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<THE TOPIC OF THIS MONTH>
Hansen's disease (Leprosy)

Hansen's disease (leprosy) is an infectious disease caused by the acid-fast bacillus *Mycobacterium leprae*. It mainly affects the skin and peripheral nerves. Until an effective treatment was available (until approximately the late 1940s), patients and their families faced stigma and discrimination due to the severe disfigurements of the face and extremities caused by the disease. Misconceptions, stigma, and discrimination towards patients and the disease have not been fully eliminated to this day.

Infection and classification of leprosy: Human infections occur in youth (mostly in infancy), when *M. leprae* is inhaled through the respiratory tract upon close contact with leprosy patients. Disease onset occurs following an incubation period varying from several years to several decades (see p. 17 of this issue).

There is individual variability in the clinical and pathologic manifestations of leprosy depending on the patient's immunity to *M. leprae*, and leprosy is categorized into several types. The primary stage of the disease is called group I (indeterminate leprosy), in which most persons clear *M. leprae* and recover based on their own immune response. In a limited number of patients, disease progresses into more advanced forms, and can be classified into two different types: type TT (tuberculoid leprosy), which involves high cell-mediated immunity specific to *M. leprae*, and type LL (lepromatous leprosy), which involves markedly deficient immunity. In-between these two types is group B leprosy (borderline leprosy), which can be further categorized into types BT, BL, and BB. The disease is also classified into paucibacillary (PB) and multibacillary (MB) types according to the number of skin lesions present. This classification (the World Health Organization [WHO] classification) is utilized for selecting treatment. Type TT is usually classified as PB (*M. leprae* is difficult to detect) and type LL is usually classified as MB (*M. leprae* is detectable).

In TT patients, various skin lesions, ranging from annular erythema to hypopigmentation, can arise, and the sensory function of the lesional skin is diminished. In LL patients, multiple disseminated nodules and erythema are found throughout the body with a symmetrical distribution. Normally, minimal loss of sensation occurs during the initial stages of the disease in LL patients. Patients with group B disease present an intermediate picture between TT and LL. Hansen's disease involves chronic progression, but acute immune response can sometimes occur, known as lepra reaction. Lepra reaction is an allergic reaction to the causative bacillus and manifests as acute inflammation of the peripheral nerves. Lack of prompt treatment at an early stage can leave patients with an irreversible loss of sensation or deformities of the hands (see p. 17 of this issue).

Diagnosis of leprosy: *M. leprae* cannot be cultured *in vitro*, and therefore, the detection is done via (1) slit skin smear testing (tissue fluid is taken by pricking the skin and then smeared onto a glass slide, stained with acid-fast staining (2) acid-fast staining of skin biopsy specimens, and (3) detection of genes specific to *M. leprae* in skin biopsy specimens using polymerase chain reaction (PCR). It is recommended that all three methods be performed whenever possible.

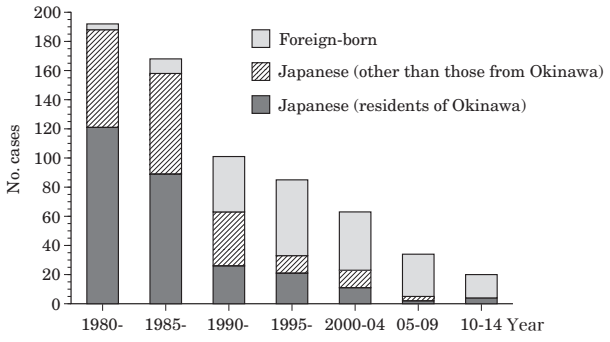
In addition, examining inflammation of the peripheral nerves is also important, using skin biopsy specimen. Some serological tests for leprosy are also utilized (see p. 18 of this issue).

In Japan, the above tests are performed as reference testing at the Leprosy Research Center, National Institute of Infectious Diseases (PCR, anti-phenolic glycolipid-I [PGL-I] antibody testing and sequence analysis of drug resistant genes) and at the Department of Dermatology, University of the Ryukyus (histopathology and PCR).

Diagnosis and treatment: Diagnosis of leprosy is made on the basis of four criteria: 1) skin lesion(s) with loss of sensation, 2) peripheral nerve damage (loss of sensation, nerve enlarge-ment, or motor impairment), 3) detection of *M. leprae*, and 4) relevant histopathological findings (granulation, inflammation of the nerves, etc.) (see p. 19 of this issue). In resource-limited settings, due to lack of physicians or laboratory capacity, patients are diagnosed with leprosy if they meet at least one of the three following criteria: 1) skin lesion(s) with loss of sensation, 2) nerve enlargement, or 3) a positive slit skin smear test.

For treatment, multidrug therapy (MDT) with a combination of rifampin, dapsone, and clofazimine is recommended by WHO. This treatment is orally administered

Figure 1. Annual number of newly detected leprosy cases in Japan, 1980-2014



(Leprosy Research Center, National Institute of Infectious Diseases)

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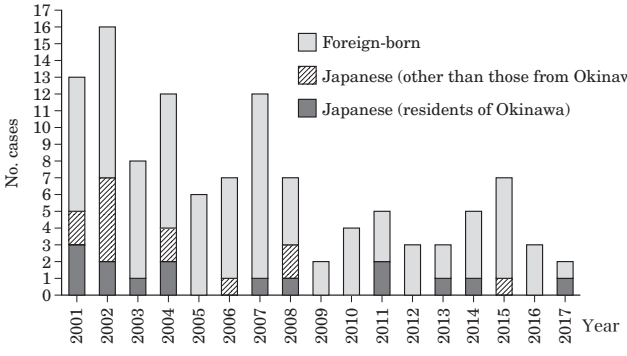
(THE TOPIC OF THIS MONTH-Continued)

for 6 months in cases of PB and a year in cases of MB. In Japan, other drugs are sometimes added to MDT or the length of treatment is extended. For lepra reaction, use of oral steroids or thalidomide are effective.

Leprosy patients in Japan: About 30,000 prevalent leprosy cases were reported in 1900, which decreased to about 16,000 by 1919. From around 1955, a rapid reduction in the number of new patients was observed, due to improvements in public hygiene/sanitation, improvement in nutritional status, decrease in patients who were a source of infection, and advances in treatment (Fig. 1 in p. 15). In recent years, 7 or fewer new patients are reported annually, including for Okinawa Prefecture, where leprosy was prevalent but has declined substantially (Fig. 2) (see p. 20 of this issue). It is speculated that new domestic cases of leprosy will occur at a rate of 0 to 1 persons per year. On the other hand, the number of imported cases started to increase around 1991. Since then, approximately 10 new patients have been reported annually. These patients are usually from high prevalence countries, such as Brazil, Nepal, and the Philippines. However, the number of imported cases has also been decreasing recently.

There are a total of 13 national leprosy sanatoriums in Japan. Around 1,450 treated patients, or 'residents', reside in these sanatoriums. Their disease (Hansen's disease) has already been cured, but they remain in the sanatoriums due to reasons such as disabilities and/or disfigurements, old age (mean age: 85 years), or being isolated from their family. Many patients who were discharged from/left sanatoriums or who were never admitted to sanatoriums were treated with a single regimen (dapsone) or received irregular treatment, and may thus require intervention for relapse or recurrence.

Figure 2. Annual number of newly detected leprosy cases in Japan, 2001-2017



(Leprosy Research Center, National Institute of Infectious Diseases)

Table. Number of newly detected leprosy cases in the world, 2016
(among countries that detected at least 1,000 new cases) (WHO)

Country	No. new cases	Country	No. new cases
India	135,485	Myanmar	2,609
Brazil	25,218	Tanzania	2,047
Indonesia	16,826	Madagascar	1,780
Democratic Republic of Congo	3,765	Philippines	1,721
Ethiopia	3,692	Nigeria	1,362
Nepal	3,054	Mozambique	1,289
Bangladesh	3,000	World total	214,783

Sri Lanka: No data in 2016 (1,977 in 2015)

Legislation relating to leprosy: In Japan, the Law Concerning the Prevention of Leprosy was promulgated in 1907 and has since been amended several times. The Leprosy Prevention Law was enacted in 1953, which stated that all leprosy patients were to be principally treated at sanatoriums. Under this law, the sanatorium directors were given the authority to employ various rules that represented violations of human dignity including: compulsory admission of patients, restricting patients' movements outside the sanatorium, in order to keep order among the residents. Once a patient was admitted to a sanatorium, they continued to live there even after their disease had been treated. Most patients stayed in the sanatoriums for life. In 1996, the Leprosy Prevention Law was abolished, and the name of the disease changed from 'leprosy' to 'Hansen's disease'. At present, new patients are seen at general hospitals and clinics. In the preamble to the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients with Infections (the Infectious Diseases Control Law) enacted in 1999, it is stated that: "The discrimination and prejudice against leprosy patients and other infectious diseases, such as acquired immunodeficiency syndrome, that existed in Japan needs to be taken seriously, and we must learn from these past mistakes as lessons learned for the future". In 2008, the Law to Enhance Problem Solving Related to Hansen's Disease was passed to help ensure solutions to the problems pertaining to Hansen's disease.

Global situation: Owing to the early detection and treatment strategy pursued by WHO, the number of new leprosy patients has considerably decreased. However, the annual number remains at around 210,000 to 250,000 in recent years (Table 1). In particular, WHO, Ministries of Health, and non-governmental organizations are working to reduce the number of new patients in countries with many incident cases, such as India, Brazil, and Indonesia. There have been interventions, such as chemoprophylaxis and reducing the treatment period (see p. 20 of this issue). Furthermore, there are efforts to promote disease control activities through integration with other neglected tropical diseases (NTDs), particularly those that present with skin manifestations (i.e. skin NTDs which include diseases such as leprosy, Buruli ulcer, yaws, leishmaniasis, mycetoma, and scabies) (see p. 22 of this issue).

The Japanese government and the Nippon Foundation are working to eradicate stigma and discrimination associated with leprosy, and also to enable recovered patients to take part in society. In addition, in 2017, the United Nations Human Rights Council Advisory Committee adopted the 'Elimination of discrimination against persons affected by leprosy and their family members (A/HRC/29/L.10')' resolution (see p. 23 of this issue).

Future concerns: The best way to treat leprosy without leaving any sequelae is through early diagnosis and treatment. To achieve this, development of simpler testing methods are desired. In addition, further research into development of drugs that are capable of treating the disease within a short time period or through combination therapy are required. Prevention of lepra reactions, along with development of safer and more effective drugs, is also necessary. Since there are still many leprosy patients present, mainly in Asia, Japan's continued collaboration in leprosy control is anticipated.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Law Concerning the Prevention of Infectious Diseases and Medical Care for Patients of Infections, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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