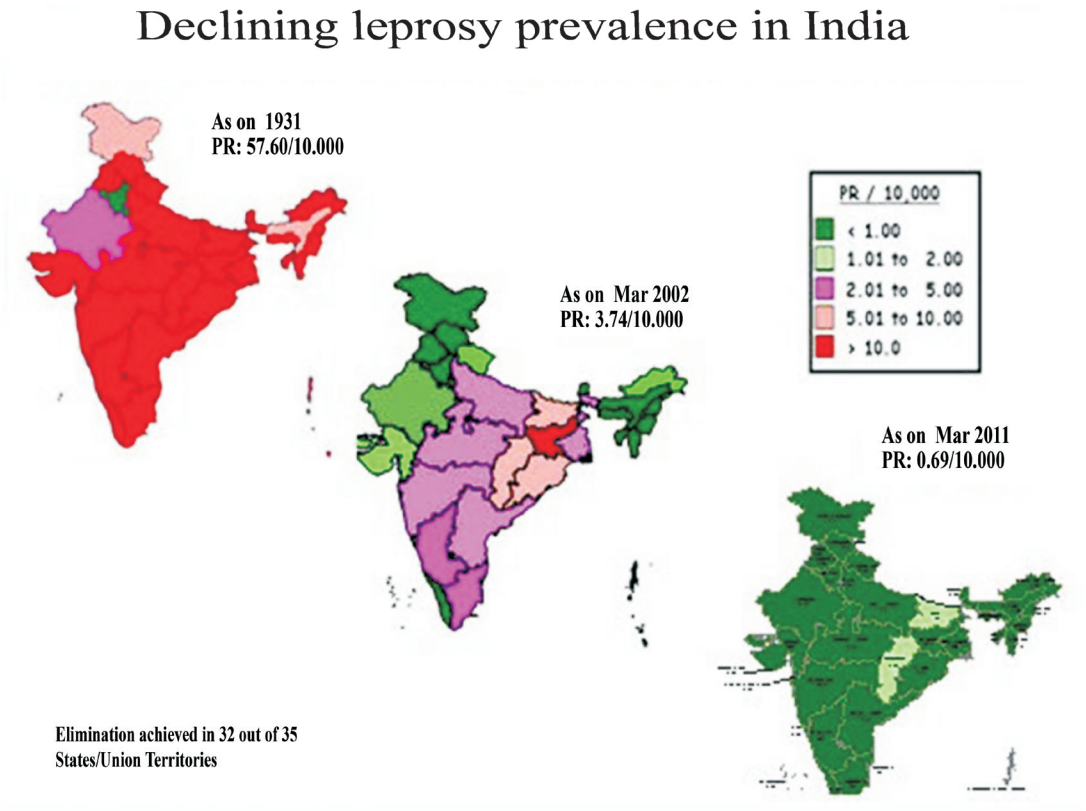

Fig. 1. The leprosy scenario in the country over a period of nearly three decades after introduction MDT in 1982[63].

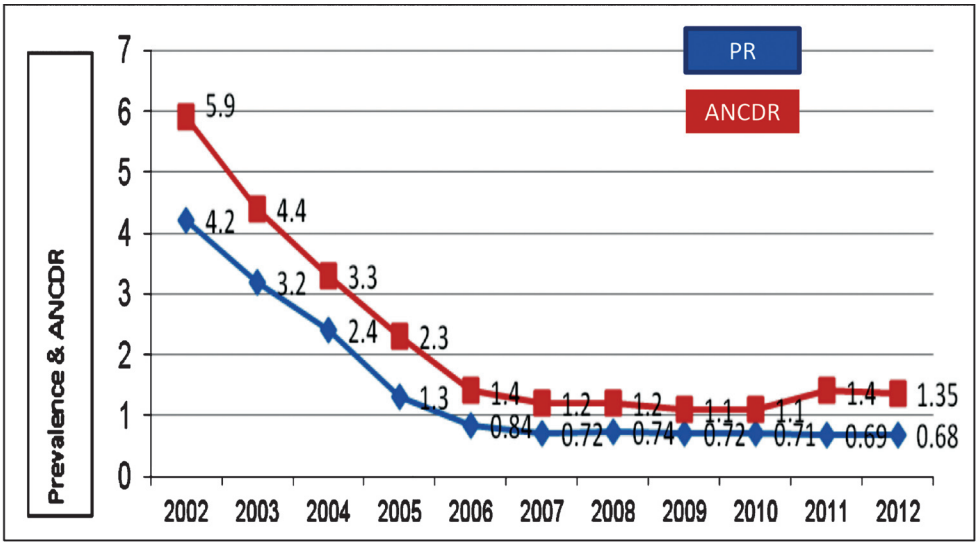

Fig. 2. Trends of leprosy prevalence (PR) and Annual New Case Detection (ANCDR) in India in last two decades.

These statistics have generated substantial hope that leprosy can be eradicated one day. Eradication is defined as "permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts," and interventional measures are no longer needed after this[8]. Leprosy is one of the few chronic illnesses that meet the demanding criteria for possible elimination, *i.e.* it can be diagnosed by practical and simple diagnostic tools or by clinical signs alone, availability of an effective modality to interrupt its transmission in the form of MDT and a single significant reservoir of infection, humans. However, despite all the encouraging parameters which are sustainable, leprosy eradication seems a distant possibility considering the current scenario[8,9]. New cases continue to occur in almost all endemic countries and high-burden pockets exist against a low-burden background. The number of new cases detected during 2011, as reported by 105 countries, was 219,075 and India topped the list with its contribution of 58.1 per cent to the pool[7]. Moreover, the number of new cases, leprosy in children and new cases with grade 2 deformities have still not changed significantly over the years[7]. Intensified and focused activities with MDT have reduced the leprosy burden but sustaining the same level of focus and commitment will be a challenge, especially in low-resource settings where equity of access is an issue.

History of leprosy and stigma

The origin of leprosy has always been a matter of uncertainty and an Indian or African origin for the disease has often been assumed based on historical sources that support an initial spread of the disease from Asia to Europe by the armies of Alexander the Great after 400 BC. Skeletal evidence for the disease was previously limited to 300-400 BC in Egypt and Thailand, till Robbins and colleagues reported on a case of leprosy in a skeleton showing changes associated with leprosy, buried around 2000 BC at the site of Balathal Rajasthan, India[10]. Early written records giving clinical descriptions generally accepted as being true leprosy date from 600 BC to possibly as early as 1400 BC in India, where a disease called *Kushta* was distinguished from vitiligo[11,12]. The ancient medical texts of Sushruta, Charaka and Vagbhata, compiled in the first to the sixth century BC, show that Indian physicians regarded leprosy as a disease that can be cured or alleviated. *Sushruta Samhita* (600 BC) recommended treating leprosy or *kushtha*, meaning "eating away" in Sanskrit with oil derived from the chaulmoogra tree; this remained a mainstay of treatment until the introduction of sulphones[12-14]. Documentation of lesions suggestive of leprosy like, numbness and loss of eyebrows in Chinese documents attest to the spread of the disease eastward to China and subsequently to Japan[14]. The disease was thought to have spread to the Middle East and westward to Greece by the conquering armies or the traders, as evident by the description of Greek physicians of a novel disease called elephantiasis graecorum. Subsequent spread to the Mediterranean basin and Western Europe may have been intensified during the Crusades by Romans[11,13].

In the Health Protection era - from antiquity until 1830s, the dominant paradigm was disease prevention through enforced regulation of human behaviour and this was mediated via legislation, cultural practices and religious doctrines[14,15]. Segregation was the main strategy for leprosy control in this era. In India, the Laws of Manu (1500 BC) mention various skin diseases translated as leprosy. The Laws prohibited contact with those affected by leprosy and punished those who married into their families. Ancient Indian society marginalized those with leprosy because of several factors: its chronic, potentially disfiguring nature; inconsistently effective therapy; association with sin; and the fear of contagion[15,16]. The Mosaic Law stated illness to be a punishment for sin and leprosy was considered to be the punishment for the most heinous sins or crimes. A purification ceremony and four sacrifices were essential before readmission to society was allowed[17]. Taboos, such as Chinese and African legends associating leprosy with necrophilia and incest, constituted a major action framework during the Health Protection era. The legacies of the Health Protection era in relation to leprosy control were largely negative, with erroneous knowledge about aetiology of leprosy resulting in stigmatisation and social exclusion of those diagnosed with the disease[15].

Unfortunately, social stigma, alienation, and violence against sufferers of leprosy are attitudes that have continued through the ages up to the 20th century and these still exist, though in a diluted form. Feeny gives a number of examples of persecution acts in the early part of the past century. In Japan "no leprosy patients in prefecture" movement started in 1930 in which absolute isolation was supported by the social belief of that day; "leprosy is a shameful disease and the purity (absence of leprosy patients) of the nation should be maintained, thus justifying isolation". In the United States, laws in some States allowed sheriffs and local health officials to arrest and confine anyone suspected of carrying the disease. In China (1937), 80 victims with leprosy, including women and children, were shot and thrown into a lime pit; and in Korea (1957), a mob beat 10 patients from a leprosarium to death[18]. Stigmatizing attitudes have even been incorporated into modern law, as demonstrated in India where the Motor Vehicles Act of 1939 forbade the granting of drivers' license to leprosy sufferers and, until recently, the Indian Christian, Muslim, and Hindu Marriage Acts included leprosy as grounds for divorce[19,20].

Leprosy in the nineteenth century: advances in the understanding and treatment

One of the first advances away from the age of superstition into the modern scientific era occurred in response to the last endemic wave of leprosy in Europe, which peaked in Norway in the mid-1800s, when approximately 3,000 cases were reported[20]. Daniel Danielssen and Carl Boeck published, *Om Spedalskhed* (On Leprosy), in 1847, after their detailed investigation on the characteristics of the disease. The book is recognized as the first authoritative publication clearly distinguishing leprosy from other diseases affecting the skin, such as syphilis, psoriasis, and scurvy, and describing the two main forms of true leprosy with illustrations[1,20]. Based on their observation of clustering of cases of leprosy in a family they suggested that leprosy was hereditary. This concept of hereditary nature of leprosy was upheld till British physician Dr Jardine, working in Hankow (now Wuhan, Central China) attributed the spread of leprosy in this part of China to "a degeneration which flourishes among a variety of climates, of soils, of staple articles of food, and of race"[1,12,13]. Colonial agencies in Australia and Canada racialised the miasma (bad air) doctrine by labelling Chinese migrant workers as unclean, leprosy-polluted races, thus justifying their stigmatisation and exclusion from mainstream society[14]. It is now known that apart from the prime transmission route of inhalation, insanitary environments and dysfunctional urbanistaion are environmental risk factors for leprosy transmission. In 1873, Gerhard Armauer Hansen, son-in-law of Danielssen was the first to identify the causative agent of leprosy, *Mycobacterium leprae*, when he discovered multiple rod-shaped bacilli while examining nasal biopsy specimen of a patient[1,12,13]. Even though Hansen identified leprosy bacillus as the human pathogen, attempts to develop standard bacteriologic or cell cultures remain unsuccessful to this day.

Although the contagion paradigm or infectious nature of the disease radically transformed the way many infectious diseases were managed, the discovery of the microbiologic origin of leprosy did not radically change its management and the stigma associated with it. Hansen too was a proponent of segregation strategy in Norway. He facilitated the formulation of Norwegian law on the seclusion of people diagnosed with leprosy. The law stipulated that all patients had to be isolated in a separate room at home or they had to be admitted to hospitals or leprosy settlements, if necessary with the help of the police[1,13]. This created

a double burden for people affected by leprosy - a widely accepted religious perspective that leprosy is divine punishment for immorality, and a scientific perspective that leprosy is an incurable infectious disease. Both perspectives intensified stigma against leprosy sufferers. The contagion theory was brought to India by Henry Vandyke Carter of the Mumbai Medical Service who was shown the putative leprosy bacillus by the discoverer himself. On his return to India, Carter urged the colonial Government with memoranda on the infectiousness of leprosy and the necessity for segregation of the affected, as a control measure[1]. Carter's contribution to the knowledge and understanding of leprosy include his beautifully self-illustrated book "On Leprosy and Elephantiasis" published in 1874[21,22] where he described two distinct forms of the disease *Elephantiasis Tuberculata* and *Elephantiasis Anaisthetos.* He is also credited with describing leprosy as a sensory peripheral nerve disease par excellence[1]. The principles which he propounded on neuro-pathogenesis were based on close clinical examination and post-mortem dissections carried out at the Jamsetjee Jejeebhoy Hospital in Bombay (now Mumbai) are valid even today[1,22].

The need for an internationally accepted classification system for leprosy was recognized long ago. After the initial reports of two distinct types of leprosy more work on classification was done during this era and various classifications were developed. The first system was proposed at an international meeting in Manila in 1931. This was followed by systems proposed in Cairo in 1938, Rio de Janeiro in 1946, Havana in 1948 and Madrid in 1953, followed by an Indian classification in 1955[23,24]. These evolving classifications were based on clinical features with some support from histological and prognostic features and lepromin testing. They separated out the tuberculoid and lepromatous poles and recognized borderline, dimorphous or intermediate categories in between. Robert Cochrane the clinician and Vasant Khanolkar the pathologist, both workers in India, were prominent in the Classification Sub-Committee at the Congress held at Madrid in 1953[1,24]. The proposal that the primary classification be based on clinical features was unanimously accepted, as was the use of the lepromin test (introduced by Mitsuda of Japan in 1920), as an immunological indicator in the study of cases, with a secondary role for histological classification. In 1966, Ridley and Jopling published a paper[25] that used clinical, histological and immunological criteria to classify leprosy patients across the spectrum, and suggested five member groups: tuberculoid (TT), borderline tuberculoid (BT), borderline borderline (BB), borderline lepromatous (BL) and lepromatous leprosy (LL). This classification recognized the complex pathogenesis and numerous clinical syndromes of leprosy[25]. The timing of this classification was important because it coincided with the initial laboratory work on the immune response to *M. leprae*, both in man and in the mouse.

At one end of the disease spectrum, was the polar tuberculoid disease (TT), characterized by a relatively well-developed cell-mediated immune response and delayed hypersensitivity. TT patients present with usually a single, well-demarcated skin lesion exhibiting definite sensory loss and well-formed granulomas with rare acid-fast bacilli (AFB) within the granuloma and affected peripheral nerve. The other end had patients with polar lepromatous (LL) with poor T-cell immunity and the presence of a marked increase in circulating antibodies. LL patients present with numerous, poorly demarcated skin lesions that exhibit variable sensory loss and, upon biopsy, reveal a disorganized immune response with large numbers of bacilli within macrophages and nerve tissue[20].

In between these two poles are the borderline categories with vast majority of patients and classifications of borderline tuberculoid, borderline borderline, and borderline lepromatous forms of the disease. These patients have an unstable immunologic response with periods of increasing immune effectiveness (upgrading) and decreasing cellular immune response (downgrading) as the disease progresses[26,27]. In recent years, WHO further simplified this classification into paucibacillary (having five or fewer skin lesions) and multibacillary (having six or more skin lesions) disease states - roughly correlating to the effectiveness of cellular immunity and corresponding bacterial load - in an effort to simplify and standardize clinical diagnosis and operational treatment regimens globally. As an operational classification it has been a great success, it has made classification simpler, determined simply by the number of skin lesions. This meant that expertise in defining the morphology of skin lesions ceased to be a prerequisite for field workers classifying leprosy patients, although health workers do have to recognize the wide range of presentations when suspecting leprosy[28].

While the multifarious manifestations of leprosy and their regional and geographical peculiarities were

noted in the 19th century, the advent of influential multi-national bodies such as the British Empire Leprosy Relief Association in 1924, the League of Nations Leprosy Commission in 1930, and the International Leprosy Association in 1931, signaled a progressive "internationalization" aimed at consolidating medical experiences, harmonizing practices across the globe and organization of the leprosy control services[1].

Treatment of leprosy

The Chaulmoogra/Hydnocarpus oil era in India

Prior to the age of antibiotics, leprosy was treated with chaulmoogra oil, an extraction from the seeds of *Hydnocarpus wightiana*, with some limited success[28]. The use of chaulmoogra oil (also called *Hydnocarpus* oil) for treatment of leprosy in India can be traced back to as early as 600 BC in Sushruta Samhita[29]. In a legend explaining the therapeutic properties of the chaulmoogra oil, a king who was banished for leprosy was advised to eat the curative seeds of this tree. It was used in both topical and parenteral routes for the treatment of leprosy[30,31]. Sir Leonard Rogers (1868-1962) introduced sodium hydnocarpate (later marketed as "ALEPOL") for treatment of leprosy and this marked the beginning of leprosy control in India[31]. Therapeutic trials were launched with sodium chaulmoograte in late 1915 and introduced in India during British Empire. The chaulmoogra syringe acquired an iconic status in the hospitals. Rogers envisioned transformation of leper asylums into leprosy hospitals for early leprosy when the disease is most amenable to the treatment[31].

The opinions of nineteenth century British colonial physicians employing "Chaulmoogra" and "Marotti" oils were divided. While the oils continued to be employed, it was by default rather than proven merit and patient satisfaction and the patients frequently refused to continue with oral treatment because of nausea and gastric irritation. Injections too did not find much favour with the patients as multiple painful needle punctures had to be given twice-weekly to deliver 5 ml of drug and were painful[1]. As one American leprosy sufferer remarked: "*Chaulmoogra oil was to be taken internally, externally, and eternally*". Hydnocarpous and chaulmoogra oils retained their place in the British Pharmacopoeia till the 1940s[1,14,32].

The modern era of leprosy treatment began in the 1940s, when Dr Guy Faget of the National Hansen's Disease Center (renamed the Gillis W. Long Hansen's Disease Center in the 1980s) in Carville, Louisiana, showed remarkable benefits of Promin in treating the disease. This discovery was heralded as "the miracle of Carville" and marked the onset of the first real hope that leprosy could be successfully treated and cured[1,20]. Further work on limiting the toxicity of treatment led to the use of dapsone, the parent compound of Promin, which was broadly used as long-term monotherapy until 1970s[12].

Introduction of dapsone simplified the treatment by paving the way for ambulatory treatment and changed the face of leprosy dramatically. Cochrane and other leading leprologists recommended that patients with paucibacillary leprosy should not be isolated as they were non-infectious and this made it feasible for some of those segregated in leprosy settlements to revert to the general community[1,32].

Emergence of resistance to dapsone

The initial enthusiasm of finding a cure for leprosy was dampened by relapses and emergence of drug resistance to dapsone in the 1970s in upto 19 per cent of patients[33,34]. The first report of primary dapsone resistance was documented in 1977[35]. This was followed by, footpad-proven secondary resistance being reported from an increasing number of countries worldwide with a frequency ranging from about 2-3 per cent[36]. With the realization of worldwide increase in dapsone resistance in *M. leprae* in the late 1970s, dapsone monotherapy was no longer considered adequate for treatment of leprosy[34,36-38]. The surveys sponsored by "Therapy for leprosy" (THELEP) and others also proved that the epidemic of dapsone resistance was sabotaging the entire leprosy control efforts[39]. Thus, there was a clear and urgent need for safe and practicable combined drug regimens effective in curing leprosy and preventing drug resistance under field conditions[40].

In response, WHO supported the establishment of the Special Programme for Research and Training in Tropical Diseases in 1976 to evaluate effective responses to dapsone resistance and promote the development of vaccines[20]. In the 1960s and 1970s various antitubercular drugs such as streptomycin, ethionamide, prothionamide, isoniazide, and thiacetazone were tried as second-line drugs; however, their inconsistent efficacy, systemic toxicity, cross-resistance and cost proved to be limiting factors[41]. The concept of MDT in leprosy arose after the availability of clofazimine and rifampicin and from the experience of rifampicin use in the therapy of tuberculosis[42-45]. Based on the theoretical considerations, leprologists

worldwide started using combined drug regimens for the treatment of leprosy on an experimental basis.

In 1981, WHO took a monumental decision and recommended MDT for leprosy[30]. Later, six case series assessing the effects of WHO MDT (monthly supervised rifampicin 600 mg and clofazimine 300 mg, plus daily unsupervised dapsone 100 mg and clofazimine 50 mg) for 24 months supported the 1981 WHO recommendations[47]. The original WHO recommendation was to treat the MB patients for two years or until skin smear negativity and to treat the PB patients with rifampicin and dapsone for six months[30,46]. By 1985, these recommendations were adopted by almost all countries. Since the introduction of MDT, the treatment of leprosy has been a subject of debate and has seen a lot of changes in terms of duration of treatment and the criteria for classification of leprosy. In the late 1980s - 1999 focus was on efforts to enhance positive health and prevent ill-health, through the overlapping spheres of health education, prevention, and health protection[40,41]. A sequential recount of important landmarks in management of leprosy is given in the Table 1.

MDT a perfect tool or the only tool to achieve elimination?

It was assumed that MDT would reduce the transmission of *M. leprae* through a reduction in the number of contagious individuals in the community, but unfortunately there is no convincing evidence for this hypothesis[49-53]. There were two large-scale studies on trend analysis available to interpret the impact of MDT globally[50,54]. In the first study[50], the authors concluded that factors such as case detection and treatment would reduce leprosy transmission is reasonable, but the reality may be more complicated. Individuals incubating the disease may already harbour many bacilli, and it is possible those individuals had already transmitted *M leprae* to others long before the onset of the disease. This is evident by the fact that there has not been a general acceleration of downward trends in the new case detection rate (NCDR) after the introduction of MDT and Meima *et al*[54] showed no general decline in case detection at global level up to 2000.

MDT is also not a perfect tool and it has its shortcomings like poor compliance, long duration of treatment, irregular treatment, minor and sometime serious side effects, rifampicin/multidrug resistance, high relapse rate 0.65 to 3.0 per cent for PB and 4 to 7 per cent for MB[3]. All these can have serious implications when we consider the large number of leprosy cases in India. Relapse and resistance to MDT call for development of new/ alternative MDT regimen, which is of short duration, more effective, free of side-effects and if possible free from the fear of emergence of resistant lepra bacilli[3,40]. However, there are other avenues to improve the treatment completion, prevent the irregularity of treatment intake, and also for early detection and referral of the patients for treatment, which may be helpful in overcoming some of the problems associated with the current MDT. For instance, accredited social health activists (ASHAs) who are introduced in the healthcare delivery system of India under the National Rural Health Mission (NRHM) may be involved in the referral of suspected cases, monitoring the drug intake by the patients, and advice on self-care to the patients. They may also be successful in reducing the stigma associated with the disease in the community because they are selected from the community. Thus, there is an excellent opportunity to improve the compliance to current MDT by ensuring regular intake of MDT amongst leprosy-affected persons through ASHAs at the field level. Counselling of the patients by the healthcare staff in relation to the disease and its management such as course of the disease, transmissibility of infection, side-effects of the drugs and self-care advice at the time of registration, during treatment and discharge from the treatment should also be stressed upon for better outcome[40].

Newer drugs

The WHO Steering Committee on Chemotherapy of Mycobacterial Diseases [THEMYC, Madras (now Chennai) 1993] recommended that the search for new drugs and new drug regimens should continue to consolidate efforts towards the goal of elimination of leprosy, improved patient compliance, develop alternate agents against dapsone/clofazimine/ rifampicin resistant bacilli, kill persistent bacilli more efficiently and to develop supervised/supervisable regimens (short) for prevention of drug resistance[33]. Some new drugs are available to compliment/replace those being currently used in MDT. These drug combinations are proposed, not with the objective of inducing quick clinical regression but with the purpose of minimizing relapses or for special situations such as drug resistance or drug intolerance. In recent years, a number of new antimicrobial agents have been shown to have excellent anti-leprosy activity both in

Table 1. The sequence of events in the leprosy elimination or control worldwide after 1970

Year	Recommendations	Outcomes
1940-1970	Dapsone (mono-therapy) for treatment for leprosy	Development of dapsone resistance worldwide
1982	WHO Study Group: Chemotherapy of Leprosy For Control Programs; Technical Report Series no. 675.[30] *Highlights*: Classification of all patients according to estimated bacterial load skin-slit smear(s) into multi- and paucibacillary leprosy: *(i)* Two regimens: one for each category of patients- pauci- or multibacillary. *(ii)* Each regimen having a supervised component and a self-administrated individual based component. *(iii)* Defined end of treatment: duration and/or smear negativity/inactive disease (whichever was later); *(iv)* Reduced follow up.	*(i)* Spectacular reduction in registered leprosy cases on treatment worldwide. *(ii)* Failure of chemotherapy/relapses in pauci-abacillary cases due to PB-MDT in some smear-positive PB leprosy was identified. Hope of eradication or least "elimination" of disease worldwide was raised and renewed efforts made.
1988	WHO Expert Committee on Leprosy: 6th Report; Technical Report Series no. 768. [47] *Highlights*: Classification/definition of paucibacillary cases made it mandatory to avoid failure of PB MDT leprosy: only skin-slit smear/AFB-ve patients classified as PB leprosy.	*(i)* Continuing dramatic fall in registration of leprosy patients worldwide. *(ii)* Fall in relapse/failure after MDT chemotherapy for PB leprosy. *(iii)* Hopes for successful "elimination" by the end of the century raised: projection made, "elimination" redefined.
1994	WHO Study Group: Chemotherapy of Leprosy for Control Programs; Technical Report Series no. 847.[33] *Highlights*: Fixed duration therapy proposed: *(i)* Duration of treatment of PB and MB leprosy fixed to six cycles in 9 months and 24 cycles in 36 months, even if there is persisting clinical activity or skin-slit smear positively at this time, MDT treatment to be stopped. *(ii)* Shift of focus of patient assessment from objective/ reproducible skin-slit smears to "clinical judgement" of field workers in view of human immunodeficiency virus pandemic.	*(i)* Large number of patients removed from treatment registry after fixed duration as defined by WHO. *(ii)* Fears of delayed relapse expressed by some workers based on long-term follow-up studies. *(iii)* Mathematical projection shows potential for drastic reduction of leprosy worldwide following MDT. *(iv)* WHO pursues "elimination" and re-organizes antileprosy measures towards achieving "elimination" of leprosy by 2000.
1998	WHO Expert Committee on Leprosy; Technical Report series no. 874.[48] *Highlights*: *(i)* Progress towards elimination and recommendations: (a) Skin-slit smear facilities no longer declared essential for MDT (not a necessity) (b) Guidelines evolving/direction for future course of action post-elimination (2000). (A). Suggestion for further reduction in duration of MDT to 12 months and treatment of single lesion PB leprosy by rifampicin, ofloxacin, minocycline (ROM) kits (B). Necessity for integrating leprosy services with general health services at grass-root level identified. (C). Requirement of leprosy referral centres, need for leprosy research beyond the year 2000 stressed and the reality of leprosy persisting well beyond 2000 identified.	*(i)* Different national programmes reduce multibacillary MDT treatment duration to 1 year, keeping in mind approaching year 2000 deadline, and operational costs. Skin-slit smears no longer performed routinely because of lack of facilities and interpretation of findings. *(ii)* Classification of patients on clinical grounds with increased possibility of over/under-classification. Over-classification justified by WHO and over-treatment recommended in case of doubt regarding classification. *(iii)* This over-treatment/over-classification of PB into MB is stated as a major reason for MB-MDT duration reduced to 12 months. *(iv)* Many PB patients given ROM as anti-leprosy therapy and informed that they are treated (and cured). *(v)* Patients rapidly removed from treatment registers within 1 year to attain "elimination" in defined areas. *(vi)* Situations exist where patients with relapse are likely to appear after leprosy is "eliminated".

PB, pauci bacillary; MB, multi bacillary; MDT, multi drug therapy; AFB, acid fast bacilli

animal studies and in clinical trials[41]. It is important to consider that newer drugs should possess an exquisite bactericidal activity, have no antagonism with existing drugs, an oral route of administration, be patient-friendly and cost-effective. Of the several new drugs, ofloxacin, moxifloxacin, minocycline and clarithromycin have been shown to display a high bactericidal activity against *M. leprae* in animal and human trials. So far, however, there is no consensus as to which combination of drugs would be most suitable[3,41].

Trials are being conducted to evolve acceptable, short duration, antileprosy regimens that are highly effective and have low incidences of toxicity and/ or side-effects. Some of the combinations/ regimens that have shown promise are monthly rifampicin, ofloxacin and minocycline (ROM), monthly dose of clarithromycin, minocycline and ofloxacin; rifapentine, moxifloxacin and minocycline (PMM) and addition of these new drugs to the WHO MDT like MDT supplemented by ofloxacin daily for the first 4 weeks, or ofloxacin plus rifampicin for 4 weeks[55-59]. The final results of these studies along with evaluation of relapse rates after long-term follow up upto 10 years will be helpful in deciding on alternative and better regimens for leprosy[3,41].

The requirement in the new millennium is for a single MDT regime of a duration that is acceptable for all categories of leprosy[60-62]. This will make errors of classification in the field irrelevant and minimize the operational and logistic difficulties of maintaining adequate supply line of drugs[2]. While the cost of therapy per month will increase, the overall cost to the programme will probably not differ much because the duration of therapy will be less and the number of patients presently being detected annually is also smaller than before. There will be some concern regarding the overtreatment of paucibacillary patients. However, a uniformally effective regimen such as for tuberculosis will do away with the potential pitfalls of incorrect classification and undertreatment, and a degree of overtreatment appears acceptable in efforts to further accelerate the progress and consolidation of leprosy elimination[3].

Leprosy control/eradication programme in India

Milestones[63] (Table II)

No data were available regarding the prevalence of leprosy prior to 1955. With the progress of National Leprosy Eradication Programme (NLEP), leprosy prevalence became clear and by mid-seventies, extensive data were collected. By 1980, a total of 40 lakh cases were recorded, giving a prevalence rate of 58 per 10,000 population. In 1982, there was a major advance in the treatment of leprosy. The most striking achievement of the programme remains the reduction of prevalence to elimination level[64].

The first attempt to deal with leprosy as a public health problem was taken up in 1952 by the Gandhi Memorial Leprosy Foundation (GMLF), an institution started under the Gandhi Memorial Trust. At that time, the only method to deal with the disease was to isolate leprosy patients in "leprosy homes" "sanatoria" or "asylums", however, such places were very few and inadequate. Dapsone was the new drug that had just been introduced. A field study was piloted at GMLF which envisaged identification of all leprosy patients in a fixed geographic area, followed by domiciliary treatment with dapsone. Rigorous health education was carried out to explain the true facts about leprosy. For the first time in a leprosy campaign, a house-to-house survey was carried out, and every man, woman and child was examined for signs of leprosy. That was the beginning of the SET (Survey, Education and Treatment) programme of GMLF. The work first started in Sewagram (Wardha) in 1952, was subsequently replicated in 12 other centres of GMLF in different States. It soon became obvious that the SET programme, initiated by GMLF, was scientific, practical and a very effective method for control of the disease, and the Government of India took it up. The National Leprosy Control Programme (NLCP) was started in 1955 and the SET method became the standard procedure for leprosy control in the entire country. Later, the WHO also endorsed the method, and it was adopted the worldover[64].

The Enhanced Global Strategy for further reducing the disease burden requires endorsement and commitment from everyone working towards the common goal of reducing the disease burden due to leprosy and its detrimental physical, social and economic consequences to move closer to achieving the common dream of "world without leprosy".

In 2005, the Government took another major step towards expansion of the NLEP. Leprosy work, which had been carried out so far as a vertical programme, was integrated into the general health services. There were no more special leprosy clinics. All hospitals,

Table II. Milestones in leprosy eradication programme

- 1955 - Government of India launched National Leprosy Control Programme (NLCP) based on dapsone domiciliary treatment through vertical units implementing survey education and treatment activities.
- 1981 - Government of India established a high power committee under chairmanship of Dr M.S. Swaminathan for dealing with the problem of leprosy.
- 1982 - The MDT came into use following the recommendation by the WHO Study Group, Geneva, in October 1981.
- 1983 - National Leprosy Eradication Programme (NLEP) was launched. Districts were covered in a phased manner and all the districts in the country could be covered only by the year 1996.
- 1991 - The World Health Assembly resolved to eliminate leprosy at a global level by the year 2000.
- 1993-2000 - The 1st Phase of the World Bank supported National Leprosy Elimination Project was launched in 1993 and completed in March 2000.
- 1998-2004 - The NLEP introduced the Modified Leprosy Elimination Campaign activities in 1997-1998. Five such campaigns were conducted upto 2004.
- 2001-2004 - The 2nd phase of the World Bank supported National Leprosy Elimination Project was launched in 2001 and completed in December 2004. During this phase, the NLEP responsibilities were decentralized from the Centre to the States/UTs through State/District Leprosy Societies. Leprosy services were also integrated with the General Health Care System from the erstwhile vertical system.
- 2002-2004 - A system of monitoring of the programme was started in the form of Leprosy Elimination Monitoring (LEM) exercise jointly by Government of India with World Health Organization, International Federation of Anti-Leprosy Associations (ILEP) in collaboration with the National Institute of Health and Family Welfare. These studies were carried out during 2002, 2003 and 2004. During the last two years a component of validation of case diagnosis was introduced.
- 2005 - A survey to monitor performance at close of the 2nd National Leprosy Elimination Project was carried out during April-May 2005 through an independent agency, the Indian Institute of Health Management and Research, Jaipur.
- 2005 - Leprosy was eliminated as a public health problem at national level in December 2005.
- 2005 onwards - Programme continues with Government of India support since January 2005. In 2005, a strategic plan for the elimination of leprosy was introduced.
- 2006-2010 - WHO introduced the "Global Strategy for Further Reducing the Leprosy Burden and Sustaining Leprosy Control Activities" to address the remaining challenges in providing services for leprosy patients under conditions of low prevalence. The main intentions were those of ensuring programme sustainability by reducing reliance on vertical infrastructure and promoting integration within the general health system. This ushered in a renewed focus on issues related to quality of services, reaching underserved communities and building effective partnerships that would further reduce the disease burden[65].
- 2011-2015 - The Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy: together with the updated Operational Guidelines was introduced to enhance the elements of the Enhanced Global Strategy[66].

dispensaries and PHCs had to treat leprosy patients. Further, the field staff of PHCs had to take up case finding and follow up along with their regular duties. This era was also significant for leprosy control in the use of culturally appropriate depictions of people living with leprosy for leprosy fundraising and public awareness campaigns. Integration of leprosy into the general health service has greatly enhanced the scope of leprosy service. By integration, discrimination against leprosy has been set to be removed and the patients have access to the services of ophthalmologists, surgeons, physiotherapists, and general physicians.

These initiatives facilitated reductions in leprosy stigma. Unfortunately, it was also the era in which the medical, epidemiological and laboratory specialists in the field of leprosy were alienated from mainstream public health practice[8]. This apparent disunity in the ranks of the public health community retarded progress in leprosy control.

There have been remarkable achievements in several aspects of leprosy control within a span of 4 to 5 decades, however, these need to be put into perspective in relation to the possibility of eradicating the disease and prevention of its resurgence[63]. Although elimination of leprosy has been achieved, new cases continue to occur and this will be seen for some more years. We need to be vigilant and see that the disease does not reappear in the community. The initial fall seen in the Annual New Case Detection Rate (ANCDR) was not seen, subsequent to 2005, and it has more or less remained at the same level[7] (Fig. 2). This is a warning sign, and an indication that there should be an active thrust to identify new cases. It is important to identify any hidden infective source cases, trace and treat.

Continuing challenges of leprosy in the post elimination era

The gray areas in leprosy control are the role of close contact transmission, the speed of transmission, and the extent of contagiousness during the incubation period. Research addressing these questions is essential to narrow down the uncertainty regarding the impact of MDT-based control. In the present times, the diagnosis and treatment of leprosy are relatively easy and most endemic countries are striving to fully integrate leprosy services into existing general health services. Most of the previous highly endemic countries have now reached elimination. However, the major problem in leprosy eradication is the delay between the onset of disease and its detection. Leprosy is a quiescent disease and hence there may be substantial delay before the patient seeks treatment. Although there are no such studies from India but in a study from Ethiopia the average detection delay exceeded 2 years[66]. It is possible that close contacts of a leprosy patient become infected rapidly[20].

We need simple and effective screening test to identify individuals or populations with subclinical disease or asymptomatic infections to decrease the delay between onset and detection. Promising technologies in the form of detecting *M. leprae* through polymerase chain reaction or with measuring antibodies to phenolic glycolipid-1 and other antigens are on the horizon but have not been implemented due to financial reasons and lack of clear specificity. In the absence of effective screening tools, the early treatment of the disease depends primarily on either self-identification by the patient or a high index of suspicion by the clinician when evaluating a patient with a skin lesion associated with sensory loss.

Stigmatization of leprosy and its impact on elimination

From antiquity to modernity, Indian society has treated leprosy as a stigma; a response shaped by both inadequate scientific knowledge and cultural attitudes. Leprosy is still called *kushta* in most Indian languages, as it was in Sushrutha's time. The word itself still evokes fear and aversion, despite Mahatma Gandhi's efforts to destigmatize the disease. India's future challenges in leprosy control include multiple systems of medicine, stigma, and educational knowledge gaps. Integrating leprosy care into the general health systems seems to have decreased the stigma associated with leprosy due to family counselling and community outreach. Efforts to decrease health inequity due to poverty, especially in rural areas with limited access to health care, may help in leprosy control. However, if cultural beliefs are not addressed, increased availability may not translate into an appropriate increase in utilization. Cultural aspects of leprosy affecting its control include traditional medicine and stigma. Only limited efforts have been made to include the numerous non allopathic (traditional) practitioners in India in leprosy control and elimination efforts, but their inclusion is important to its success. Sustaining the gains made so far and further reducing the disease burden in India require an innovative, holistic approach that includes ongoing education, efforts to identify interventions that dispel stigma, and the inclusion of non allopathic practitioners in disease control programmes[67].

Reactions, deformities and rehabilitation

The hallmark of leprosy is the unique ability of *M. leprae* to survive within the Schwann cells of peripheral nerves as well as within macrophages. The bacterium itself is of very low virulence and is essentially nontoxic to tissues. However, the infected nerves and surrounding tissues can be damaged as the host mounts an immune response to bacterial antigens. Two types of immune reactions are seen in leprosy. Type 1, or "reversal reaction," is a delayed-type hypersensitivity reaction; Type 2, erythema nodosum leprosum (ENL), is thought to be an immune complex disorder. The factors that trigger these immune responses are not well understood, and the reactions can occur during the natural course of untreated disease, during therapy, or after completion of therapy. If the reactions are not medically managed appropriately, the patient will experience permanent sensory, motor, and/or autonomic peripheral or other nerve damage, which may result in severe disability (*e.g.*, claw hands, claw toes, and/or foot drop). Deformities, secondary infections and disfiguring injuries due to loss of sensation in the affected areas can further compound physical disabilities and have marked social consequences related to stigma, in addition to impairing patients abilities to earn a living and care for themselves.

Although we have achieved the goal of leprosy elimination in 2005, even those patients who have successfully completed their treatment continue to manifest late or recurrent reactions in settings of poorly available expertise or services to manage these episodes. The recognition and management of these reactions is the most essential/significant task in the post elimination era because these reactions and nerve function impairment are the major cause of morbidity in leprosy. Reactions are the main cause of acute nerve damage and disability in leprosy and occur in about one third of people with leprosy. Various estimates of the frequency of these reactions have been given by several authors[68-71]. Published reports indicate that the frequency of reversal reaction at the time of diagnosis varies between 2.6 and 6.4 per cent[69]. ENL reactions have been reported to occur in more than 50 per cent of lepromatous leprosy (LL) cases and in about 25 per cent of borderline lepromatous (BL) cases in the pre-MDT era[70]. Although the incidence of ENL appears to have decreased with the introduction of MDT, possibly due to the combined bactericidal effect of rifampicin and the anti-inflammatory effect of clofazimine[72]; a hospital-based study from Nepal reported a high frequency of ENL reactions (28.6%) in LL, but only 7.5 per cent in BL cases[70]. Another study from north India reported 47.4 per cent of LL cases and 10.5 per cent of BL cases manifesting ENL reactions[71]. Sequelae of reactions are: paralytic deformities, non-paralytic deformities, extensive scarring and renal damage. Over the last three decades, work has centred around finding who are more prone to develop reactions, identifying the risk factors and improving the management of reactions to alleviate the suffering and prevent and reverse the nerve damage consequent to reactions. Though several new drugs have been tried and found useful, corticosteroids and thalidomide continue to be the mainstay in the management of leprosy reactions[72].

Leprosy is primarily an infection of the peripheral nervous system, and MDT alone is not effective in the control of nerve damage. Nerve conduction studies (NCS) provide valuable information for detecting nerve function impairment (NFI) and evaluating appropriate therapeutic regimes. In a cohort of 400 newly detected MB cases, >95 per cent of patients showed impairment of one or more nerves by NCS at registration, regardless of reaction, indicating that nerve damage is more widespread than clinically ascertained[73]. Early detection with prompt and adequate therapy is the key to reduce recurrence of reactions and to minimize NFI and deformities due to reactions in leprosy. Corticosteroids are the drugs of choice for acute severe reactions and nerve damage, but the long-term effect of corticosteroids is uncertain and the optimal regimen has not been established yet. A considerable proportion of people treated for nerve damage do not benefit from corticosteroid treatment and overall nerve function improvement levels vary approximately between 60 and 80 per cent after steroid therapy[74]. Although randomized controlled trials (RCTs) comparing three corticosteroid regimens confirmed that a longer duration of prednisolone treatment gave better outcomes than a short course of prednisolone[74], there is a need for high-quality RCTs to establish the value and optimal dose of corticosteroid regimens and to examine the efficacy and safety of new therapies.

Another area which has been ignored is chronic neuropathic pain among patients with leprosy who have completed effective anti-leprosy treatment. Various epidemiological studies have documented prevalence ranging from 29-58 per cent[75]. The natural history, pathogenesis and management of neuropathic pain is also not clear and needs to be studied. In future, we may encounter more of patients who have completed

MDT but neuropathic pain may persisit and in the absence of expertise or established guidelines they may be mismanaged as reactions or relapse. Future trials should pay more attention to non-clinical aspects, such as costs and impact on quality of life, because these are highly relevant indicators for both policy makers and participants. With the expertise that is available to intensify research, we continue to anticipate that a more effective treatment will eventually be developed to address the risk and management of reactions and NFI. Deformities in leprosy cases affect the image of the disease and impact of health programme in the minds of people. While millions of cases of leprosy have been treated, there still remain a considerable number of cured leprosy patients with disabilities who will need physical and socio-economic rehabilitation. The Government of India has adopted an approved plan for disability prevention and medical rehabilitation[76,77]. Objectives of prevention of disabilities are preservation of nerve function, preservation of vision, to regain functional ability and self-esteem. Early detection and treatment with MDT will remain the best strategy for preventing the occurrence of disabilities. Other measures include training of leprosy patients to perform self-care practices, providing them with protective aids and referring the cases for surgery if indicated. Counselling and holding care and concern camps for prevention of disability (POD) are very much integrated with the prevention of disabilities. The problem, in social, economic and human terms is enormous and will need many partners to solve it, including the affected communities[77]. It is predicted that there will be approximately one million cases with WHO grade-2 deformities in the year 2020[66]. Prevention of deformities may not require advanced technology but will require advanced thinking[67].

A comprehensive approach to rehabilitation is needed to maximize the benefit for the individual, family and society at large. Physical rehabilitation includes physiotherapy and occupational therapy, orthotics and prosthetic services, assistive and protective devices and sometimes corrective surgery. Social and economical rehabilitation aims at social integration, equal opportunities and economic advancement[76]. Community based rehabilitation (CBR) approach emphasizes community participation and empowerment of the individual involved. Poverty has been identified as one of the major problems causing and aggravating disability. Addressing poverty is, therefore, an essential part of rehabilitation. Government of India (GOI)/State Government should have more schemes for providing financial support to disabled persons. We have to ensure that persons affected with leprosy are also included in these schemes[78].

The Ministry of Health & Family Welfare and Ministry of Social Justice and Empowerment, GOI are expanding rehabilitation services to the persons with disabilities. For example, Ministry of Health & Family Welfare is under the process of establishing physical medicine and rehabilitation department in medical colleges and regional hospitals. Additional support is being provided to institutions carrying out polio disability related corrective surgeries. In addition, there are several NGOs /institutions supported by the Leprosy Mission of India and the International Federation of Anti-Leprosy Association (ILEP) partners for carrying out rehabilitation services[77].

Persons affected by leprosy, who are in need of rehabilitation, should have access to any existing (general) rehabilitation services. Similarly, where leprosy specific rehabilitation services are available, people with other disabilities should be given access. This facilitates integration, helps to break stigma and promotes sustainability of rehabilitation services. Harmonization of rehabilitation services provided by public and private sectors would be crucial in making such services a realty.

The ultimate goal of all these rehabilitation activities is empowerment of the disabled by providing them with the tools they need to attain independence and self determination. We need empowerment measurement tools, such as the Empowerment Scale of Rogers to assess the efficacy of these interventions. These tools should be adapted to the context people live in, with factors such as religion, social beliefs and social habits being embedded in them. This is an important concept that should be utilized in assessing the impact of various rehabilitation programmes[79].

The World Health Organization's 2011-2015 global strategy for leprosy control focuses on reducing the rate of new leprosy cases with grade-2 disabilities per 100 000 population by at least 35 per cent of 2010's level by the end of 2015[66]. Achieving such reduction would indicate that leprosy is being detected and treated early, before nerve damage leading to stigmatizing deformities can develop. Successive public health movements have eroded adverse socio-religious construct of leprosy-related stigma. Given that a major contemporary precursor of stigma is deformities, emphasis on integrated management at

primary (vaccination), secondary (effective multi-drug chemotherapy delivered through primary health care units) and tertiary (surgical rehabilitation) prevention levels is the most comprehensive approach so far to control leprosy and address leprosy-related stigma. More efforts are required to integrate community arts into leprosy stigma reduction, as well as actively involve people affected by leprosy in stigma reduction initiatives[80].

Relapse and resistance in post-elimination era

Bacterial persistence and relapse due to persisters is another unsolved problem. Contrary to expectations, use of MDT has not solved the problem of persistence of *M. leprae*, that by definition are drug sensitive organisms which remain dormant[81]. Understanding the biology of dormant organism is important and needs to be addressed at a different level. Findings from a prospective cohort study indicated a poor sterilizing effect of a 12-month MDT regimen in MB cases[82]. Over 15 per cent of 65 borderline lepromatous (BL) cases assessed at 6 months post-release from 12 months MDT regime showed presence of viable *M. leprae* as evidenced by the growth in foot pads of non-immunosuppressed mice[82]. This suggests that long term follow up of multibacillary cases is required after they complete their treatment.

There is a lack of an efficient surveillance system for relapse, drug resistance and treatment dropouts. Also, there is no recording and tracking system to assess the number of patients who discontinued their treatment. This is a matter of concern in view of the public health risk posed by the likelihood of infection due to active relapse cases and treatment dropouts. Relapses following MDT in both PB and MB cases are being reported worldwide, and so is the stray incidence of resistance of *M. leprae*, proven either in the mouse foot pad or using molecular tools[83,84]. Relapse statistics are of considerable interest, because of their potential relevance to drug resistance. In 2011, 690 relapses were reported from India which is probably much less than the actual numbers due to lack of defined criteria for relapse and inability of the field staff to suspect relapse[7].

The multi-drug therapy which has worked successfully against leprosy for the last three decades and is likely to do so for many more years, is not fully protected against the usual fate of first line drugs, *i.e.* resistance. We should be prepared with alternative regimens that are as robust as MDT in case the problem of resistance to first line drugs emerges. There are newer regimens available to treat leprosy, but rifampicin is still considered as the sheet anchor in the treatment of leprosy. Although rifampicin resistance has not yet been reported to occur on a larger scale, we should be aware of this possibility in future and evolve alternative strategies. Emergence of rifampicin resistance would create a lot of difficulties for an individual patient, and its widespread dissemination would pose a problem to the community and a threat to leprosy control. Secondary rifampicin resistance could probably exist in patients who have relapsed after completion of MDT. Although rifampicin resistance was not reported in any of the more than 10 million patients who completed MDT, this could be due to two reasons: *(i)* Post-MDT surveillance for relapse has been discontinued in many parts and the names of the patients who complete their treatment are removed from the records, and *(ii)* Rifampicin susceptibility testing is difficult to carry out. Mouse foot pad culture is cumbersome and a lengthy procedure. However, newer modalities like PCR-based DNA sequence analysis of the *rpoB* gene of *M. leprae* are sensitive and specific and easy to use with faster results. Wider use of these new molecular methods for evaluating drug resistance is required to keep a vigil on drug resistance[85]. There have been some reports on multidrug resistance in *M. leprae*. Besides resistance to rifampicin, the resistance was also seen to one or more drugs other than dapsone, including ofloxacin and sparfloxacin[86,87]. Though the number of multidrug-resistant strains is small, their occurrence is an alarm bell and must be closely monitored. In a recent study, across three countries it was found that from new cases 3 per cent were dapsone-resistant and 2 per cent were rifampicin-resistant. In samples from relapsed patients, 15 per cent were dapsone-resistant and 8 per cent were found to be rifampicin-resistant[88].

Acknowledging the seriousness of the matter, the WHO now has taken an initiative for drug resistance surveillance using molecular tools[89]. There is also a need for backing this study with a broader understanding of drug resistance pattern and state of persistence of *M. leprae* and correlation with clinical outcomes.

Vaccines in leprosy: advances and hurdles

More than 18 million cases have been detected and treated with MDT between 1982 and 2011. Nevertheless, many new cases are still detected yearly and future projections of the global leprosy burden

indicate that at least 5 million new cases will arise between 2000 (the year of leprosy elimination) and 2020[90]. Population health experts believe that further progress toward eradicating leprosy is dependent on better understanding and new tools to interrupt its transmission. Such tools include more sensitive diagnostic and epidemiological approaches, better chemotherapeutic regimes, immunotherapy and vaccination. We need an effective vaccine with potential for both prophylactic and therapeutic use to prevent the re-emergence of leprosy and to further help in efforts toward eradication.

A prophylactic vaccine should protect against both drug-susceptible and drug-resistant strains and so help curb the emergence of drug resistance. However, immunoprophylaxis in leprosy continues to be largely speculative because of the defiance of Koch's postulates by *M. leprae* and recovery of the organism *in vitro* has been the major handicap in the preparation of a "lepra vaccine". The vaccine that has been studied most in leprosy is BCG. Experience with BCG vaccination for leprosy remains enigmatic in that levels of protection vary from 20 to 80 per cent[90]. Mass BCG vaccination for the prevention of tuberculosis (TB) at national levels has had a positive effect on leprosy decline and is often overlooked as an important factor in current leprosy control programmes. However, randomized cluster studies show that re-vaccination with BCG has no additional protective effect against leprosy[91]. Because BCG provides incomplete protection against both TB and leprosy, newer more effective vaccines are being developed. The impact that application of these vaccines will have on current leprosy control programmes is unclear. Nevertheless, several other biologically identical organisms such as the BCG + *M. leprae*, Indian Cancer Research Centre (ICRC) vaccine and *Mycobacterium W (Mycobacterium indicus pranii)* vaccine were used for the purpose, with equivocal outcome[90,92]. New approaches to identify genes from completed *M. leprae* genome sequences are being applied using standardized bioinformatic tools[92].

Immunotherapy with vaccines is another aspect that needs to be evaluated in field conditions. A therapeutic vaccine can be used to supplement MDT in patients with multibacillary leprosy that can take care of the immunological unresponsiveness seen in this subset of patients. Examples of the successful use of a therapeutic vaccine to enhance leprosy chemotherapy include *Mycobacterium W*, BCG and other vaccines in combination with BCG[92-96]. The immunotherapy treated patients has been shown to have accelerated granuloma clearance, histological upgrading and non-specific healing without granuloma formation compared with the control group. Thus, rather than causing reactions, the addition of immunotherapy actually reduced the frequency of type-2 reactions and time period of reactions by 33 per cent in addition to accelerated bacterial clearance[93-96].

Leprosy eradication - real or statistical?

The most striking trend in global leprosy in recent years is the decreased prevalence in India. India's contribution to the global leprosy burden has declined from 73 to 54 per cent of the total newly detected leprosy cases over these years[7]. It is unclear of the extent to which this decline reflects changes in ascertainment and criteria for new cases to be counted especially in India. It is doubtful whether single lesion cases are being systematically counted[90,97]. Without such information, this important trend in India's statistics remains difficult to interpret. Leprosy statistics pose particular problems for surveillance for several reasons[98]. There are problems with diagnosis and classification of the disease in the field even in good programmes. Then stigma and confidentiality also affect reporting practices and official data. There have been major operational changes in the recent years in many countries. There are often delays in reporting from some countries. Statistics have emphasized only prevalence, which is difficult to interpret. Political pressures associated with elimination initiative, appear to have influenced the manner of reporting statistics[90,98].

Terminology of elimination of diseases as a public health problem comprises two important facets of elimination strategy namely elimination of disease and elimination of infection. While elimination of diseases is defined as the reduction to zero of the incidence of a specified disease in a defined geographical region, elimination of infection is defined as a reduction to zero incidence of infection caused by a specific agent as the result of deliberate efforts. In both cases continued intervention measures are required. In case of leprosy, elimination efforts were directed to control the diseases rather than infection, by using prevalence instead of incidence of disease[99]. Further, it appears that people, including health planners and those who fund health care, have not understood the concept of elimination being equated to a prevalence of < 1 case per 10 000 population, thinking instead that it means an absence of active cases[9,99]. Using the global population as the denominator, it was possible to declare the global elimination of leprosy as achieved by the year

2000. However, when we consider the epidemiological concept of "new case detection rate (NCDR)", it was observed that this rate continued to increase in some settings, such as in Bahia, Brazil, where it increased from 0.2 to 1.4 cases per 10,000 population between 1974 to 1997 despite no significant change in case finding strategies[9]. Even in India, in contrast to the sharp decline in leprosy prevalence, NCDR has remained stable[7]. These counterintuitive findings indicate that achievement of the leprosy elimination goal should not be construed as implying that leprosy is no longer a public health problem[9].

Though the target of leprosy elimination was achieved at national level in 2005, a large proportion of leprosy cases reported globally still come from India. In 2012, of the 219, 075 new cases reported globally, 127, 295 were detected in India. Among them 10 per cent were children which strongly indicates that active transmission is occurring[7]. The reduction in registered prevalence is, therefore, clearly not based only on a declining incidence, and can be explained by the shortening of treatment duration and cleaning of the registers[81,90,97].

The combination of biological and epidemiological evidence suggests that the leprosy cannot be eliminated by MDT alone[99,100]. Some people are of the opinion that leprosy should be grouped under the chronic stable diseases that are being successfully controlled. This disheartening scenario has led many to consider the alternative to elimination or the concept of "living with leprosy" but rendering it harmless. Recognizing the high cost and apparent futility of elimination campaigns in the most highly leprosy-endemic regions of the world, this approach calls for improved tools for management of the infection and its complications and better methods for the prevention and treatment of nerve injury. Both of these paradigms, as well as the tension between these, reflect the continuing challenges of leprosy[26,100]. The evaluation report by Global Alliance to Eliminate Leprosy recommended that the WHO should pass a resolution that makes it clear to the world that leprosy has not been eliminated[100-103].

Eradication of leprosy may be a politically desirable aspiration but the scientific case for such a strategy cannot be justified at the moment[104]. Major research advances in developing new diagnostic and epidemiologic tools, chemoprophylactic regimens and vaccine are needed to develop an eradication strategy[105]. It might be more productive to work towards overcoming our knowledge gaps with regard to leprosy microbiology and therapy.

The decision regarding declaration of strategies pertaining to eradication, elimination or control of a disease should be open to scientific scrutiny and techno-managerial considerations. The approach should be thoroughly professional and scientific. Political spicing or value addition in the form of "a strong political will" or "political commitment" may be more desirable[9].

Sustaining progress and future efforts

Although in the last two decades, the reported global prevalence of active leprosy infection has dropped by almost 90 per cent; yet a parallel drop in the incidence or new case detection has not been seen. From 1994 through 2011, the NCDR has persistently been more than 10 >100,000 new cases annually[7]. The last three decades brought a tremendous and hard-earned success in fighting leprosy, thanks to the impressive co-operation of various highly committed actors from civil society, government, and the private sector. As the last mile is always the hardest to go, a fresh and future-oriented debate about sustainability is highly desirable at this point in the campaign against this disease.

The Global Strategy (2006-2010) defines sustainability as 'the capacity of a programme to maintain quality and coverage of services at a level that will provide continuing control and further reduction of a health problem at a cost that is affordable to the programme and the community"[65]. This is a major challenge for leprosy having changed from a well-supported, high priority specialized programme to one that is now mainly integrated within general health and social services. Radical re-thinking is necessary if we want to sustain early case detection, treatment, prevention of disability, and reduction in the consequences of leprosy including stigma. Anti-leprosy work keeps aiming at rapidly pushing the disease further and further back. Thus, in this context sustaining exactly the same efforts as in the past is not enough and future success will depend on changing familiar patterns and approaches, keeping in mind the resources needed[106,107].

Sustainability is a huge challenge to all leprosy activities everywhere. It is a common problem for all elimination and eradication programmes that have made great progress but now find it harder as the problem appears to get smaller, polio eradication being a good example where the end-game seems tough. The

priority of leprosy relative to other health problems in a country diminishes as the number of new cases comes down, and the cost per patient treated increases steadily[106].

The key approach to sustainability has been integration of the delivery of leprosy services into basic health and primary care. Sustainability is fundamentally an ecological concept, but when applied to health care, it tends to largely focus on financing. We want to ensure that leprosy funds do not find their way to assisting other programmes. Integrated programmes often become what has been termed 'combined vertical programmes'[108] rather than truly integrated. However, many previous vertical programmes like leprosy are trying to integrate into the weak, fragile infrastructure of primary health care. Integration can only be successful if the primary health services are strong or competent enough to cope with this integration.

A second view might reveal, for instance, that the leprosy-related portion of a national health budget should not only be based on the current situation, weighing the leprosy burden against that of other diseases. There is a potential risk that this progress will lessen the perception of the benefit in continuing to spend resources on leprsoy, as other competing priorities (*e.g.*, human immunodeficiency virus/ acquired immunodeficiency syndrome, malaria, and tuberculosis) may appear to be of relatively greater importance. We should not forget the resurgence of drug-resistant tuberculosis in the USA after public health resources were diverted to other priorities. This implies the need for allocation of appropriate resources to leprosy to enable the care givers to manage permanent disabilities in one to two million individuals around the globe[20]. However, management of leprosy requires both treating the bacterial infection as well as minimizing the potential for permanent nerve damage and subsequent impairment. Thus today's window of opportunity requires more resources than a short-term analysis would indicate.

Another possibility that needs to be considered is the paradoxical delay in treatment and subsequent increase in the severity of impairment. As a disease or condition becomes more rare, it takes a higher index of suspicion for a treating physician to appropriately diagnose or refer a patient for care. Leprosy is rare in America and the average time from initial presentation to diagnosis is about two years[109] and during this period of missed diagnosis, there is a risk of avoidable permanent tissue and nerve damage. We can assume that a lowered index of suspicion and delay in diagnosis may lead to increase in proportion of multibacillary cases and increased incidence of disability in some countries where even marked success in treating leprosy has occurred[20,110].

Leprosy programmes have been slow to develop areas such as integration, multi-disciplinary research, involvement of people affected with and by leprosy, community-based rehabilitation and community participation. Many of these changes potentially threaten the position of those responsible for leprosy activities; we can be as isolated in our thinking and methods as people affected by leprosy. Research is a good example; leprosy research centres have become progressively isolated, using old technology, with little significant output[111]. There is sometimes even criticism when leprosy researchers work in any other area than leprosy. Yet, the reality is that leprosy research is most productive when it is conducted in a multidisciplinary research environment which exchanges ideas, technologies and resources with other research areas[111,112].

Prevention of disability is one area that has been innovative, with self-care, community and family involvement, participation of groups of people affected by leprosy, and the use of available, affordable, acceptable appliances such as footwear. For sustainable prevention of disability the ownership of prevention of disability has to pass to people and communities[113,114]. Advocacy must play an increasing role to bring about change. It involves influencing those who are responsible to ensure that leprosy is included in health care and social care, and that people affected are fully included in all aspects of society[106]. Ever since John Snow produced his famous cholera maps of London in 1854, mapping of diseases has been recognized as an essential tool in public health. The latest tool for this pupose is the Geographical Information System (GIS) which besides mapping diseases, manages, analyses and presents data that are linked to geographical locations. Its specific strength is that it can visualise, establish relationships and analyse different features that share the same location. GIS has become an essential tool to be used with care and wisdom to establish the burden of disease, identify risk factors, and to plan, monitor and evaluate control interventions[115].

Conclusion

Leprosy (or Hansen's disease) is one of the oldest and notorious, but least understood diseases of man

which continues to be a challenge to health worldwide, with about 250,000 new cases being currently detected every year. A third of newly diagnosed patients have nerve damage and might develop disabilities, although the proportion varies according to several factors, including level of self-care[116]. Leprosy was not a specified disease in the Millennium Development Goals, but improvements in other areas these cover, such as education and levels of poverty will help leprosy patients and services.

Mahatma Gandhi's dream of ''Empowerment of People Affected by Leprosy,'' can only be fulfilled by removing the stigma associated with leprosy and giving them equal rights. On 30th September 2010, a set of Principles and Guidelines on the Elimination of discrimination against persons affected by leprosy and their family members was approved with the Human Rights Council's adoption of the resolution (A/HRC/15/L.18)[117]. These guidelines should be implemented and patients with leprosy or disabilities due to leprosy should be given the rights to work, serve the public, on an equal basis with others.

We have won the battle but the war is still on and there is a need for research on early diagnosis, treatment, and prevention, such as further use of molecular analysis of the *M. leprae* genome, implementation of BCG vaccination, and administration of chemoprophylaxis or effective immunoprophylaxis to household contacts. There is a need to sustain and provide quality leprosy services to all persons through general health system, including good referral system. Efforts need to be made to reduce deformity through early detection, self care, physiotherapy and reconstructive surgery and developing sound surveillance systems.

Hopefully, the progress made to date will be maintained rather advanced through the application of the sustained political will of governments, ongoing research into basic understanding of the disease and improved treatments or vaccines. The most important step in eradication of any communicable disease is to knock out the last case. This can be achieved essentially by community participation for which vigorous information, education, communication (IEC) activities are required. It is only the enlightened public that can provide the solution to any social or public health problem.

With all the remarkable achievements in the fight against leprosy, the stage is now set for the final assault. It is hoped that the disease will be eradicated in the near future. The health authorities are highly capable and are fully armed, with political will that has sustained the NLEP all these years, India could well be leprosy-free - finally.

References

1. Pandya SS. Historical background. In: Kar HK, Kumar B, editors. *IAL textbook of leprosy*. New Delhi: Jaypee; 2008. p. 1-18.
2. World Health Organization. *Global strategy for further reducing the leprosy burden and sustaining leprosy control activities (plan period: 2006-2010)*. Geneva: WHO; 2005.
3. Bhattacharya SN, Sehgal VN. Reappraisal of the drifting scenario of leprosy multi-drug therapy: new approach proposed for the new millennium. *Int J Dermatol* 2002; *41* : 321-6.
4. Becx-Bleumink M. Duration of multi-drug therapy in paucibacillary leprosy patients; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation training Center (ALERT) in Ethiopia. *Int J Lepr* 1992; *60* : 436-44.
5. Becx-Bleumink M. Relapses amongst leprosy patients treated with multi-drug therapy; experience in the leprosy control program of the All Africa Leprosy and Rehabilitation Training Center (ALERT) in Ethiopia; practical difficulties with diagnosing relapses; operational procedures and criteria for diagnosing relapses. *Int J Lepr* 1992; *60* : 421-35.
6. Bhattacharya SN, Sehgal VN. Leprosy in India. *Clin Dermatol* 1999; *17* : 159-70.
7. World Health Organization. Global leprosy situation 2012. *Wkly Epidemiol Record* 2012; *34* : 317-28.
8. Dowdle WR. The principles of disease elimination and eradication. *Bull World Health Organ* 1998; *76* : 22-5.
9. Patro BK, Madhanraj K, Singh A. Is leprosy 'Elimination' a conceptual illusion? *Indian J Dermatol Venereol Leprol* 2011; *77* : 549-51.
10. Robbins G, Tripathy VM, Misra VN, Mohanty RK, Shinde VS, Gray KM. *et al*. Ancient skeletal evidence for leprosy in India (2000 B.C.). *PLoS One* 2009; 4.
11. Monot M, Honore N, Garnier T, Araoz R, Coppée JY, Lacroix C, *et al*. On the origin of leprosy. *Science* 2005; *308* : 1040-2.
12. Browne SG. The history of leprosy. In: Hastings RC, editor. *Leprosy*, 1st ed. Edinburgh: Churchill Livingstone; 1985. p. 1-14.
13. Trautman JR. A brief history of Hansen's disease. *Star* 1990; *50* : 3-16.
14. Gussow Z. *Leprosy, racism and public health: social policy in chronic disease control*. Boulder, Colo: Westview Press; 1989.
15. Awofeso N. Leprosy control, public health paradigms and stigma. *Aust NZ J Public Health* 2011; *35* : 9-11.
16. Jacob JT, Franco-Paredes C. The stigmatization of leprosy in India and its impact on future approaches to elimination and control. *PLoS Negl Trop Dis* 2008; *2* : e113.
17. Short RA. *The Bible and modern medicine*. London: Paternoster Press; 1953. p. 77.

18. Feeny P. *The fight against leprosy*. New York: American Leprosy Missions; 1964.
19. Brown W. Can social marketing approaches change community attitudes towards leprosy? *Lepr Rev* 2006; *77* : 89-98.
20. Bennett BH, Parker DL, Robson M. Leprosy: Steps along the journey of eradication. *Public Health Rep* 2008; *123* : 198-205.
21. Carter HV. *On leprosy and elephantiasis*. Eyre and Spottiswoode; 1874. p. 211.
22. Carter HV. "Note on the Pathology of Leprosy", Maharashtra State Archives General Department, Publication No: 14494, Appendix p. 7, 1883.
23. Lockwood DNJ, Sarno E, Smith WC. Classifying leprosy patients - searching for the perfect solution? *Lepr Rev* 2007; *78* : 317-20.
24. Dharmendra, Leprosy Classification. In: Hastings RC, editor. *Leprosy*, 2nd ed. Edinburgh: Churchill-Livingstone; 1994.
25. Ridley DS, Jopling WH. Classification of leprosy according to immunity. A five-group system. *Int J Lepr Other Mycobact Dis* 1966; *34* : 255-73.
26. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. *Clin Microbiol Rev* 2006; *19* : 338-81.
27. Montoya D, Modlin RL. Learning from leprosy: Insight into the human innate immune response. *Adv Immunol* 2010; *105* : 1-24.
28. Skinsnes OK. Origin of chaulmoogra oil - another version. *Int J Lepr* 1972; *40* : 172-3.
29. Bhishagratna KK. *The Sushruta Samhita*, vol. II. Varanasi: Chowkhamba Sanskrit Series Office; 1963. p. 36-40.
30. WHO. *Chemotherapy of leprosy for control programmes*. WHO Tech Rep Ser No.675. Geneva: WHO; 1982. p. 1-33.
31. Rogers L. The treatment of leprosy, *Indian Medical Gaz*, April 1920, *4* : 125-8.
32. Cochrane RG. A comparison of sulphone and hydnocarpus therapy of leprosy. *Int J Lepr* 1948; *16* : 139-44.
33. Anonymous. *Chemotherapy of leprosy*. Report of a WHO Study Group. WHO Tech Rep Ser 847. Geneva: WHO; 1994. p. 1-24.
34. Pettit JHS, Rees RJW. Studies on sulphone resistance in leprosy. An experimental and clinical study. *Lancet* 1964; *26* : 673-4.
35. Pearson JM, Haile GS, Rees RJ. Primary dapsone resistant leprosy. *Lepr Rev* 1977; *48* : 129-32.
36. Sansarricq H. Leprosy in the world today. *Lepr Rev* 1981; *52* : 15-31.
37. Pettit JH, Rees RJ. Studies in sulfone resistance in leprosy with the riminophenazine derivative B 663. *Int J Lepr* 1966; *34* : 391-7.
38. Waters MF, Laing AB, Rees RJ. Proven primary dapsone resistance in leprosy- a case report. *Lepr Rev* 1978; *49* : 127-30.
39. World Health Organization. *Report of the third meeting of the Scientific Working Group (SWG) on the Chemotherapy of leprosy (THELEP)*, document TDR/THELEP-SWG/80.3; 1980.
40. Gautam VP. Treatment of leprosy in India. *J Postgrad Med* 2009; *55* : 220-4.
41. Sehgal VN, Sardana K, Dogra S. The imperatives of leprosy treatment in the pre- and post-global leprosy elimination era: Appraisal of changing the scenario to current status. *J Dermatol Treat* 2008; *19* : 82-91.
42. Levy L, Shepard CC, Fasal P. The bactericidal effect of rifampicin on *M. leprae* in man: A) single doses of 600, 900 and 1200 mg; and b) daily doses of 300 mg. *Int J Lepr Other Mycobact Dis* 1976; *44* : 183-7.
43. Browne SG, Hogerzeil LM. "B-263" in the treatment of leprosy: Preliminary report of pilot trial. *Lepr Rev* 1962; *33* : 6-10.
44. Rees RJ, Pearson JM, Waters MF. Experimental and clinical studies on rifampicin in the treatment of leprosy. *Br Med J* 1970; *1* : 89-92.
45. Leiker DL, Kamp H. First results of treatment of leprosy with Rifadin. *Lepr Rev* 1970; *41* : 25-30.
46. Minutes of the seventh meeting of the Steering Committee of the Chemotherapy of Leprosy (THELEP) Scientific Working Group, Geneva, April 24-25, 1980. Geneva, World Health Organization (restricted document). Annex: General protocol for field trials of chemotherapy of multibacillary leprosy.
47. *WHO expert committee on leprosy*. 6th Report, WHO Tech Rep Ser No. 768. Geneva: WHO; 1988.
48. *WHO expert committee on leprosy*. 7th Report 9 WHO Tech Report Ser No. 874. Geneva: WHO; 1998.
49. Richardus JH, Habbema JDF. The impact of leprosy control on the transmission of *M. leprae*: is elimination being attained? *Lepr Rev* 2007; *78* : 330-7.
50. Meima A, Gupte MD, van Oortmarssen GJ, Habbema JD. Trends in leprosy case detection rates. *Int J Lepr Other Mycobact Dis* 1997; *65* : 305-19.
51. Fine PE, Warndorff DK. Leprosy by the year 2000 - what is being eliminated? *Lepr Rev* 1997; *68* : 201-2.
52. Smith WC. We need to know what is happening to the incidence of leprosy. *Lepr Rev* 1997; *68* : 195-200.
53. Anonymous. Report of the International Leprosy Association Technical Foum. 25-28 February 2002. Paris, France. *Lepr Rev* 2002; *73* (Suppl): S3-61.
54. Meima A, Richardus JH, Habbema JD. Trends in leprosy case detection worldwide since 1985. *Lepr Rev* 2004; *75* : 19-33.
55. Ji B, Jamet P, Perani EG, Sow S, Lienhardt C, Petinon C, *et al*. Bactericidal activity of single dose of clarithromycin plus minocycline, with or without ofloxacin, against *Mycobacterium leprae* in patients. *Antimicrob Agents Chemother* 1996; *40* : 2137-41.
56. Banerjee DK, McDermott-Lancaster RD, McKenzie S. Experimental evaluation of possible new short-term drug regimens for treatment of multibacillary leprosy. *Antimicrob Agents Chemother* 1997; *41* : 326-30.

57. Ji B, Grosset JH. Combination of rifapentine - moxifloxacin-minocycline (PMM) for the treatment of leprosy. *Lepr Rev* 2000; *71* (Suppl): 581-7.
58. Daumerie D. Current World Health Organization-sponsored studies in the chemotherapy of leprosy. *Lepr Rev* 2000; *71* : S88-90.
59. Ji B. Prospects for chemotherapy of leprosy. *Indian J Lepr* 2000; *72* : 187-98.
60. Pattyn SR. Search for effective short-course regimen for the treatment of leprosy. *Int J Lepr* 1993; *61* : 76-81.
61. Pattyn S, Grillone S. A 6 weeks quadruple drug regimen for the treatment of multi-bacillary leprosy. *Lepr Rev* 2000; *71* : 43-6.
62. Grosset JH. The new challenges for chemotherapy research. *Lepr Rev* 2000; *71* (Suppl): 100-4.
63. Joshi PL.National Leprosy Eradication Programme and new paradigms; In: Kar HK, Kumar B, editors. *IAL textbook of leprosy*. New Delhi: Jaypee; 2008. p. 35-43.
64. Desikan KV. Elimination of leprosy & possibility of eradication - the Indian scenario. *Indian J Med Res* 2012; *135* : 3-5.
65. WHO/SEARO. Regional strategy for sustaining leprosy services and further reducing the burden of leprosy - 2006-2010. SEA-LEP-162. 2009. p. 1-21.
66. World Health Organization. *Enhanced global strategy for further reducing the disease burden due to leprosy 2011-2015*. SEAGLP- 2009. p. 3.
67. Jacob JT, Franco-Paredes C. The stigmatization of leprosy in India and its impact on future approaches to elimination and control. *PLoS Negl Trop Dis* 2008; *30* : e113.
68. Becx-Bleumink M, Berhe, D. Occurrence of reactions, their diagnosis and management in leprosy patients treated with multidrug therapy: experience in the Leprosy Control Program of the All Africa leprosy and Rehabilitation Training Center (ALERT) in Ethiopia. *Int J Lepr Other Mycobact Dis* 1992; *60* : 173-84.
69. Lienhardt C, Fine, PEM. Type 1 reaction, neuritis and disability in leprosy. What is the current epidemiological situation? *Lepr Rev* 1994; *65* : 9-33.
70. Van brakel WH, Khawas IB, Lucas S. Reactions in leprosy: an epidemiological study of 386 patients in West Nepal. *Lepr Rev* 1994; *65* : 190-203.
71. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. *Int J Lepr Other Mycobact Dis* 2004; *72* : 125-33.
72. Van Veen NH, Lockwood DN, Van Brakel WH, Ramirez J Jr, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. *Lepr Rev* 2009; *80* : 355-72.
73. Shetty VP, Khambati FA, Ghate SD, Capadia GD, Pai VV, Ganpati R, *et al*. The effect of corticosteroids usage on bacterial killing, clearance and nerve damage in leprosy; Part 3 - Study of two comparable groups of 100 multibacillary (MB) patients each, treated with MDT + steroids versus MDT alone, assessed at 6 months post-release from 12 months MDT. *Lepr Rev* 2010; *81* : 41-58.
74. van Veen NH, Nicholls PG, Smith WC, Richardus JH. Corticosteroids for treating nerve damage in leprosy. A Cochrane review. *Lepr Rev* 2008; *79* : 361-71.
75. Saunderson P, Bizuneh E, Leekassa R. Neuropathic pain in people treated for multibacillary leprosy more than ten years previously. *Lepr Rev* 2008; *79* : 270-6.
76. Mahato ME. Disability prevention and medical rehabilitation (DPMR) - prevention of disability and timely referral in leprosy. *J Indian Med Assoc* 2006; *104* : 682-5.
77. *NLEP-Operational guidelines. Disability prevention & medical rehabilitation*. New Delhi: Central Leprosy Division, Directorate General of Health Services; 2007.
78. Ganapati R, Pai VV. Community based comprehensive leprosy work. In: Kar HK, Kumar B, editors. *IAL textbook of leprosy*. New Delhi: Jaypee; 2008. p. 538-44.
79. Bakker L ,Van Brakel WH. Empowerment assessment tools in people with disabilities in developing countries. A systematic literature review. *Lepr Rev* 2012; *83* : 129-53.
80. Awofeso N, Rammohan A. Community arts and health advocacy in HIV/AIDS activism. *Hektoen Int* 2010. Available from: *http://www.hektoeninternational.org/kindredparadigms_ AIDSadvocacy.html*, accessed on October 18, 2012.
81. Shetty VP. Challenges facing the control of leprosy in the Indian context. *Ann Acad Med Singapore* 2010; *39* : 1-3.
82. Sharma A, Sharma VK, Rajwanshi A, Das A, Kaur I, Kumar B. Presence of *M. laeprae* in tissues in slit skin smear negative multibacillary (MB) patients after WHO-MBR. *Lepr Rev* 1999; *70* : 281-6.
83. Maeda S, Matsuoka M, Nakata N, Kai M, Maeda Y, Hashimoto K, *et al*. Multidrug resistant *Mycobacterium leprae* from patients with leprosy. *Antimicrob Agents Chemother* 2001; *45* : 3635-9.
84. Shetty VP, Wakade AV, Ghate S, Pai VV, Ganapati R, Antia NH. Viability and drug susceptibility testing of *M. leprae* using mouse footpad in 37 relapse cases of leprosy. *Int J Lepr Other Mycobact Dis* 2003; *71* : 210-7.
85. Honorı N, Cole ST. Molecular basis of rifampin resistance in *Mycobacterium leprae. Antimicrob Agents Chemother* 1993; *37* : 414-8.
86. Cambau E. Molecular detection of rifampin and ofloxacin resistance for patients who experience relapse of multibacillary leprosy. *Clin Infect Dis* 2002; *34* : 39-45.
87. Matsuoka M, Kashiwabara Y, Namisato M. A *Mycobacterium leprae* isolate resistant to dapsone, rifampin and sparfloxacin. *Int J Lepr Other Mycobact Dis* 2000; *68* : 452-5.
88. Matsuoka M, Budiawan T, Aye KS, Kyaw K, Tan EV, Cruz ED, *et al*. The frequency of drug resistance mutations in *Mycobacterium leprae* isolates in untreated and relapsed patients from Myanmar, Indonesia and the Philippines. *Lepr Rev* 2007; *78* : 343-52.
89. WHO. *Guidelines for global surveillance of drug resistance in leprosy*. SEA-GLP-2009.2. Geneva: WHO; 2009.
90. Prasad P, Kaviarasan PK. Leprosy therapy, past and present: Can we hope to eliminate it? *Indian J Dermatol* 2010; *55* : 316-24.
91. Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, Maroja Mde F, *et al*. BCG revaccination does not protect against leprosy in the Brazilian amazon: A cluster randomized trial. *PLoS Negl Trop Dis* 2008; e167.

92. Duthie MS, Gillis TP, Reed SG. Advances and hurdles on the way toward a leprosy vaccine. *Hum Vaccin* 2011; *7* : 1172-83.

93. Talwar GP, Zaheer SA, Mukherjee R, Walia R, Misra RS, Sharma AK, *et al*. Immunotherapeutic effects of a vaccine based on a saprophytic cultivable mycobacterium, *Mycobacterium w* in multibacillary leprosy patients. *Vaccine* 1990; *8* : 121-9.

94. Katoch K, Katoch VM, Natrajan M, Sreevatsa, Gupta UD, Sharma VD, *et al*. 10-12 years follow-up of highly bacillated BL/LL leprosy patients on combined chemotherapy and immunotherapy. *Vaccine* 2004; *22* : 3649-57.

95. Kaur I, Dogra S, Kumar B, Radotra BD. Combined 12-month WHO/MDT MB regimen and *Mycobacterium w.* vaccine in multibacillary leprosy: a follow-up of 136 patients. *Int J Lepr Other Mycobact Dis* 2002; *70* : 174-81.

96. Narang T, Kaur I, Kumar B, Radotra BD, Dogra S. Comparative evaluation of immunotherapeutic efficacy of BCG and *Mw* vaccines in patients of borderline lepromatous and lepromatous leprosy. *Int J Lepr Other Mycobact Dis* 2005; *73* : 105-14.

97. Rao PN, Lakshmi TS. Final push of leprosy in India: What is being pushed? *Indian J Dermatol Venereol Leprol* 2005; *71* : 226-9.

98. Fine PE. Leprosy′s global statistics- still room for improvement. *Lepr Rev* 2008; *79* : 235-8.

99. Molyneux DH, Hopkins DR, Zagaria N. Disease eradication, elimination and control: The need for accurate and consistent usage. *Trends Parasitol* 2004; *20* : 347-51.

100. Lockwood DN, Suneetha S. Leprosy: Too complex a disease for a simple elimination paradigm. *Bull World Health Organ* 2005; *83* : 230-5.

101. Braber KL. An evaluation of GAEL, the Global Alliance for the Elimination of Leprosy. *Lepr Rev* 2004; *75* : 208-13.

102. Durston T. What lessons can we learn from the evaluation of GAEL? *Lepr Rev* 2004; *75* : 214-6.

103. Ji B. Comments on the report entitled ‘Independent evaluation of the Global Alliance for the Elimination of Leprosy’. *Lepr Rev* 2004; *75* : 217-20.

104. Smith C, Richardus JH. Leprosy strategy is about control, not eradication. *Lancet* 2008; *371* : 969-70.

105. Awofeso N. The place of leprosy in the control-elimination-eradication spectrum. *Bull World Health Organ* 2005; *83* : 558.

106. Smith WCS. Sustaining anti-leprosy activities requires radical changes. *Lepr Rev* 2010; *81* : 281-3.

107. Lunau Y. Sustainability in fighting leprosy - revitalising high ambitions. *Lepr Rev* 2010; *81* : 284-6.

108. Feenstra P. Sustainability of leprosy control services in low endemic situations. *Int J Lepr* 1994; *62* : 599-608.

109. Molyneux DH. “Neglected” diseases but unrecognized successes-challenges and opportunities for infectious disease control. *Lancet* 2004; *364* : 380-3.

110. Saunderson PR. Leprosy elimination: Not as straightforward as it seemed. *Public Health Rep* 2008; *123* : 213-6.

111. Curtiss R, Blower S, Cooper K, Russell D, Silverstein S, Young L. Leprosy research in the post-genome era. *Lepr Rev* 2001; *72* : 8-22.

112. Rodrigues LC, Lockwood DNJ. Leprosy now: epidemiology, progress, challenges, and research gaps. *Lancet Infect Dis* 2011; *11* : 464-70.

113. Li J, Mu H, Ke W. The sustainability of self-care in two counties of Guizhou Province, Peoples’ Republic of China. *Lepr Rev* 2008; *79* : 110-7.

114. Madhavan K, Vijayakumaran P, Ramachandran L, Manickam C, Rajmohan R, Mathew J, *et al*. Sustainable leprosy related disability care within integrated general health services: findings from Salem District, India. *Lepr Rev* 2007; *78* : 353-61.

115. Bakker MI, Scheelbeek PFD, Van Beers SM. The use of GIS in leprosy control. *Lepr Rev* 2009; *80* : 327-31.

116. Vlassoff C, Khot S, Rao S. Double jeopardy: women and leprosy in India. *World Health Stat Q* 1996; *49* : 120-6.

117. A/HRC/15/30, annex: (English). Available from: *http://www.ilep.org.uk/fileadmin/uploads/Documents/ News_documents/ Principles_and_Guidelines_FINAL_English.pdf*, accessed on October 20, 2012.

Reprint requests: Dr Bhushan Kumar, Former Professor & Head, Department of Dermatology, Venereology & Leprology, Postgraduate Institute of Medical Education & Research, H.No. 81, Sector 16, Chandigarh 160 015, India
e-mail: kumarbhushan@hotmail.com