Hansen Disease in the United States in the 21st Century
A Review of the Literature

Heather Anderson, MD; Barbara Stryjewska, MD; Bobby L. Boyanton, Jr, MD; Mary R. Schwartz, MD

In this article we review the recent literature on Hansen disease (leprosy). We searched published literature through PubMed (National Library of Medicine) and extracted data through direct review of the literature and pathologic slides. Hansen disease continues to occur in the United States, including among the native-born population. Inclusion of the disease in the differential diagnosis is key to confirmation. Current epidemiology, classification systems, prevention measures, and therapy are reviewed.

(Arch Pathol Lab Med. 2007;131:982–986)

Even though the infamous leper colonies are fortunately no longer needed, Hansen disease (HD), also known as leprosy, persists in the United States. As the disease has become uncommon, physicians may not recognize early manifestations and pathologists may not include HD in their differential diagnosis. Infected individuals may not develop clinically evident disease for years, while they unknowingly infect others. Knowledge of the disease is critical for early detection and accurate diagnosis. A recent case in a middle-aged, native-born American, Hispanic man led us to review what is new in the arena of HD. In this review we highlight key clinical and pathologic findings, as well as new concepts of pathogenesis, diagnostic modalities, and therapies.

PREVALENCE

Hansen disease persists in the United States; 133 cases of HD were reported to the National Hansen's Disease Registry in 2002. Most of these cases were found in immigrants, but there is an endemic focus in Texas around the Gulf Coast. The average annual incidence rate for Texas ranges from 1.9 to 2.4 cases per million, but from 1973 to 1997 the rate for the Texas Gulf Coast counties of Goliad and Bee was more than 30 cases per million. In 2002, California had the most cases of HD with 42, but only 3 cases were found in native-born Americans. Texas had the most cases found in native-born Americans, with 8 of its 11 total cases. Forty-eight percent of the 413 native-born Americans with HD between 1973 and 1997 were identified as Hispanic.

California, New York, Texas, Hawaii, and Louisiana accounted for 64.7% of the 133 cases of HD reported in 2002, but HD can occur anywhere. In the middle 19th century, an outbreak of HD occurred among Scandinavian emigrants in the midwestern United States. More recently, HD developed in 3 US soldiers who had emigrated from endemic countries.

CLINICAL FEATURES AND CLASSIFICATION

The bacillus is only part of the HD story. Isolates do not seem to vary in virulence. Instead, the way in which an individual’s immune system responds to the infection, that is, whether it mounts a cell-mediated or humoral response, determines the course of the disease. Tuberculoid HD is the result of a cell-mediated response, while lepromatous HD develops in those who mount a humoral response.

The disease can also be complicated by 3 reactional states. Type 1, or lepra, reaction occurs when the body’s cell-mediated immunity changes, leading to a type IV hypersensitivity reaction, usually within the first 6 months. Left uncontrolled, it can permanently damage nerves. Type II, or erythema nodosum leprosum, reaction is caused by a Coombs type III reaction with immune complex vasculitis. Lucio phenomenon, which occurs in primary diffuse lepromatous HD, a subtype of lepromatous HD, correlates with vascular occlusion leading to skin necrosis. Lucio phenomenon refers specifically to the skin findings whereby symmetrical, necrotic, stellate lesions appear on the extremities and sometimes the face. The autoimmune phenomenon may be caused by the host having antigenic determinants identical to the antigens of Mycobacterium leprae.

Although HD may have classic features such as erythematous or hypopigmented plaques and alopecia (Figures 1 and 2), HD is like a chameleon. Clinically, it can resemble many entities, such as tinea, contact dermatitis, vitiligo, pityriasis alba, and myxedema. Histologically, HD ranges from paucibacillary forms, in which there are essentially no bacilli, to multibacillary forms, with countless bacilli. Mycobacterium leprae requires a modified acid-fast bacilli stain such as Fite or Wade for visualization. With these modified stains, the degree of acid and alcohol removal of carbol-fuchsin is less than in classic acid-fast
Figure 1. Bilateral erythematous lesions on a patient’s torso and a hypopigmented patch lateral to the umbilicus.

Figure 2. Clinical photograph demonstrating complete loss of eyebrows and eyelashes.

Figure 3. Skin biopsy. Diffuse dermal infiltrate of histiocytes without granuloma formation (hematoxylin-eosin, original magnification ×10).

Figure 4. Vacuolated mononuclear histiocytes or lepra cells admixed with occasional small lymphocytes (hematoxylin-eosin, original magnification ×40).

Figure 5. Fite stain demonstrating innumerable acid-fast bacilli throughout the dermis, indicative of Mycobacterium leprae (original magnification ×40).

Figure 6. Numerous acid-fast bacilli, Mycobacterium leprae, in nerve (Fite stain, original magnification ×40).
bacilli stains used for detection of other mycobacteria. To diagnose HD, one must first consider it.

According to the World Health Organization, a patient with HD is defined as ‘having one or more of the following features, and who has yet to complete a full course of treatment: 1) hypopigmented or reddish skin lesion(s) with definite loss of sensation, 2) involvement of the peripheral nerves, as demonstrated by definite thickening with loss of sensation, 3) skin smear positive for acid-fast bacilli.’ The World Health Organization classification divides cases into 3 types: paucibacillary single-lesion (1 lesion), paucibacillary (2–5 lesions), and multibacillary (more than 5 lesions). The Ridley Jopling classification uses clinical, bacteriologic, histologic, and pathologic criteria to divide HD into 5 categories ranging from tuberculoid tuberculoid to lepromatous (6 categories when indeterminate is also included). The Table explains all classifications of HD.

### Diagnostic Tests

Tests for HD include serologic assays, slit-skin smears, biopsies, probes, polymerase chain reaction (PCR), and the lepromin test. Serologic assays for *M. leprae* can detect phenolic glycolipid 1, as well as lipoarabinomannan. Phenolic glycolipid 1 is believed to be specific for *M. leprae*, but lipoarabinomannan is shared by other mycobacteria. The anti-phenolic glycolipid 1 Ab titer correlates with bacterial load, being higher in lepromatous than tuberculoid cases. It can be useful for monitoring chemotherapy as titers correlate with the bacterial index following treatment.

Slit-skin smears provide both bacteriologic indices (ie, measurement of the bacterial load) as well as morphologic indices, which signify viability. The inability to detect bacilli places a case in the paucibacillary categories (indeterminate and tuberculosis tuberculoid). The demonstration of bacilli defines it as multibacillary (borderline lepromatous) and *M. lepraem*; thus, it is not commonly used to assess treatment, slit-skin smears can be used to assess response to treatment.

In endemic areas, a diagnosis may be made without biopsy, in part because the correlation between the clinical diagnosis and histopathology is low. However, careful scrutiny of Fite-stained sections can partially overcome this. In areas in which HD is not endemic, the slit-skin smear provides inadequate information, only whether bacilli are present. A biopsy is needed to assess other po-

### Classification of Hansen Disease*

<table>
<thead>
<tr>
<th>Type</th>
<th>Cutaneous Findings</th>
<th>Nerve Changes</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1 to a few hypopigmented macule(s) that may be well or poorly defined</td>
<td>Nerve thickness and/or sensation may or may not be affected</td>
<td>Lymphocytes and histiocytes around neurovascular bundles and adnexa, some bacilli without well-formed granulomas</td>
</tr>
<tr>
<td>TT</td>
<td>1–3 sharply outlined dry, flaky, hairless, erythematous or hypopigmented plaques, papules</td>
<td>Nerve is thickened and/or tender; pain, touch, and temperature sensation destroyed</td>
<td>Granulomas of epithelioid cells, giant cells and numerous lymphocytes along neurovascular bundles; rare bacilli</td>
</tr>
<tr>
<td>BT</td>
<td>3–10 lesions with satellites pathogenic to monic</td>
<td>Nerve thickened and/or tender; sensation impaired or completely lost</td>
<td>Epithelioid cell granulomas along neurovascular bundles and infiltrating ector pili and sweat glands, granulomas not in epidermis, bacilli scant</td>
</tr>
<tr>
<td>BB</td>
<td>Resembles BT and LL, many lesions</td>
<td>Nerve tender and/or thickened; loss of sensation variable</td>
<td>Granulomas with epithelioid cells and lymphocytes, but not giant cells; grenz zone, many bacilli</td>
</tr>
<tr>
<td>BL</td>
<td>BT and LL-like lesions, but more LL-like; lesions tend to be symmetrical, numerous, and punched-out appearing</td>
<td>Symmetrical, thickened, and/or tender nerves; sensory loss minimal to definite</td>
<td>Diffuse, poorly to moderately defined granulomas in the mid and lower dermis made up of histiocytes, sheets of lymphocytes, and macrophages with bacilli; histiocyte invasion produces “onion skin” nerves, many bacilli</td>
</tr>
<tr>
<td>LL</td>
<td>Numerous, symmetrical hypopigmented or erythematous nodules and macules</td>
<td>Multiple nerve thickening; if large peripheral nerves involved, nerve paralyses and decreased sensation result with neural changes later than skin changes</td>
<td>Numerous dermal histiocytes with numerous bacilli extending into subcutis; grenz zone without granulomas or prominent lymphocytes; lepra cells (foamy macrophages) with globi of bacilli</td>
</tr>
<tr>
<td>PBSL</td>
<td>1 skin lesion</td>
<td></td>
<td>No bacilli on skin smear</td>
</tr>
<tr>
<td>PB</td>
<td>2–5 skin lesions</td>
<td></td>
<td>No bacilli on skin smear</td>
</tr>
<tr>
<td>MB</td>
<td>More than 5 lesions</td>
<td></td>
<td>May be skin-shear positive</td>
</tr>
</tbody>
</table>

* Data are derived from Sugita, Sehgal, World Health Organization, and Jacobson and Krahnenbuhl. I indicates indeterminate; TT, tuberculoid tuberculoid; BT, borderline tuberculoid; BB, borderline borderline; BL, borderline lepromatous; LL, lepromatous; PBSL, paucibacillary single-lesion; PB, paucibacillary; and MB, multibacillary.
tentia. Skin biopsies should be taken from the most active edge of a lesion, include full dermal thickness, and be stained using the Fite-Faraco method or the Wad stain.

Molecular probes have been developed to detect *M. leprae*, targeting both DNA and RNA. With molecular methods, 40% to 50% of cases missed on histologic evaluation can be detected. However, the probes require a minimum amount of genetic material, 10⁴ copies of DNA, and can miss paucibacillary cases. Katoch et al. noted that rRNA-targeting systems can be 10 to 100 times more sensitive.

Polymerase chain reaction has been found to be sensitive to 1 to 10 organisms and is positive in almost all borderline lepromatous/lepromatous cases and the majority of tuberculoid leprosy. Its utility in indeterminate and paucibacillary cases, however, is controversial. Drawbacks to the sensitivity of PCR are that it detects DNA from dead bacteria and a signal persists even after effective treatment. This limits its usefulness in monitoring treatment, and in distinguishing late reactions from relapses. The reverse transcriptase PCR assay targeting the 16S rRNA of *M. leprae* may overcome the problem of detecting genetic material from dead bacteria as the 16S rRNA quickly degrades after cell death.

The lepromin test gauges the patient’s cell-mediated immune response to *M. leprae*. The result is negative in lepromatous HD and positive in tuberculoid leprosy HD. Because the lepromin test is negative in lepromatous HD, it cannot be used to diagnose or confirm HD reliably, but it can assist in classification of recognized cases.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of HD is as varied as the disease itself. Conclusive diagnosis can be made on finding Kinyoun-negative acid-fast bacilli in an appropriate histologic background such as in nerves or in foamy histiocytes (lepra cells) (Figures 3 through 6). The diagnosis is less clear in paucibacillary lesions and/or treated cases. Several granulomatous conditions are foremost in the differential diagnosis of HD.

Granulomatous dermatitides can be divided into those with vasculitis and those without vasculitis. Tuberculoid lesions may also have granulomas with a scant lymphocytic infiltrate and no, or infrequent, bacilli. Nerve involvement is usually relied on to clinch the diagnosis of HD, but sarcoidosis may produce granulomas within peripheral nerve, although apparently not in the dermis. Tuberculoid granulomas are necrotic more often than those of sarcoidosis, and they track nerves. Ideally, the presence of bacilli will distinguish sarcoidosis from HD, but without bacilli and conclusive histologic findings, clinical correlation is essential to the diagnosis.

Malignant lymphoma may resemble tuberculoid HD with tumor-associated noncaseating tuberculoid granulomas encircling eccrine glands, follicles, and enlarged nerves in the reticular dermis. The clinical picture, the presence of a malignant lymphoid infiltrate, and demonstration of bacilli can differentiate the conditions. Other mycobacterial infections, including atypical ones, can produce multibacillary lesions, but will not involve nerves. In particular, *Mycobacterium avium* complex often has foamy histiocytes filled with acid-fast bacteria that can resemble HD.

The necrosis that occurs in the granulomas of type 1 reactions can resemble necrobiosis lesions such as granuloma annulare. Location of the necrotic granuloma in a nerve is diagnostic of HD.

**TREATMENT**

Making the initial diagnosis of HD can be a challenge, and so too may be the treatment: HD requires years of treatment and even more years of follow-up, complicated by reactional states. Hansen disease was previously treated with monotherapy, such as dapsone or rifampin. Monotherapy, however, led to drug resistance. Multidrug therapy was introduced by the World Health Organization in 1982 and includes use of dapsone, rifampin, and clofazimine.

In areas of the United States where HD is uncommon, physicians may not recognize the disease early in the course, especially in the native-born patient. It is critical to be aware that *M. leprae* continues to occur in this country, its clinical and histologic presentations are variable, and a critical key to its timely diagnosis is the consideration of it in the differential diagnosis.

**References**