Early diagnosis of leprosy and the care of persons affected by the disease in a low endemic area
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CHAPTER 1

General introduction
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In 1981 an estimated 12 million leprosy cases were being treated worldwide. After the introduction of multi-drug therapy (MDT) in that year, the prevalence of leprosy declined dramatically, because of the change from life-long treatment with dapsone monotherapy to treatment of fixed duration with MDT and the changes in record-keeping. After the 44th World Health Assembly resolved to eliminate leprosy by the year 2000 and the final push toward elimination of the disease was implemented in areas worldwide where it is endemic, the number of newly detected cases further declined. In 2006 a total of 259,017 new leprosy cases were reported globally, a reduction of 13.4% compared to the number of new cases reported in 2005. At the beginning of 2007 the number of cases treated with MDT was 224,717, a reduction from the number of new cases reported in 2006. Only four countries had not achieved the elimination of leprosy, defined as less than 1 case in 10,000 population.

Despite this great progress, changing trends in case detection should be viewed with caution, since undetected cases are not included in these statistics. Furthermore, patients with leprosy are not evenly distributed in countries where the disease is endemic, particularly in those with a large population, such as India and China. Therefore, even in the post-elimination era, efforts are needed to further reduce the disease burden and to sustain control activities, including the detection of remaining hidden and new cases. Efforts are also needed to deal with problematic patients, such as whose at high risk for disability, those with drug reactions and those already disabled by leprosy. Furthermore, leprosy has not only a physical effect, but also a social and economic impact.

Clinical manifestations, classification and treatment of leprosy

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*), an acid-fast bacillus. Although its transmission is still not fully understood, the upper respiratory tract is generally considered to be the main route for the spreading of *M. leprae*. Most people have a natural resistance to the infection, and only a few have a genetically related susceptibility to it. The onset of leprosy is very insidious with a long incubation period, and it is difficult to determine the exact onset of the disease.

Clinically, leprosy can simulate many kinds of skin diseases and neuropathic problems, making early diagnosis difficult. The disease spectrum varies from a single self-healing hypopigmented macule to a generalized illness with varying degrees of nerve damage. In the late stage, it can affect bones and internal organs. Skin lesions may be hypopigmented or reddish macules, plaques, or nodules, which
may be localized or symmetrically distributed over the entire body. Peripheral nerve involvement is common and characteristic of the disease, often leading to secondary impairments that are the main cause for social and economic problems.

Various classifications of leprosy based on clinical and bacterial observations have been used. The commonly used Madrid classification is based on clinical observations. It divides cases into 4 types: indeterminate (I), tuberculoid (T), mid-borderline (B), and lepromatous (L). Each of the four classes includes subclasses according to the clinical presentations. In 1966 for the purpose of research, Ridley and Jopling proposed a 5-group classification system based on the host immune response and the histological and clinical manifestations. This classification has now been adopted all over the world. In the Ridley-Jopling system, tuberculoid (TT) leprosy and lepromatous leprosy (LL) lie at the two ends of the spectrum, each showing comparative stability of immunology in the host. At the tuberculoid pole, only a few skin lesions can be seen, and skin smears are negative. At the lepromatous pole, numerous different kinds of skin lesions are symmetrically distributed all over the body, with large amounts of bacilli revealed in the skin smears (≥5+). The borderline category stands between the two ends, with an unstable immune response to the bacilli and a variety of clinical manifestations, ranging from a few lesions with few bacilli in skin smears (borderline tuberculoid, BT) to a mid-borderline (BB) type of leprosy and, finally, to many lesions with a significant amount of bacilli in skin smears (borderline lepromatous, BL). The indeterminate (I), or early type of leprosy, can develop into any of these five categories, depending on the immunity of the host. The purely neuritic cases do not fall within this spectrum.

To prevent the drug resistance that occurs when only one drug is given, MDT was introduced in 1981. To guide this therapy, in the same year the World Health Organization (WHO) developed a 2-group classification system based on the probable number of *M. leprae* present in a patient. The patients with paucibacillary (PB) disease were treated daily with dapsone (100 mg) and monthly with rifampicin (600 mg), with 6 months of supervision. The patients with multibacillary (MB) disease were treated daily with dapsone (100 mg) and clofazimine (50 mg), as well as monthly with clofazimine (300 mg) and rifampicin (600 mg), with a minimum of 24 months of supervision or, where possible, until the skin smear became negative. In 1994, after more information was collected on the efficacy and the low risk of relapse, the duration of treatment for patients with MB leprosy was fixed at 24 months, while the regimen for those with PB disease remained at 6 months. To accelerate the elimination of leprosy in most countries where the disease is endemic, the duration of the MDT-MB regimen was further reduced to one year in 1998. However, the long-term efficacy and the risk of relapse of this shorter regimen is unknown.

In China, the Madrid classification was used from the beginning of the control programme until 1986, when MDT was implemented nationwide. At almost the same time, both the Ridley-Jopling and WHO-MDT classifications were introduced and
adopted. The national leprosy control programme in China requires that the use of both classifications.\textsuperscript{21} At present, the WHO-recommended regimen of 2 years of chemotherapy for MB patients and 6 months for PB patients is in use.\textsuperscript{22}

**Case detection**

Many methods of case detection, such as population surveys, school surveys, rapid (village) surveys (RVS), contact examination, and referral of suspected cases from general health services, have been employed. A nation's choice of method is based on the epidemiological situation and the goals of the control programme. Each of these methods has its advantages and shortcomings. Since active case detection is not cost-effective in countries where leprosy is endemically low, a control programme there should encourage self-referral by increasing public awareness of the early signs and symptoms of the disease and by removing barriers that prevent persons from reporting for examination.\textsuperscript{23}

Compared with a total population survey, RVS is a rapid, simple, and inexpensive method for detecting cases of leprosy.\textsuperscript{24,25} The main purpose of RVS is to assess the extent of the disease in a certain area (district, state, or even a country). During the RVS, only a small sample of villages, rather than the entire population, is examined.\textsuperscript{24,25} This method can also be applied as a case-finding tool in relatively low endemic conditions.\textsuperscript{24}

RVS, also known as a "clue survey" in China, has been used as a main method of case-finding.\textsuperscript{26} Any person who has signs, or "clues", of leprosy, such as lagophthalmos, claw hands, collapsed nose, foot ulcers of unknown cause and anaesthetic skin lesions, or enlarged peripheral nerves, is asked to report to the survey team. In addition, key informants, such as village leaders, rural doctors, and schoolteachers, are asked to report such a person. This method has played an important role in detection of cases in the control programme in China,\textsuperscript{26} including in Shandong.\textsuperscript{27}

The populational distribution of leprosy tends to be in clusters, and so, contact examination is important in detecting new cases. Studies have shown that physical distance, the type of leprosy in the index case, and genetic relationship are determinants for the development of leprosy.\textsuperscript{28} Thus, persons in households with leprosy patients are at increased risk for the development of the disease,\textsuperscript{28-32} and in endemic areas chemoprophylaxis has been recommended for household contacts.\textsuperscript{33,34} In China, including Shandong Province, contact examination has been one of the routine detection methods since the leprosy control programme started in the 1950s.\textsuperscript{35}
Problems in early diagnosis of leprosy

The diagnosis of leprosy must be established as early and as accurately as possible, because both under- and over-diagnosis will lead to undesired consequences for individuals as well as the community. Accurate diagnosis is also vitally important to all aspects of a control programme, including epidemiology, chemotherapy, prevention of disability, and assessment of interventions. Three cardinal signs found on clinical examination (anaesthetic skin lesions, enlarged peripheral nerves, and acid-fast bacilli in the skin smear) form the basis of the diagnosis of leprosy. Many advanced diagnostic tools have been developed, but these are used mainly in research. Serology cannot be used as a single diagnostic test because the majority of the PB patients are seronegative, and current serological tests are not specific enough to distinguish a patient with clinically overt infection from one with subclinical infection. Also, DNA amplification tests require trained personnel and expensive equipment, thus limiting their use in the field.

The diagnosis of leprosy is not straightforward because it can mimic many skin diseases, the sensory testing of a skin lesion has not been standardized, and the test result is judged subjectively rather than objectively. Therefore, several factors impact the accuracy of the testing and the palpation of peripheral nerves. Apart from the inter-examiner reliability, peripheral nerve enlargement may not be apparent in some early cases. Although a positive result on examination of skin smears has near 100% specificity in the diagnosis of leprosy, many PB patients have a negative result. To logistically ensure the quality of such an examination, the taking, staining, reading and reporting of smears must be controlled. Skin-smear examination is not usually available in general health services. Furthermore, ignorance of general health problems, lack of awareness of leprosy, and stigmatization in the general population may prevent persons from seeking help. In view of these factors, many patients visit general health care services/dermatologist several times before the diagnosis of leprosy is made, especially in a low endemic area. Delay in diagnosis will result in increased impairment of nerve functions. However, the level of impairment at the time of diagnosis cannot simply be used as a general performance indicator for programme evaluation because the degree of impairment with the same diagnostic delay in other populations can differ considerably. This is true particularly in cases of PB leprosy, indicating that other, unknown factors may also play an important role in nerve damage.

To detect the few incident patients with leprosy in a low endemic area, mobilization of general health workers and dermatologists at different levels of health care may be one option in the earlier detection of cases. On the basis of this consideration, knowledge and skills for the early diagnosis of leprosy were assessed to obtain information that could be used in the design of a training programme. Anaesthesia of skin lesions and enlarged peripheral nerves are the two main clinical signs of leprosy.
However, use of these two signs to accurately make the diagnosis depends on the reliability of the individual examination. Improved skills in the testing of skin lesions and in the palpation of peripheral nerves can increase the accuracy in the diagnosis of leprosy.

**Consequences of leprosy, prevention of disability, and socioeconomic rehabilitation**

The World Health Organization describes health as not merely the absence of disease, but ‘a state of complete physical, mental and social well being’. Leprosy is a complex condition that affects patients not only physically, but also socially and psychologically. Individuals with leprosy have been made to leave their families and communities and forced to live as outcasts in separate colonies. The stigma attached to leprosy is very common in societies around the world and has a negative impact on a patient’s health-seeking behaviour, adherence to treatment, and resumption of normal life, even after cure. It also affects one's entire life, including marriage, employment, interpersonal relationships, leisure activities, and attendance at social and religious functions. In efforts to control leprosy, the stigma is so important that many studies have been conducted to address it.

Although many factors contribute to this stigma, a complex mix of reasons is associated with it in each society. Disability (impairments) caused by peripheral nerve damage is one of the important factors. In the last two decades, much progress has been made in understanding the risk factors for nerve damage. Corticosteroids are still the mainstay in the treatment of peripheral neuropathy in leprosy. Several recently published clinical trials have tested the use of steroids to prevent immunological reactions and peripheral neuropathy prophylactically, to treat neuropathy with a duration of more than 6 months, and to treat mild sensory impairment. For those disabled before the diagnosis was made or those who have developed permanent disability during the course of the disease, projects aimed at preventing secondary impairment (prevention of disability, or POD) have been undertaken in many leprosy control programmes worldwide, including China and Shandong. Social and economic rehabilitation (SER) programmes with a community-based approach are needed to target the disadvantaged affected by leprosy (most of whom are elderly, former leprosy patients who have some degree of social and economic difficulty, with or without disability). These programmes should by nature be holistic and participatory, sustainable, integrated into existing services and provided by communities, sensitive to special needs, particularly those of women, and meaningful to the targeted individuals.

Before the era of chemotherapy, isolation of patients in specific colonies or settlements (leprosy villages or leprosaria) was used for control. Many patients were
held in these places for as long as they lived. Some countries like Japan forced this segregation by law.\textsuperscript{72} China maintained a similar policy of isolation until 1986, when the MDT was introduced. The development, role, and present status of leprosy villages/leprosaria in Shandong has been reported elsewhere.\textsuperscript{73}

**Leprosy control programme in Shandong province**

Shandong Province, a semi-island, is located in the north-eastern part of China, with a land area of 150,000 square kilometres (almost four times the size of The Netherlands). North of the Yellow River is alluvial plain; hilly terrain is found in the east, northeast, and south of the province; and the remainder is flat and fertile land. Shandong province is situated in the temperate zone, with four distinct seasons. The eastern province has an ocean climate, and the western has a continental climate.

This coastal province, with a population of 9.3 million, is divided into 17 prefectures and subdivided into 139 counties/districts. Shandong is one of the original places of Chinese culture in China, where the hometown of Confucius is located. According to the record in “Lunyu” (503 CE), Confucius’ student, Yan Geng (Yan Boniou), suffered from leprosy.\textsuperscript{74} This may be the first recorded case of leprosy in China.

As throughout China, the leprosy control programme in Shandong Province was started in the 1950s. The epidemiological situation and associated factors in the province have been reported,\textsuperscript{75,76} and the policies, strategies, and activities have been described elsewhere.\textsuperscript{77} Briefly, after more than 40 years’ effort in combating the disease, the epidemic of leprosy appears to be under control, i.e., the prevalence of leprosy has fallen below 1/10,000, and the goal of elimination was achieved in 1994. In the past 10 years, on average, approximately 50 new cases have been detected each year. Since 1995, several collaborative projects with foreign missionaries and the provincial disabled federation on POD have been conducted for those who are disabled. Economic rehabilitation was not undertaken because of the financial constraint and scattered provincial distribution of those affected by leprosy. However, in recent years, with economic development, central and local governments have been able to pay more attention to the leprosy control programme and to the care of the disadvantaged affected by leprosy; 220 million RMB (1 Euro = 10.6 RMB) has been allocated to reconstruct the remaining leprosy villages, supplemented by a series of policies that have increased the standard of living and medical care.

**Outline of this thesis**

This thesis focuses on the early diagnosis of leprosy and the needs of former patients in a late phase of the control programme in Shandong Province, the People’s Republic of China. Since leprosy was eliminated in 1994 in the province (the prevalence is less
than 1 in 100,000 population), only a few new cases have been detected in each of the last 13 years. In order to test whether leprosy has been truly eliminated or whether cases are simply not being found, a rapid survey was conducted. Chapter 2 presents the results of this survey in a previously high endemic county of the province.

Chapter 3 includes an assessment of knowledge and skills in the early diagnosis of leprosy in two cross-sectional studies. The first one, conducted in 2000, describes the knowledge and skills in early diagnosis of leprosy in general health services at different levels. The second study focuses on assessing the knowledge and skills of doctors working in dermatological services around the province in the early diagnosis of leprosy, including their attitudes towards leprosy. Chapter 4 discusses inter-observer reliability and describes the results of an assessment of sensibility of skin lesions and enlargement of peripheral nerves in leprosy patients, an important issue related to the early diagnosis of leprosy. The value of contact examination in case detection is discussed in Chapter 5.

Chapter 6 describes our experiences with a collaborative project on the prevention of disability in leprosy. Chapter 7 explores the social, economic, and medical needs of former patients living in leprosy villages in a qualitative study based on the information obtained in our two previous studies of former patients living in communities and leprosy villages throughout the province.

In Chapter 8, the general discussion and main findings are included and then related to recent literature. The implications for leprosy control are discussed, and recommendations for future research are presented.

REFERENCES


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