UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI MEDICINA E CHIRURGIA

# Lebbra: epidemiologia attuale, quadri clinici, diagnosi e terapia

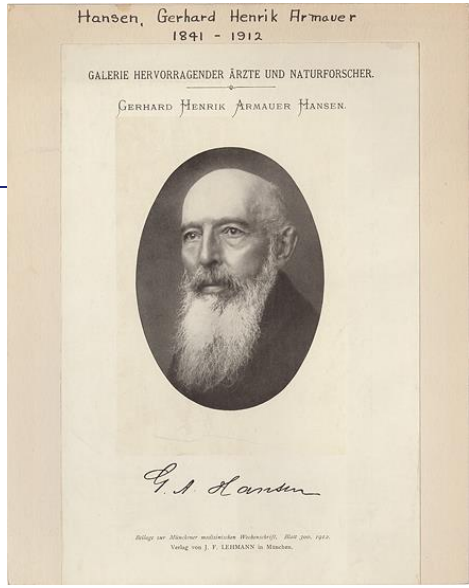
**Spinello Antinori**

**Dipartimento di Scienze Biomediche e Cliniche "Luigi Sacco"**


**Milano, 16 aprile 2019**

Vecchie e nuove patologie: arbovirosi e lebbra

# Leprosy or Hansen's disease




Leprosy (Hansen's disease) is a chronic debilitating infectious disease caused by *Mycobacterium leprae*

Very old disease described in from India 600 BC

First global data on prevalence published in 1966 (WHO estimated 10,786,000 cases)

1982 approval and wide use of multidrug therapy

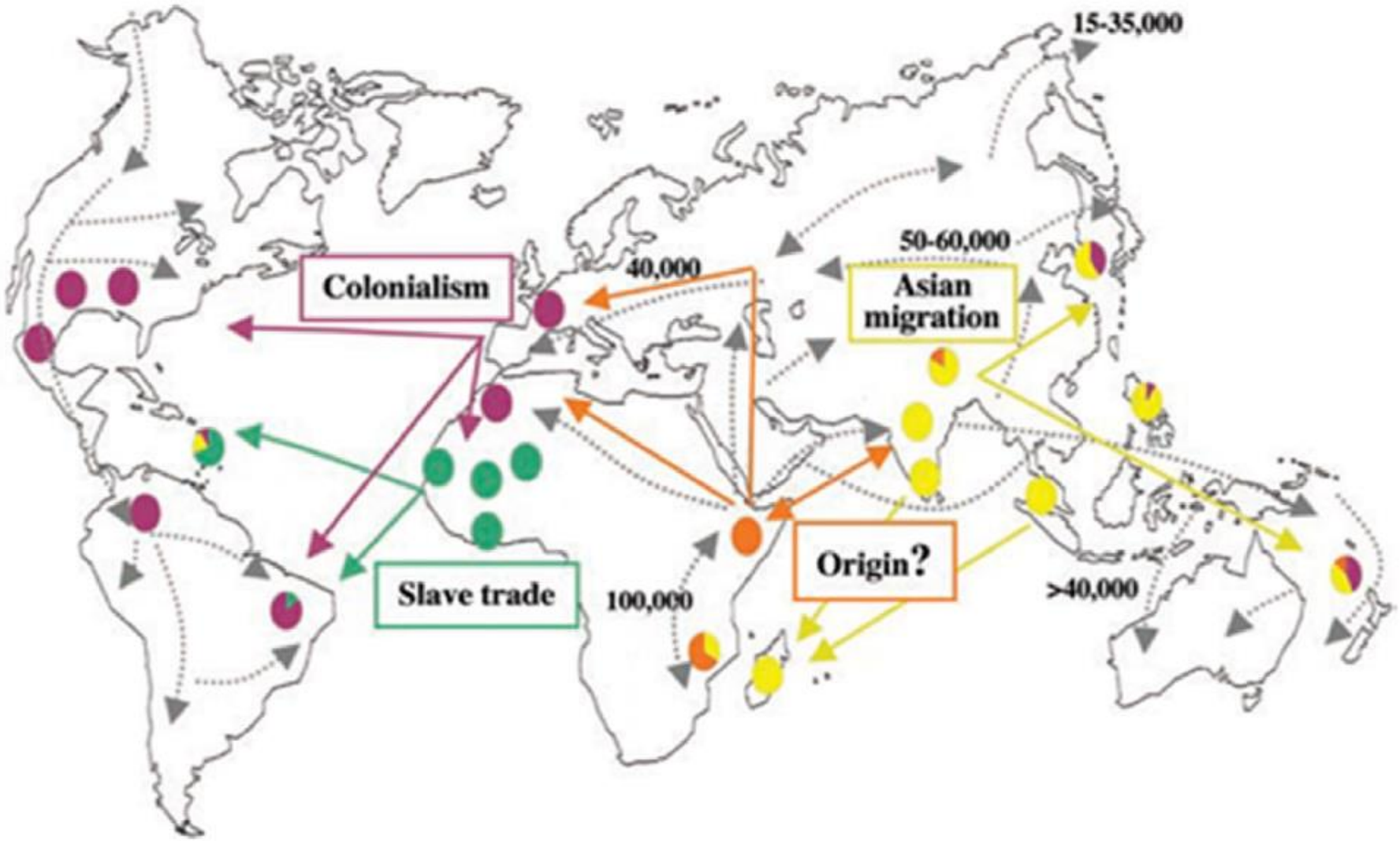
Key dates of significant importance in the history of leprosy.

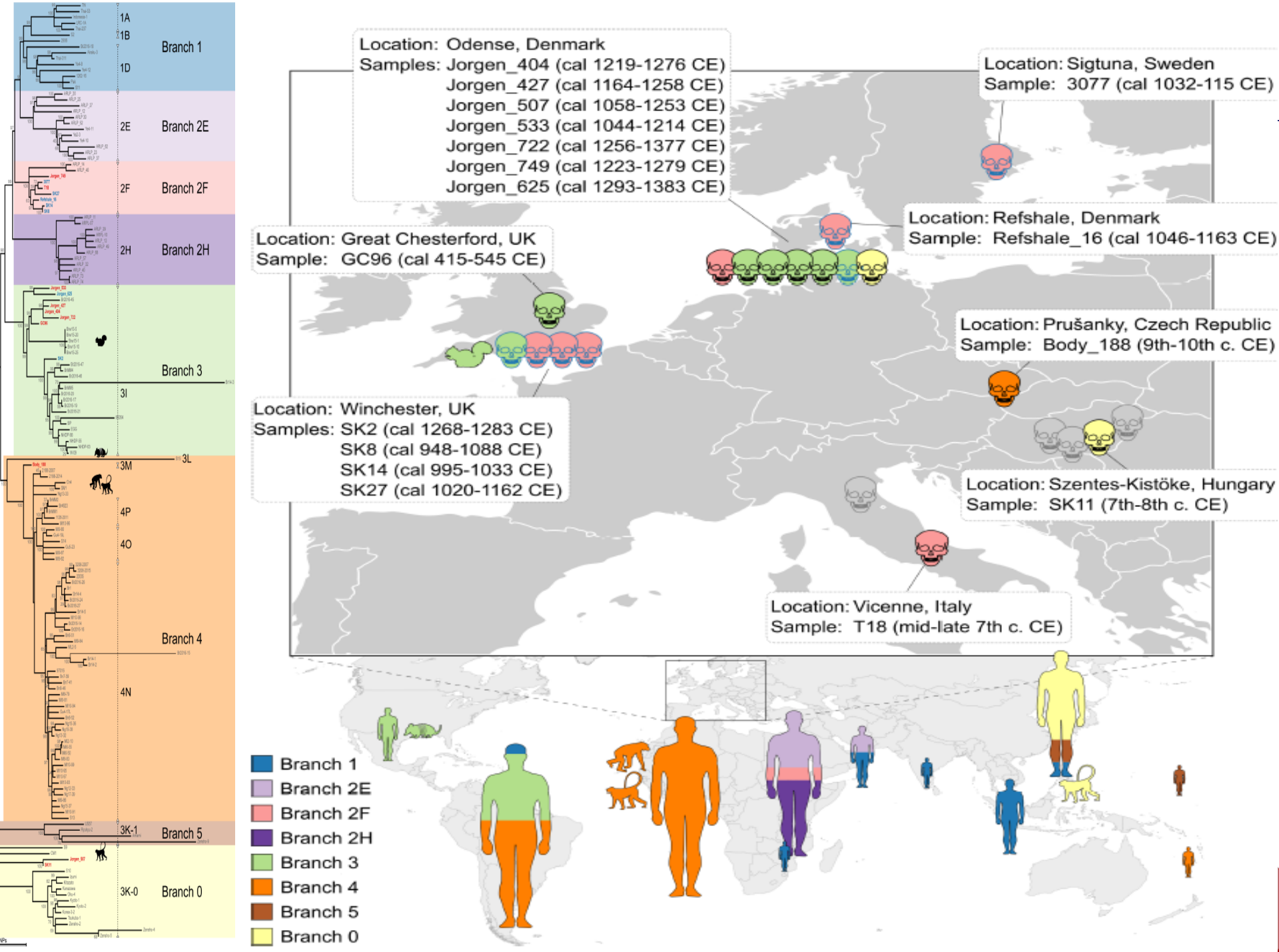
*Principales dates associées à un évènement marquant dans l'histoire de la lèpre.*

| | |
|---|---|
| 600 BC | 1st clinical description of leprosy in an Indian treaty |
| 1873 | Armauer Hansen identifies the disease-causing agent of leprosy [9] |
| 1941 | 1st publication by Faget supporting the effectiveness of dapsone [54] |
| 1960 | Shepard succeeds in quantifying the multiplication of the leprosy bacillus in a mouse footpad [10] |
| 1964 | First reported case of resistance to dapsone [65] |
| 1970 | A new and effective agent in the treatment of leprosy is identified: rifampicin [56] |
| 1971 | Kirchheimer and Storrs manage to obtain a significant multiplication of the leprosy bacillus inoculating the disease to the nine-banded armadillo [11] |
| 1981 | WHO recommends the use of multidrug therapy [57] |
| 1997 | A "single dose" regimen is suggested for patients presenting with a single nodular lesion: ROM (rifampicin/ofloxacin/minocycline) [64] |
| 2001 | Whole genome sequencing of an Indian strain of *M. leprae* isolated from the Tamil Nadu (TN) region [15] |
| 2008 | A new species of *Mycobacterium* causing lepromatous leprosy is identified: *M. lepromatosis* [12] |

First hyphoteses: East African origin: spread to East (Asia) and West (Europe)

Second hyphotesis: origin of leprosy in Asia




1A
1B
1D
Branch 1
2E
Branch 2E
2F
Branch 2F
2H
Branch 2H
Branch 3
3I
3L
3M
4P
4O
Branch 4
4N
3K-1
Branch 5
3K-0
Branch 0
Location: Odense, Denmark
Samples: Jorgen_404 (cal 1219-1276 CE)
Jorgen_427 (cal 1164-1258 CE)
Jorgen_507 (cal 1058-1253 CE)
Jorgen_533 (cal 1044-1214 CE)
Jorgen_722 (cal 1256-1377 CE)
Jorgen_749 (cal 1223-1279 CE)
Jorgen_625 (cal 1293-1383 CE)
Location: Sigtuna, Sweden
Sample: 3077 (cal 1032-115 CE)
Location: Refshale, Denmark
Sample: Refshale_16 (cal 1046-1163 CE)
Location: Great Chesterford, UK
Sample: GC96 (cal 415-545 CE)
Location: Prušanky, Czech Republic
Sample: Body_188 (9th-10th c. CE)
Location: Winchester, UK
Samples: SK2 (cal 1268-1283 CE)
SK8 (cal 948-1088 CE)
SK14 (cal 995-1033 CE)
SK27 (cal 1020-1162 CE)
Location: Szentes-Kistöke, Hungary
Sample: SK11 (7th-8th c. CE)
Location: Vicenne, Italy
Sample: T18 (mid-late 7th c. CE)
Branch 1
Branch 2E
Branch 2F
Branch 2H
Branch 3
Branch 4
Branch 5
Branch 0

# Microbiology

*M. leprae* belongs to the *Mycobacterium* genus and to the Mycobacteriaceae family. The rod-shaped bacillus appears motionless at microscopic analysis, and is 1 to 8 μm long for 0.3 μm large (Fig. 3). *M. leprae* is a micro-aerophilic bacterium and ideally grows at a temperature ranging from 30 to 35 °C. The bacilli group together in highly infected tissues to form clumps of bacilli (known as globi) that can contain hundreds of bacilli.

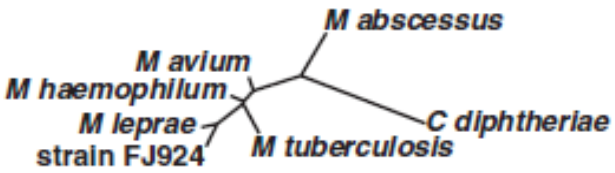
The inability to culture *M. leprae* in vitro is one of the main specificities of that bacterium, and can be explained by its very long doubling time (14 days). For matters of comparison, the doubling time of *M. tuberculosis* is 24 hours and

The exact method of transmission of leprosy is still unknown. The human being is the main reservoir of infection even though transmission through African green monkeys [21,22] and armadillos in Louisiana [23] has been reported. The most contagious presentation of the disease is the lepromatous leprosy as patients usually carry a very large number of leprosy bacilli. Some patients can carry up to 7 billion leprosy bacilli per one gram of tissue.

# A New *Mycobacterium* Species Causing Diffuse Lepromatous Leprosy

*Xiang Y. Han, MD, PhD,[1] Yiel-Hea Seo, MD, PhD,[1*] Kurt C. Sizer, MD,[1] Taylor Schoberle, MS,[1] Gregory S. May, PhD,[1] John S. Spencer, PhD,[2] Wei Li, PhD,[2] and R. Geetha Nair, MD[3]*

**A**




**B**

| | | |
|---|---|---|
| Strain FJ924 | | AAAGGTCTCTTAATACTTAAACCTATTAAAGAT |
| *Mycobacterium leprae* | | AAAGGTCTCTAAAAAATC---TTTTTTAGAGAT |
| *Mycobacterium haemophilum* | | AAAGGTCTCT----------TCGGAGAT |
| *Mycobacterium malmoense* | | AAAGGTCTCT----------TCGGAGAT |
| *Mycobacterium tuberculosis* | | AAAGGTCTCT----------TCGGAGAT |
| *Mycobacterium avium* | | AAAGGCCTCT----------TCGGAGGT |
| *Mycobacterium abscessus* | | AAAGGCC-CT----------TCGG-GGT |
| *Corynebacterium diphtheriae* | | AAAGGCCT--AGCTTGCT----------AGGT |
| *Staphylococcus aureus* | | ACGGACGAGAAGCTTGCT-------TCTCTGAT |
| *Escherichia coli* | 70 | AACAGGAAGAAGCTTTCT--------CTTTGCT |



*Am J Clin Pathol* 2008;130:856-864

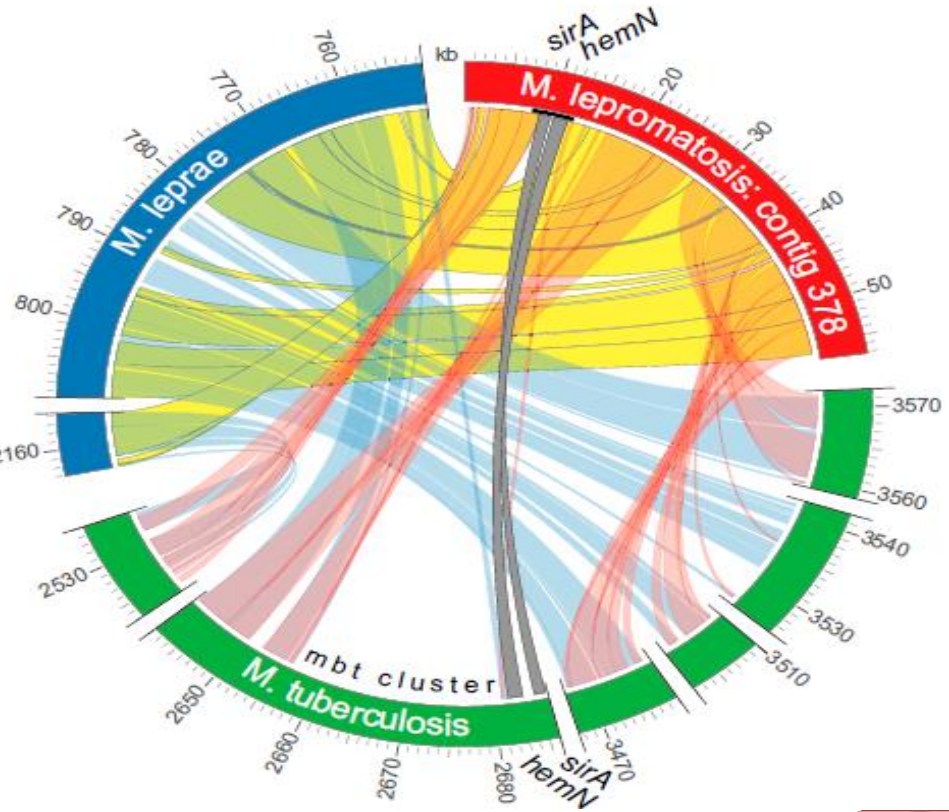
# Microbiology

# Insight into the evolution and origin of leprosy bacilli from the genome sequence of *Mycobacterium lepromatosis*

Pushpendra Singh[a,1,2], Andrej Benjak[a,1], Verena J. Schuenemann[b], Alexander Herbig[b], Charlotte Avanzi[a], Philippe Busso[a], Kay Nieselt[c], Johannes Krause[b,d,e], Lucio Vera-Cabrera[f], and Stewart T. Cole[a,3]

## Significance

Leprosy was thought to be exclusively caused by infection of humans by *Mycobacterium leprae*. In 2008, Han et al. proposed that *Mycobacterium lepromatosis*, a separate unculturable species, might be responsible for a rare yet severe form of the disease called diffuse lepromatous leprosy. Here, by using comparative genomics, we show that the two species are very closely related and derived from a common ancestor that underwent genome downsizing and gene decay. Since their separation 13.9 Mya, the two species have continued to lose genes, but from different regions of the genome, and *M. leprae* appears to be more recent. In a phylogeographic survey, by using differential PCR, we found that *M. lepromatosis* was scarce and restricted to patients from Mexico.



# Incubation period

Difficult to define and extremely variable

US military personnel (exposed for a relatively short periods of time):

-Tubercoloid leprosy= 2.9-5.3 years

-Lepromatous leprosy=9.3-11.6 years

# Host susceptibility

Linked with or associated with HLA DR2 and the *Taq*1 polymorphism of the vitamin D receptor gene

Alleles in the *PARK2* and *PACRG* region on chromosome 6 (susceptibility) in Vietnamese and Brazilian patients

Sex

The number of leprosy cases reported in adults is consistently higher among men, with a male to female sex ratio ranging between 1.5 and 2 [25]. Few exceptions of a sex ratio <1 have been described in some African countries such as Burkina Faso, Kenya, or Uganda [26]. Exposure, reporting, or access to care biases cannot fully explain such a difference: during a massive outbreak on the island of Nauru in the Pacific (where leprosy affected a third of the population during the 1920s and where these biases are expected to play a minor role), the sex ratio was

# Transmission

**Portal of exit:** nasal secretions; desquamating skin(?)

African Green monkeys; armadillos (Lousiana)

Probable Zoonotic Leprosy in the Southern United States

Richard W. Truman, Ph.D., Pushpendra Singh, Ph.D., Rahul Sharma, Ph.D., Philippe Busso, Jacques Rougemont, Ph.D., Alberto Paniz-Mondolfi, M.D., Adamandia Kapopoulou, M.S., Sylvain Brisse, Ph.D., David M. Scollard, M.D., Ph.D., Thomas P. Gillis, Ph.D., and Stewart T. Cole, Ph.D.

N Engl J Med 2011;364:1626-33.

The unique tropism of *Mycobacterium leprae* to the nasal epithelial cells can be explained by the mammalian cell entry protein 1A

Viesta Beby Fadlitha[1], Fuki Yamamoto[1], Irfan Idris[2], Haslindah Dahlan[2], Naoya Sato[3,4], Vienza Beby Aftitah[5], Andini Febriyanda[2], Takao Fujimura[1,4]*, Hiroaki Takimoto[6]

Human being is the main reservoir

Molecular Evidence for the Aerial Route of Infection of *Mycobacterium leprae* and the Role of Asymptomatic Carriers in the Persistence of Leprosy

Sergio Araujo,[1,2] Larissa Oliveira Freitas,[1] Luiz Ricardo Goulart,[1,2,3,4] and Isabela Maria Bernardes Goulart[1,2]

Clinical Infectious Diseases® 2016;63(11):1412–20

**Portal of entry:** upper respiratory tract (nasal mucosa); skin

Our thorough analysis of the data set and careful characterization of the study participants generated robust findings and provided molecular evidence in support of our theory that the upper respiratory tract, particularly the nose, is the main portal for the entry and exit of *M. leprae*; exposure leads to infection of nasal mucosa, which elicits immune responses (cell mediated and humoral); if colonization is successful, *M. leprae* is transported through the bloodstream and disseminated to favorable sites of growth (ie, myelin-producing Schwann cells).

Table 1 **Registered prevalence of leprosy and number of new cases detected, by WHO Region, 2016**

Tableau 1 **Prévalence enregistrée de la lèpre et nombre de nouveaux cas dépistés, par Région OMS en 2016**

| WHO Region – Région OMS | Number of cases registered (prevalence/ 10 000 population), first quarter of 2017 – Nombre de cas enregistrés (prévalence/ 10 000 habitants), premier trimestre 2017 | Number of new cases detected (new-case detection rate/100 000 population), 2016 – Nombre de nouveaux cas dépistés (taux de dépistage des nouveaux cas/100 000 habitants), 2016 |
|---|---|---|
| African – Afrique | 21 465 (0.3) | 19 384 (2.0) |
| Americas – Amériques | 26 365 (0.31) | 27 356 (2.7) |
| Eastern Mediterranean – Méditerranée orientale | 3102 (0.01) | 2834 (0.4) |
| South-East Asia – Asie du Sud-Est | 115 180 (0.6) | 161 263 (8.2) |
| Western Pacific – Pacifique occidental | 5820 (0.03) | 3914 (0.2) |
| Europe | 16 | 32 |
| **Global total – Total mondial** | **171 948 (0.23)** | **214 783 (2.9)** |

WEEKLY EPIDEMIOLOGICAL RECORD, NO 35, 1ST SEPTEMBER 2017

Table 2 **Trends in the detection of new cases of leprosy, by WHO Region, 2007–2016**

Tableau 2 **Tendances observées dans le dépistage de nouveaux cas de lèpre, par Région OMS, 2007-2016**

| WHO Region – Région OMS | Number of new cases detected – Nombre de nouveaux cas dépistés | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
| African – Afrique | 34468 | 29814 | 28935 | 25345 | 20213 | 20599 | 20911 | 18597 | 20004 | 19384 |
| Americas – Amériques | 42135 | 41891 | 40474 | 37740 | 36832 | 36178 | 33084 | 33789 | 28806 | 27356 |
| Eastern Mediterranean – Méditerranée orientale | 4091 | 3938 | 4029 | 4080 | 4357 | 4235 | 1680 | 2342 | 2167 | 2834 |
| South-East Asia – Asie du Sud-Est | 171576 | 167505 | 166115 | 156254 | 160132 | 166445 | 155385 | 154834 | 156118 | 161263 |
| Western Pacific – Pacifique occidental | 5863 | 5859 | 5243 | 5055 | 5092 | 5400 | 4596 | 4337 | 3645 | 3914 |
| Europe | | | | | | | | | 18 | 32 |
| **Global total – Total mondial** | **258133** | **249007** | **244796** | **228474** | **226626** | **232857** | **215656** | **213899** | **210740** | **214783** |

Reduction rate 2% annually

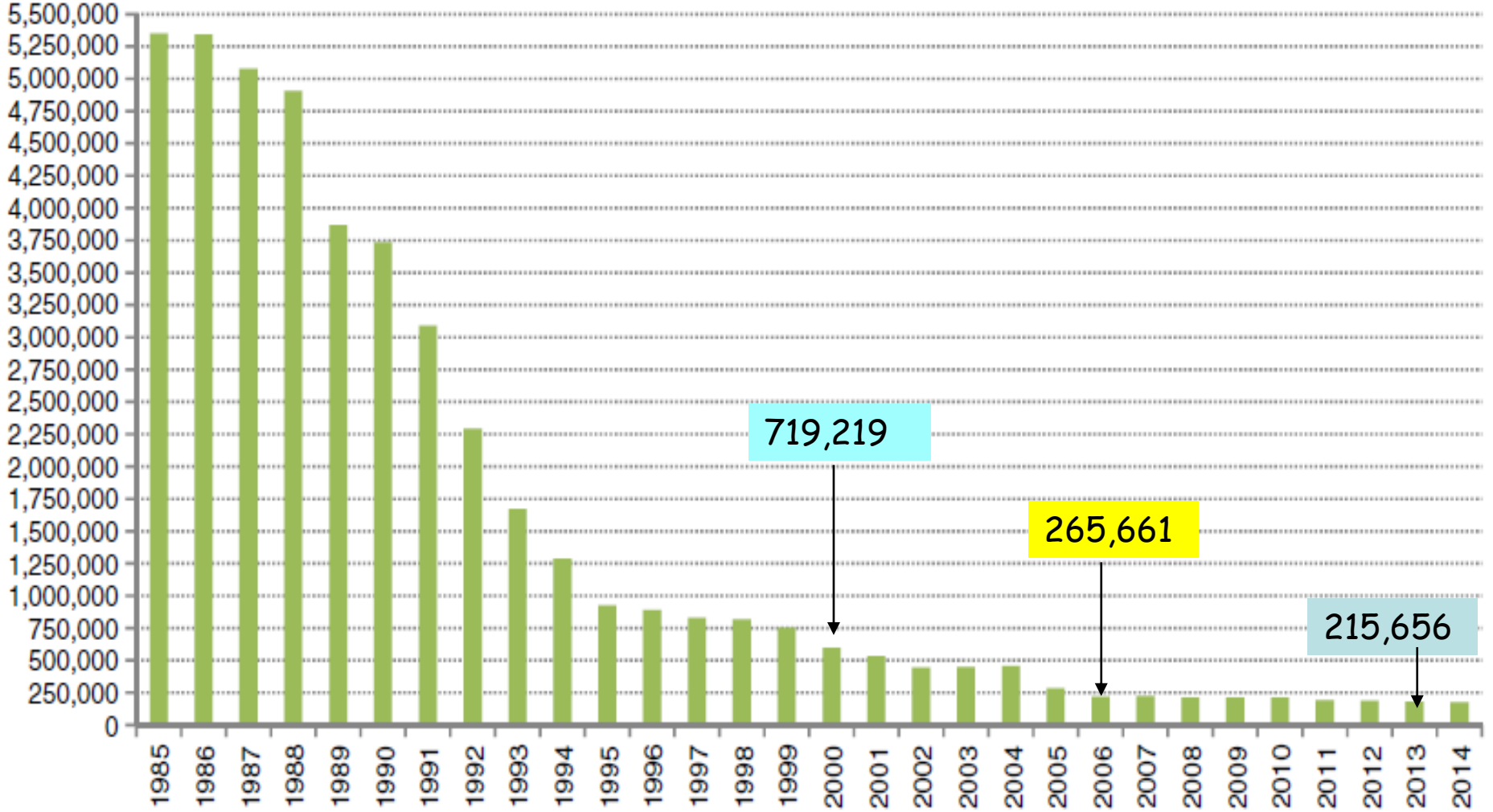



**Fig. 1** Global registered point prevalence of leprosy from 1985 to 2014 (WER 2015).

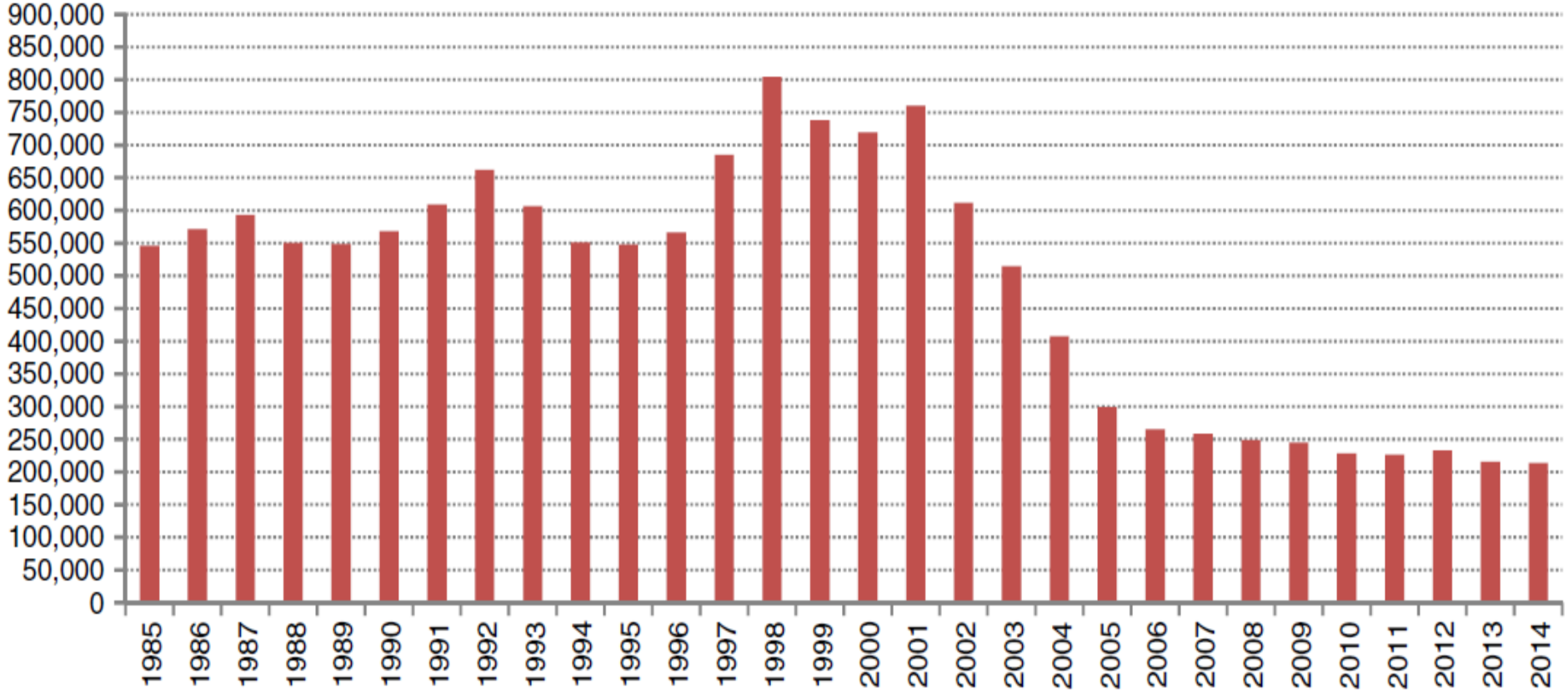
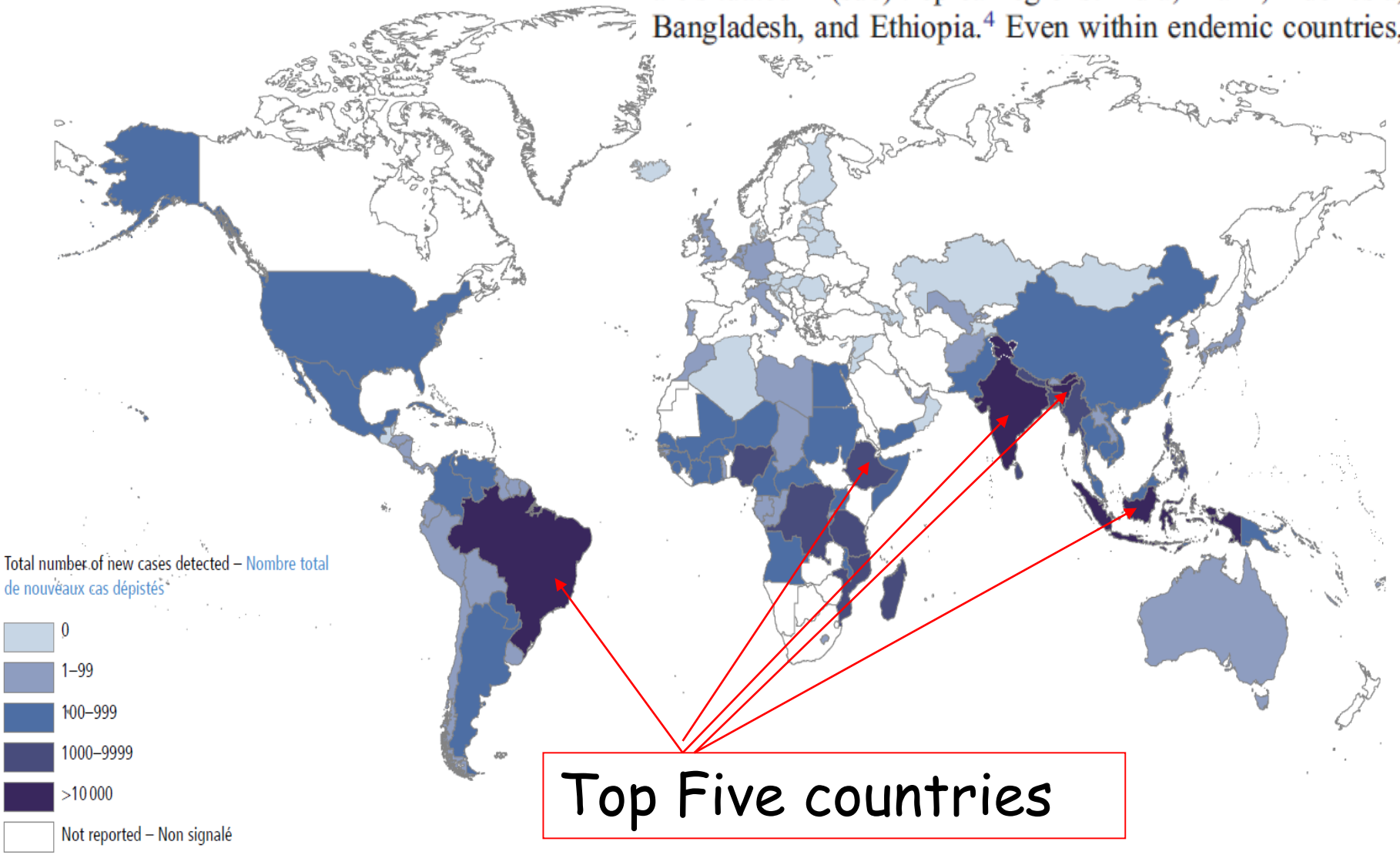



**Fig. 5** Global new cases of leprosy (new case detection) from 1985 to 2014.

Currently, the top five countries that are home to more than 80% of the new leprosy cases that are detected annually are situated in (sub) tropical regions: India, Brazil, Indonesia, Bangladesh, and Ethiopia.[4] Even within endemic countries,

Map 1 **Geographical distribution of new leprosy cases, 2016**
Carte 1 **Répartition géographique des nouveaux cas de lèpre en 2016**




The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. – Les limites et appellations figurant sur cette carte ou les désignations employées n'impliquent de la part de l'Organisation mondiale de la Santé aucune prise de position quant au statut juridique des pays, territoires, villes ou zones, ou de leurs autorités, ni quant au tracé de leurs frontières ou limites. Les lignes en pointillé sur les cartes représentent des frontières approximatives dont le tracé peut ne pas avoir fait l'objet d'un accord définitif.

Table 6 **New cases and foreign-born patients from 30 countries, 2016**
Tableau 6 **Nouveaux cas et patients nés à l'étranger (provenant de 30 pays différents), 2016**

| Country – Pays | No. of new cases reported – Nbre de nouveaux cas signalés | Foreign born patients – P nés à l'étranger |
|---|---|---|
| Australia – Australie | 19 | 15 (79%) |
| Brazil – Brésil | 25 218 | 3 (0%) |
| Chad – Tchad | 89 | 34 (38%) |
| Chile – Chili | 1 | 1 (100%) |
| China, Hong Kong Special Administrative Region – Chine, Région administrative spéciale de Hong Kong | 3 | 3 (100%) |
| Colombia – Colombie | 314 | 1 (0%) |
| Equatorial Guinea – Guinée équatoriale | 10 | 1 (10%) |
| Germany – Allemagne | 2 | 2 (100%) |
| Guam | 16 | 15 (94%) |
| Italy – Italie | 12 | 11 (92%) |
| Japan – Japon | 3 | 3 (100%) |
| Kuwait – Koweït | 6 | 6 (100%) |
| Lebanon – Liban | 1 | 1 (100%) |
| Lesotho | 2 | 1 (50%) |
| Malaysia – Malaisie | 206 | 85 (41%) |
| Maldives | 6 | 2 (33%) |
| Netherlands – Pays-Bas | 5 | 5 (100%) |
| Northern Mariana Islands – Îles Mariannes du Nord | 2 | 1 (50%) |
| Pakistan | 397 | 1 (0%) |
| Paraguay | 341 | 3 (1%) |
| Portugal | 4 | 4 (100%) |
| Qatar | 36 | 36 (100%) |
| Republic of Korea – Rébublique de Corée | 4 | 2 (50%) |
| Senegal – Sénégal | 332 | 6 (2%) |
| Singapore – Singapour | 7 | 5 (71%) |
| Surinam – Suriname | 25 | 1 (4%) |
| Thailand – Thaïlande | 163 | 40 (25%) |
| United Arab Emirates – Emirats arabes unis | 40 | 40 (100%) |
| United Kingdom – Royaume Uni | 5 | 5 (100%) |
| Venezuela (Bolivarian Republic of) – Venezuela (République bolivarienne du) | 303 | 2 (1%) |

ORIGINAL ARTICLE

# Imported leprosy in Italy

C. Massone,[†,‡,*,1] A.M.G. Brunasso,[§,¶,1] S. Noto,[**,††] T.M. Campbell,[‡‡] A. Clapasson,[**] E. Nunzi[‡,**]

Retrospective analysis from 2003 to 2009

Italian Leprosy register and WHO official data

59 immigrants diagnosed with leprosy: 28 legally resident (47%), 31 (53%) illegal resident immigrants; 41 (69.5%) men; median age 30 yrs (8-55 yrs). 30 multibacillary (51%), 19 (32%) GD2 disabilities

Seventeen countries of origin were identified: Bangladesh, Bolivia, Brazil, Cameroon, Colombia, Ecuador, Egypt, India, Nigeria, Pakistan, Philippines, Senegal, Sierra Leone, Sri Lanka, Sudan, Venezuela and Tanzania.



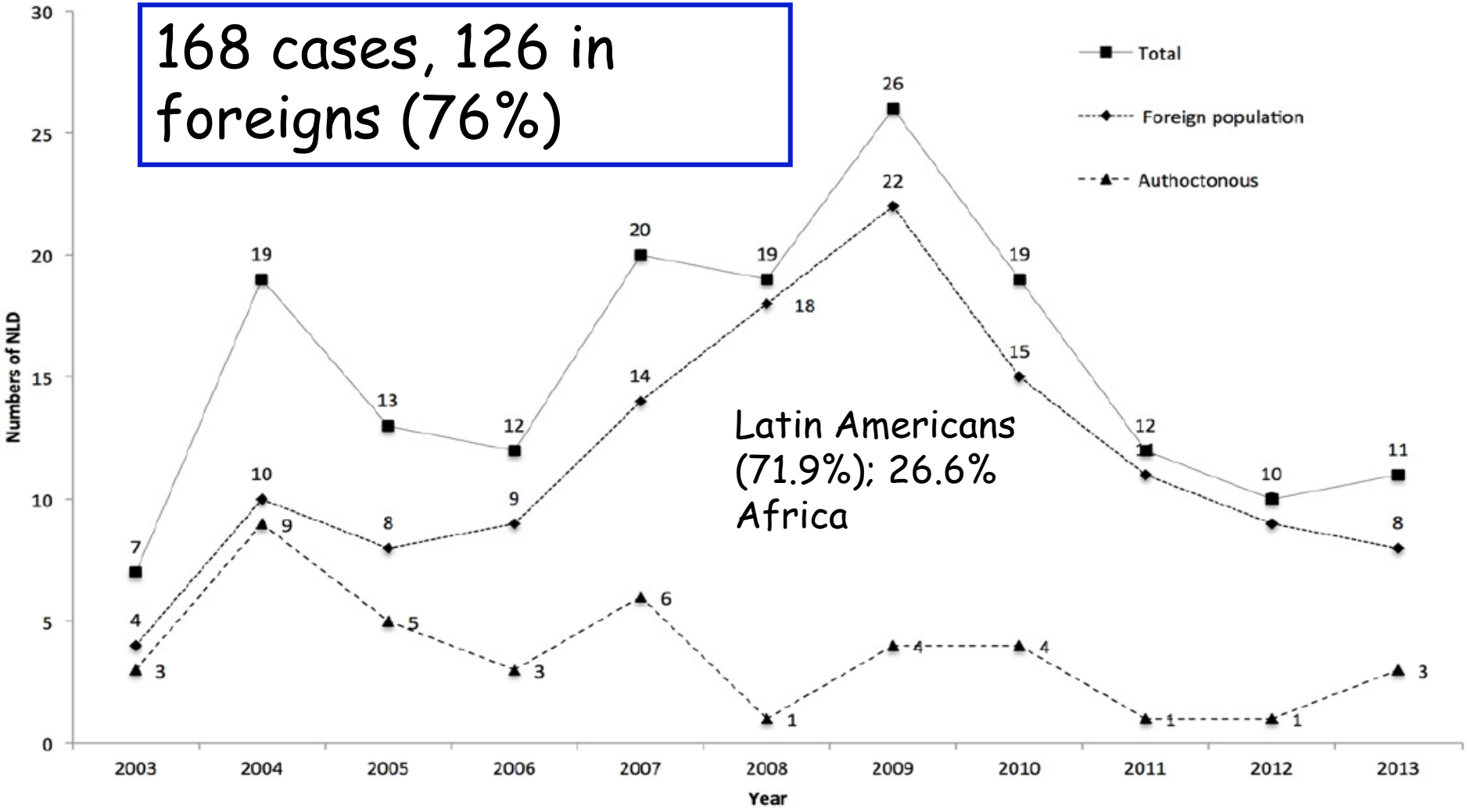
*JEADV* 2012, 26, 999–1006 Journal of the European Academy of Dermatology and Venereology

# Epidemiology of Leprosy in Spain: The Role of the International Migration

José M. Ramos[1,2]*, David Romero[3], Isabel Belinchón[2,3]

PLOS | NEGLECTED TROPICAL DISEASES

168 cases, 126 in foreigns (76%)




Latin Americans (71.9%); 26.6% Africa

Fig 1. Trends of new leprosy cases detected during study period (2003–2013) in total, in foreign and autochthonous Spanish populations.

## Box 1. Different Classifications of Leprosy

**Madrid (1953):** T (Tuberculoid), B (Borderline) and L (Lepromatous), according to clinical (skin and nerve lesions), bacteriological (bacteriological index [BI]—a measure of the number of acid-fast bacilli in the dermis expressed in a logarithmic scale), immunological (lepromin reaction), and histological (infiltrate's nature) criteria.

**Ridley–Jopling (1966):** TT (Tuberculoid Tuberculoid), BT (Borderline Tuberculoid), BB (Borderline Borderline), BL (Borderline Lepromatous), and LL (Lepromatous Lepromatous), defined according to clinical, bacteriological, immunological, and histological criteria.

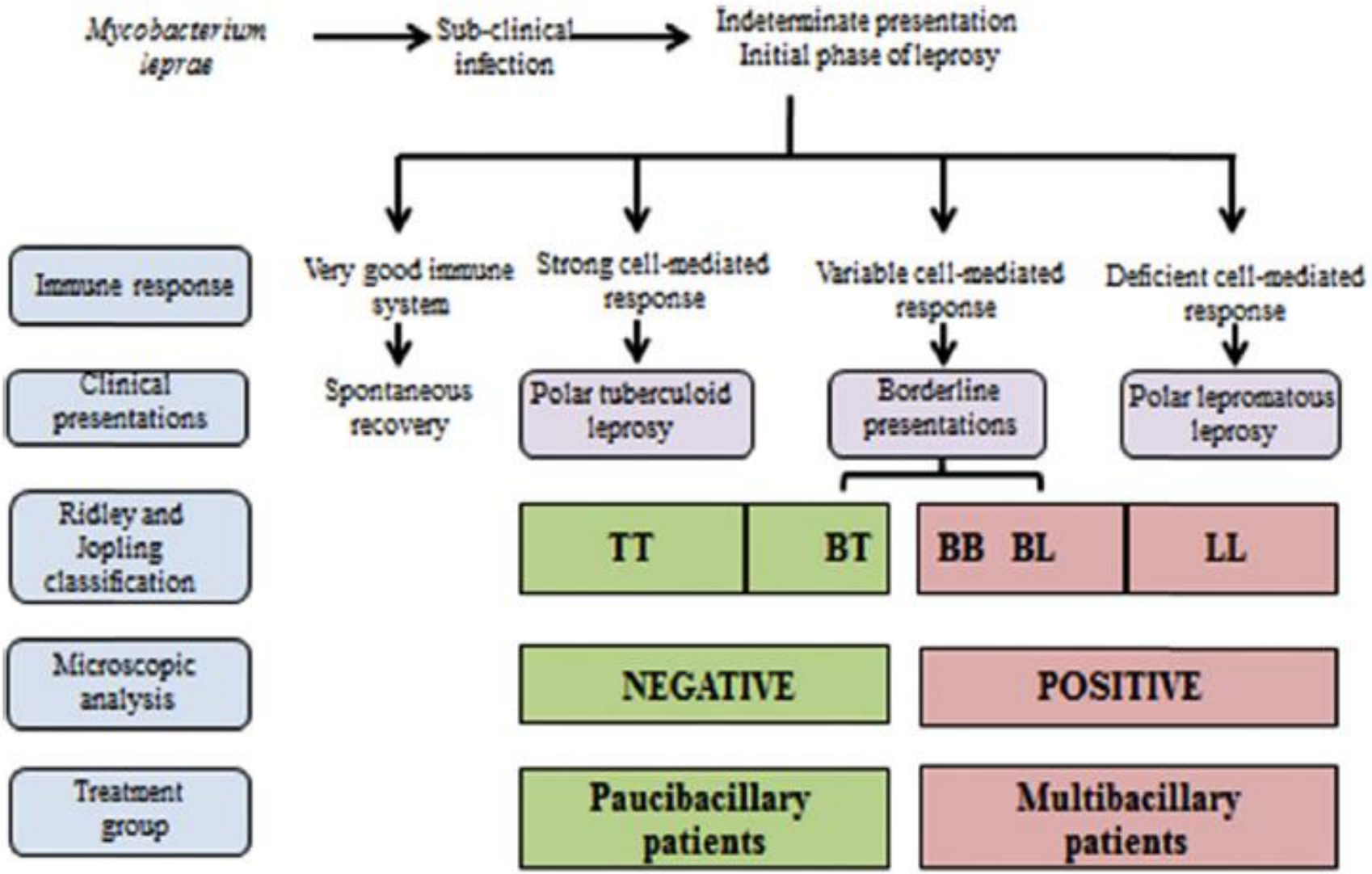
**WHO (1982):** Paucibacillary (PB) or Multibacillary (MB) according to Ridley–Jopling (or Madrid) classifications and the BI. PB = TT + BT (or T) and BI $\leq$ 1; MB = BB + BL + LL (or B + L) or BI $\geq$ 2.

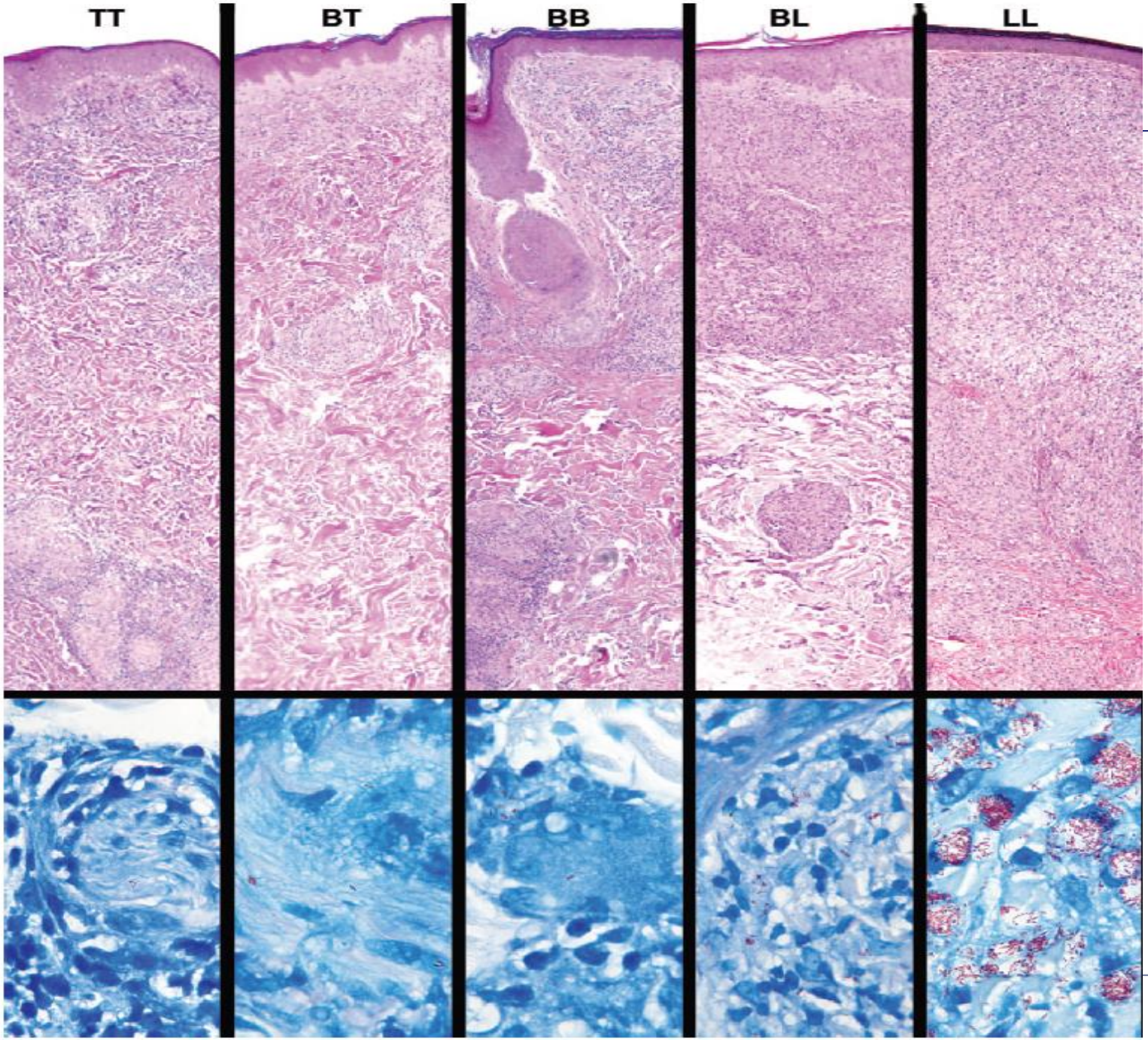
**WHO (1988):** PB = TT + BT and BI = 0; MB = BB + BL + LL or BI $\geq$ 1.

**WHO (1996):** PB or MB according to the sole number of skin lesions ($\leq$/>5).

*****

**Polarization:** process that drives an infected individual towards the PB or the MB form (in our manuscript, irrespective of the classification used to define PB and MB cases).


Mycobacterium leprae
Sub-clinical infection
Indeterminate presentation
Initial phase of leprosy
Immune response
Very good immune system
Strong cell-mediated response
Variable cell-mediated response
Deficient cell-mediated response
Clinical presentations
Spontaneous recovery
Polar tuberculoid leprosy
Borderline presentations
Polar lepromatous leprosy
Ridley and Jopling classification
TT
BT
BB
BL
LL
Microscopic analysis
NEGATIVE
POSITIVE
Treatment group
Paucibacillary patients
Multibacillary patients


TT
BT
BB
BL
LL

# Human Immunodeficiency Virus and Leprosy: An Update

Diana N.J. Lockwood, MD, FRCP*, Saba M. Lambert, MBBS

Table 1
Summary of impact of human immunodeficiency virus-1 on leprosy: expected versus actual

| | | Theory | In Practice |
|---|---|---|---|
| Epidemiologic | Incidence | Increase in leprosy | No change |
| Clinical | Tuberculoid leprosy | Decreased | Increased |
| | Treatment response | Worsened | No change |
| | Type-1 reactional states | Fewer | Increased |
| | Neuritis | Worsened | ? |
| | Novel findings | Presentation as immune reconstitution inflammatory syndrome | |
| Histopathological | Granuloma formation | Decreased | No change |
| | Bacterial index | Increased | No change |

# Leprosy – an overview of clinical features, diagnosis, and treatment

Marcellus Fischer

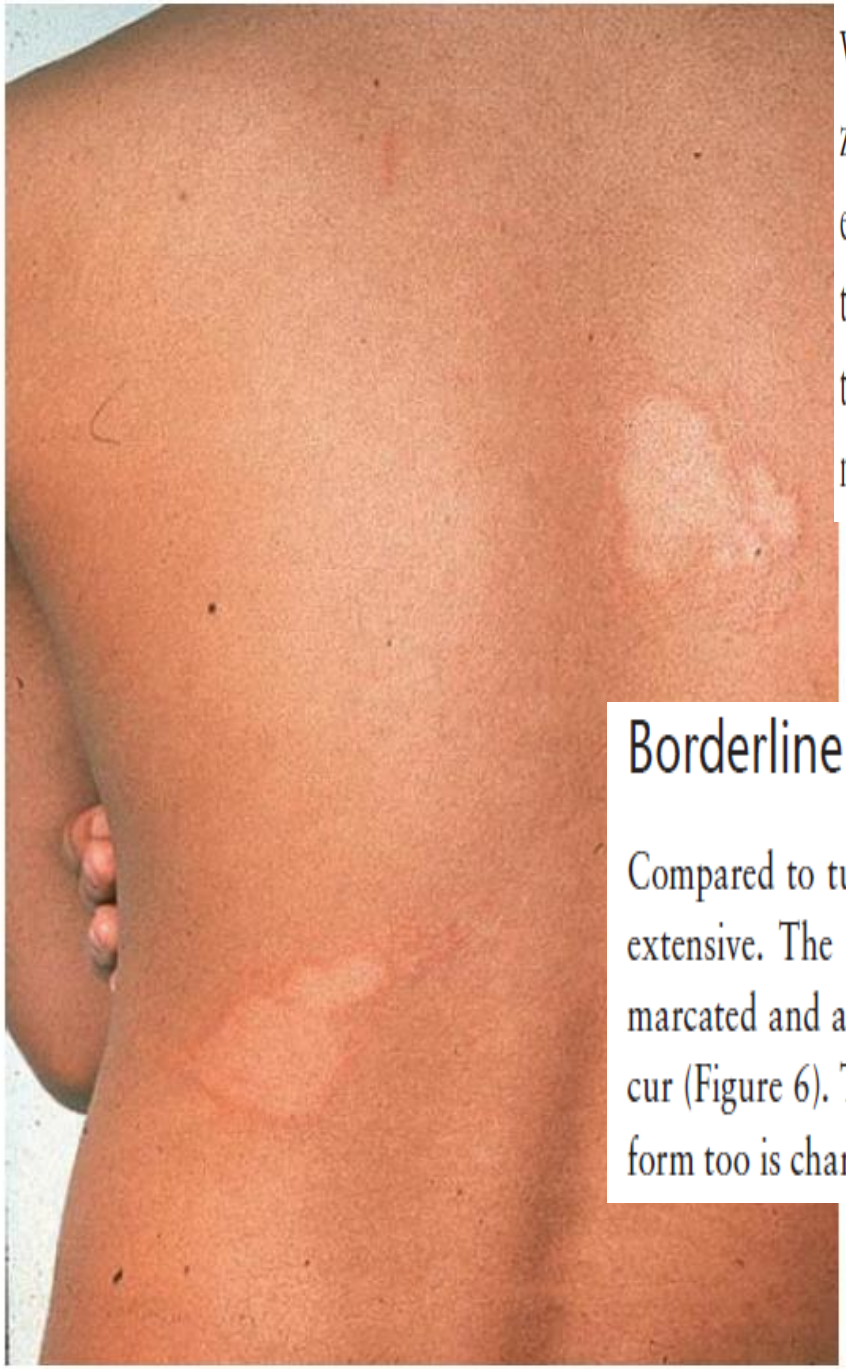
Journal of the German Society of Dermatology

The initial stage of leprosy is characterized by one or more hypopigmented macules.

The lesions are macular, hypochromic and sometimes poorly demarcated. Initially, there is neither erythema nor infiltration. These hypopigmented macules can occur anywhere on the body. Even in endemic regions, the predominantly young patients are frequently misdiagnosed as having tinea versicolor, pityriasis alba associated with atopic diathesis, vitiligo, or postinflammatory hypopigmentation associated with eczema. Indeterminate leprosy can last for up to five years. Towards the end of

diagnosis to be made. Even using molecular biology methods, the detection of *Mycobacterium leprae* is extremely rare at this stage. Given that the occurrence

**Figure 2** Indeterminate leprosy. Manaus, Brazil, 2001.



When host immunity is good, leprosy presents in its tuberculoid form, characterized by solitary papules and plaques. These may coalesce into sharply demarcated erythematous plaques with raised borders and an annular appearance. At the center, the lesions are frequently atrophic and hypopigmented. Showing an asymmetrical distribution, tuberculoid leprosy lesions predominantly occur on the extremities. They are reminiscent of tinea corporis, which is a frequent misdiagnosis in

## Borderline tuberculoid form (BT)

Compared to tuberculoid leprosy, the skin lesions are more numerous and more extensive. The erythematous infiltrates with prominent borders are sharply demarcated and arranged in an asymmetrical fashion; at times, satellite lesions occur (Figure 6). There is sensory and motor nerve involvement. Histologically, this form too is characterized by granulomatous infiltrates, which may extend into the

**Figure 6** Borderline tuberculoid leprosy (BT).

# Borderline borderline form (BB)

In this form, there is an overall increase in the number of lesions. They are distributed nearly symmetrically and may exhibit clinical features of both tuberculoid and lepromatous leprosy (Figure 7). Hair growth and sweating are hardly affected. Depending on the lesion, few or numerous bacteria may be detected. The histological picture is increasingly less characterized by granulomas. Peripheral nerves exhibit motor and sensory deficits.

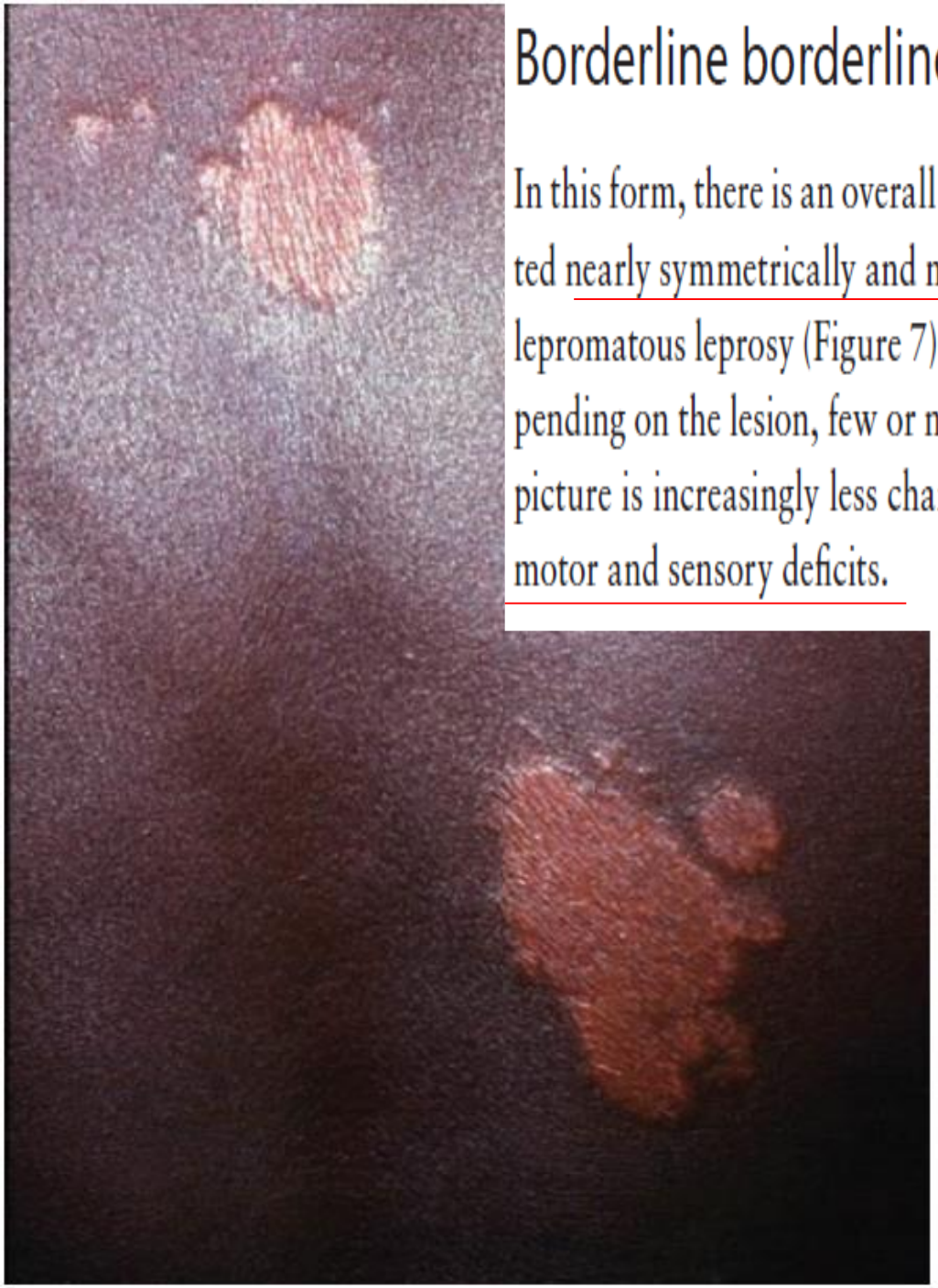
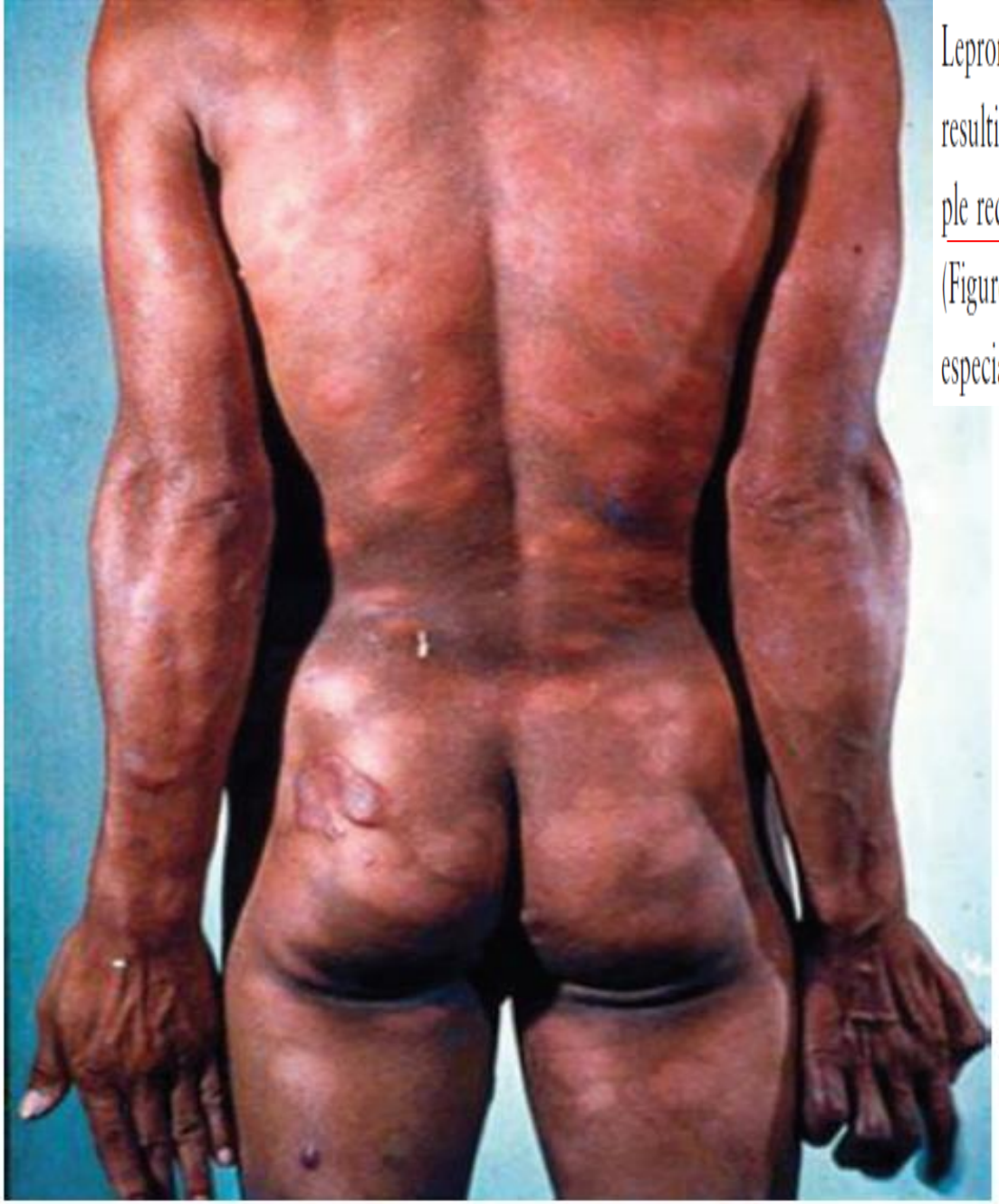


**Figure 7** Borderline borderline leprosy (BB).

## Borderline lepromatous form (BL)

Multiple, poorly demarcated, hypopigmented papules, nodules, and infiltrated plaques are the hallmark of this form (Figure 8). Lesions are largely distributed symmetrically; unaltered skin can still be recognized as such. Hair growth and sweating are hardly affected. There is extensive peripheral nerve involvement. Histology is marked by the absence of granulomas with epithelioid and giant cells. Perineurally, there are histiocytic infiltrates. A vast number of mycobacteria arranged in clusters can be found.

**Figure 8** Borderline lepromatous leprosy (BL). The auricle is also affected. The patient was initially referred with the diagnosis of urticaria.



Lepromatous leprosy occurs in infected individuals with impaired T-cell immunity resulting in anergy. Clinically, this multibacillary form is characterized by multiple red-brown nodular infiltrates (lepromas) in the skin and mucous membranes (Figure 3). Predilection sites for these diffuse infiltrates are the face and auricles, especially the earlobes (Figure 4). The lesions occur symmetrically.

**Figure 3** Lepromatous leprosy: multiple infiltrated lesions across the entire body (lepromas).

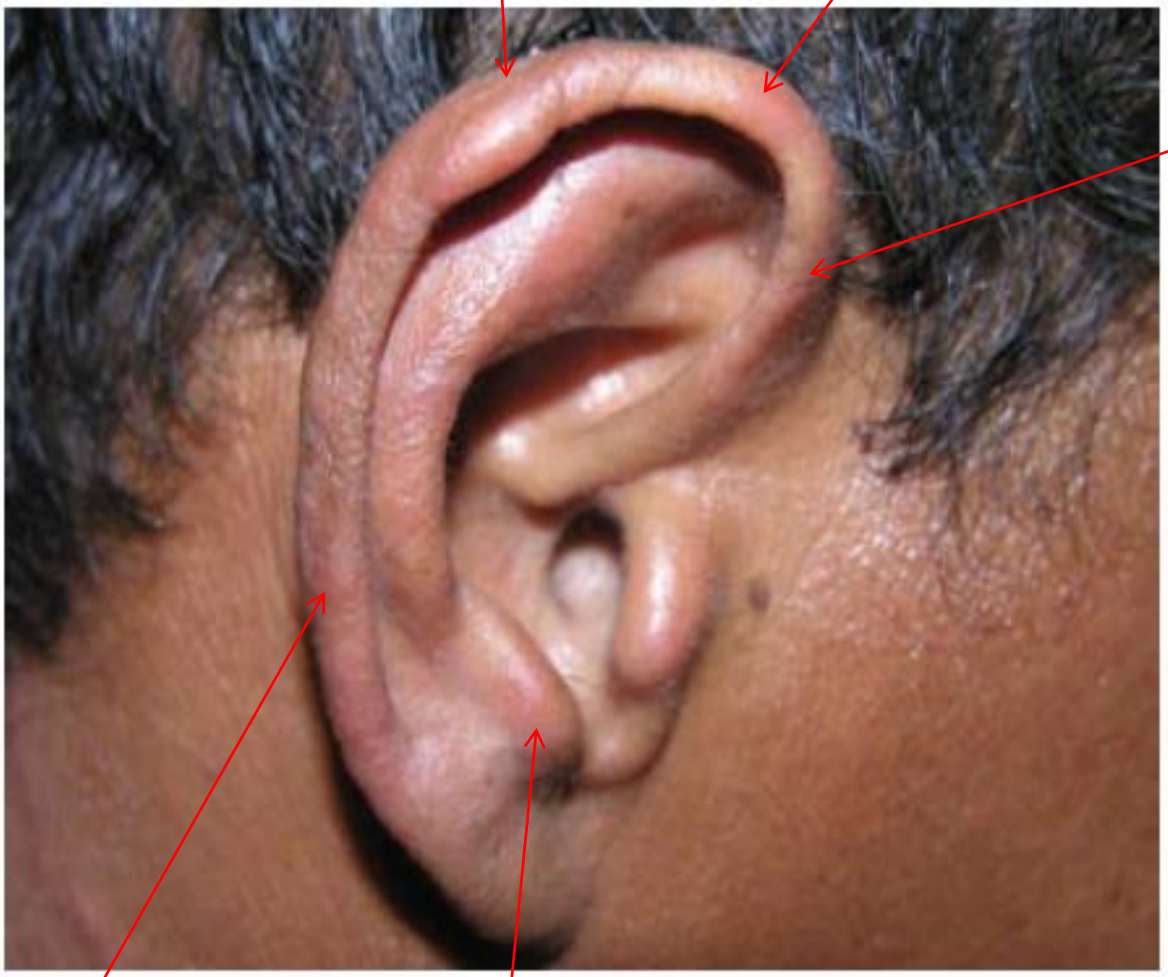
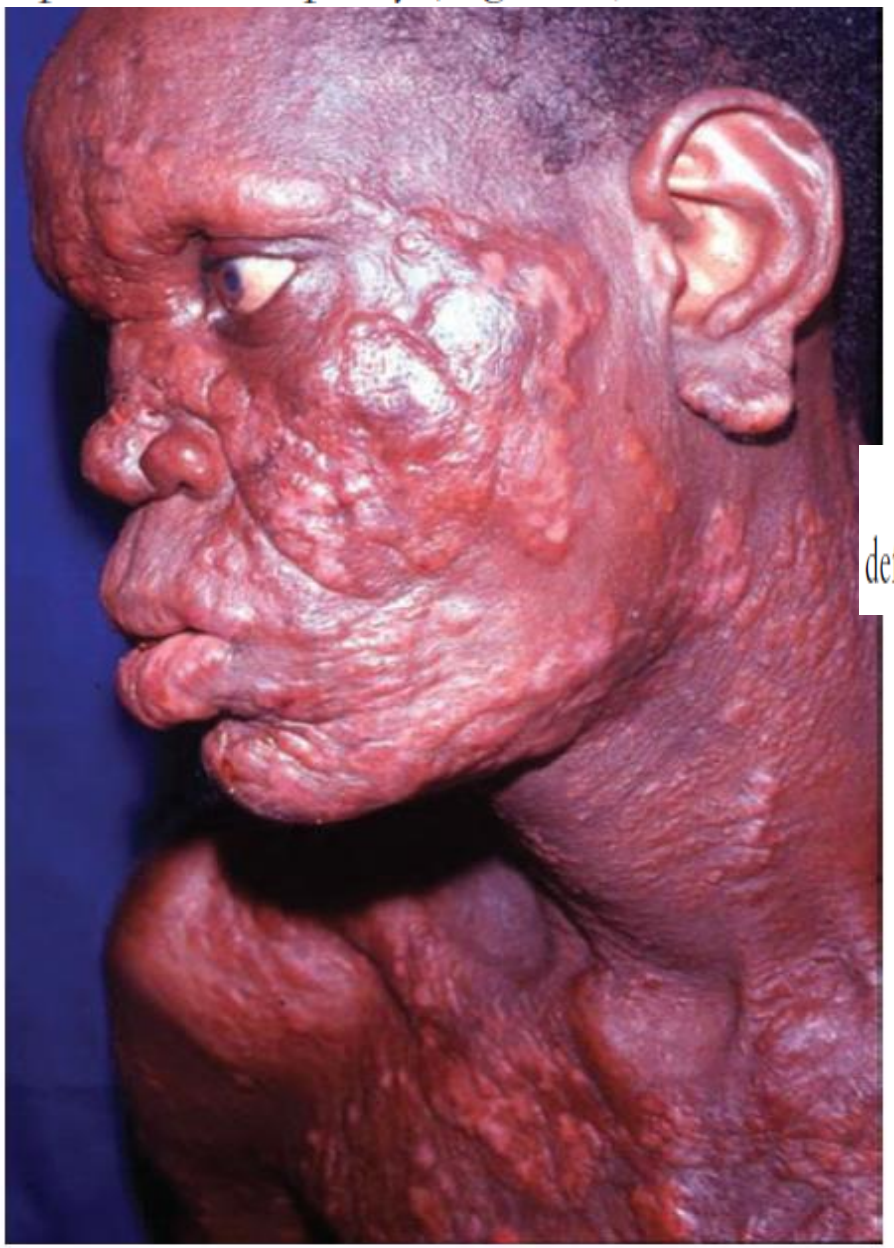


**Figure 4** Lepromatous leprosy: characteristic infiltration of the auricle.

The symmetrical centrofacial distribution of the cushion-like lesions is referred to as "leonine facies"; loss of the eyelashes and eyebrows is also typical of lepromatous leprosy (Figure 5).



In lepromatous leprosy, the individual bacterial mass in the human body may amount to several kilograms.

Involvement of the nasal mucosa leads to destruction of the septum and deformity of the nasal skeleton (saddle nose). Subsequently, this destructive

**Figure 5** Lepromatous leprosy: cushion-like centrofacial infiltrates (leonine facies) (courtesy of: Dr. P. Traoré, Mali).

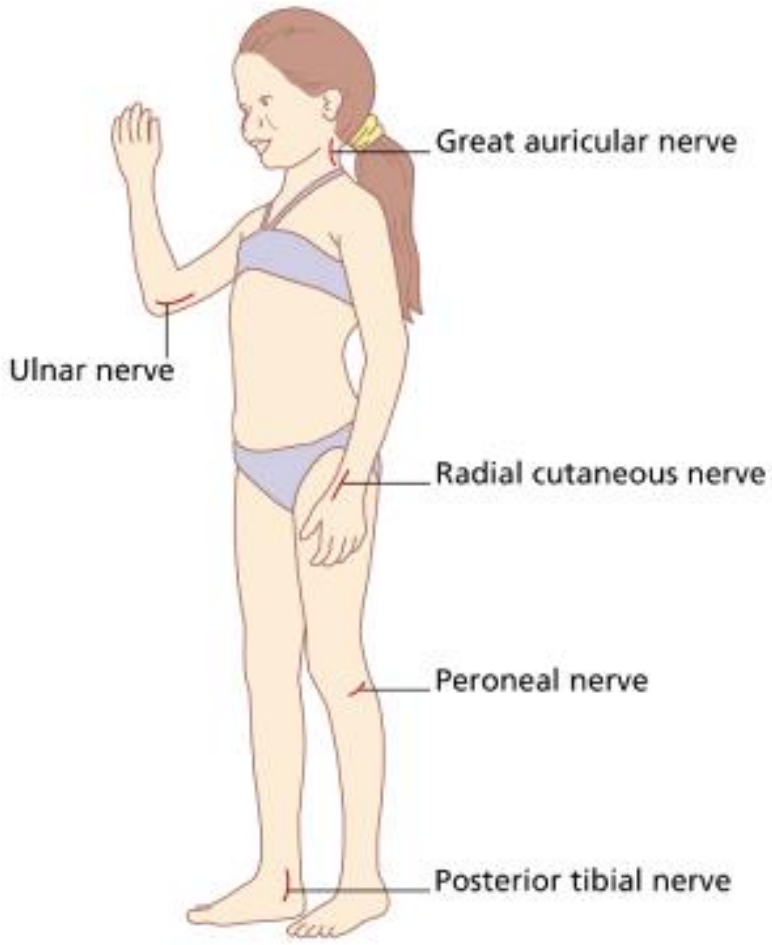
One complication that is particularly feared with regard to the multibacillary forms of leprosy is ocular involvement, which leads to permanent loss of vision including complete blindness in up to 10 % of patients. Pathophysiologically, the cause of blindness is multifactorial.

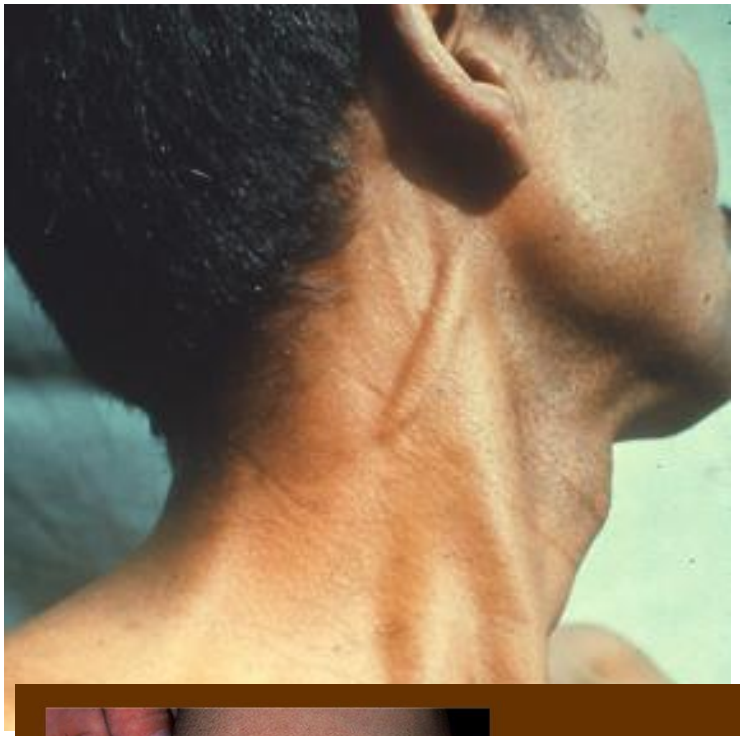
Lymphatic and hematogenous spread of *M. leprae* can lead to involvement of the kidneys (glomerulonephritis with nephrotic syndrome and subsequent amyloidosis), the liver (hepatitis and periportal fibrosis), and to acute orchitis. Osseous involvement presents with multibacillary bone marrow lepromas; joint involvement results in joint effusions.

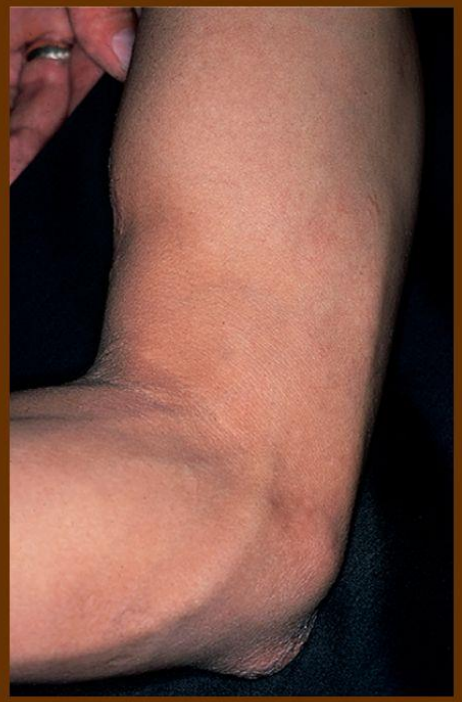
**Table 2** Nerves that are particularly affected and clinically palpable in advanced stages.

- Ulnar nerve in the ulnar groove
- Median nerve prior to entering the carpal tunnel
- Common peroneal nerve at the level of the fibular head
- Posterior tibial nerve behind the medial malleolus
- Superficial branch of the radial nerve; nerve compression syndrome (Wartenberg's syndrome) with sensory deficits (dorsoradial aspect of the hand)
- Sural nerve behind the lateral malleolus
- Great auricular nerve at the posterior margin of the sternocleidomastoid muscle
- Facial nerve, frontal branches and cervical branches

Nerve involvement is found in all forms of leprosy and may also occur in the absence of skin lesions [9].





Nerve enlargement, palpable or visually enlarged nerve may be a sign of leprosy.

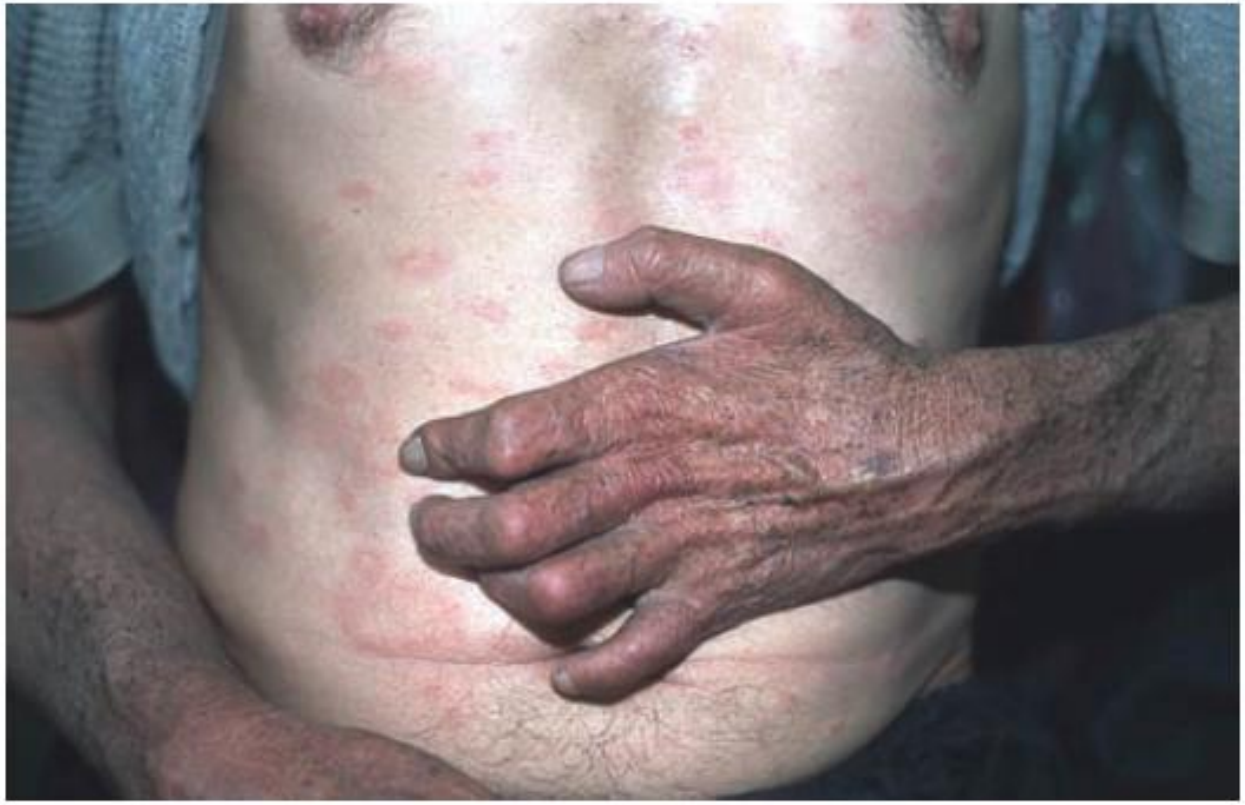


**Figure 11** Claw hand due to damage of the ulnar nerve. Kabul, Afghanistan, 2002.

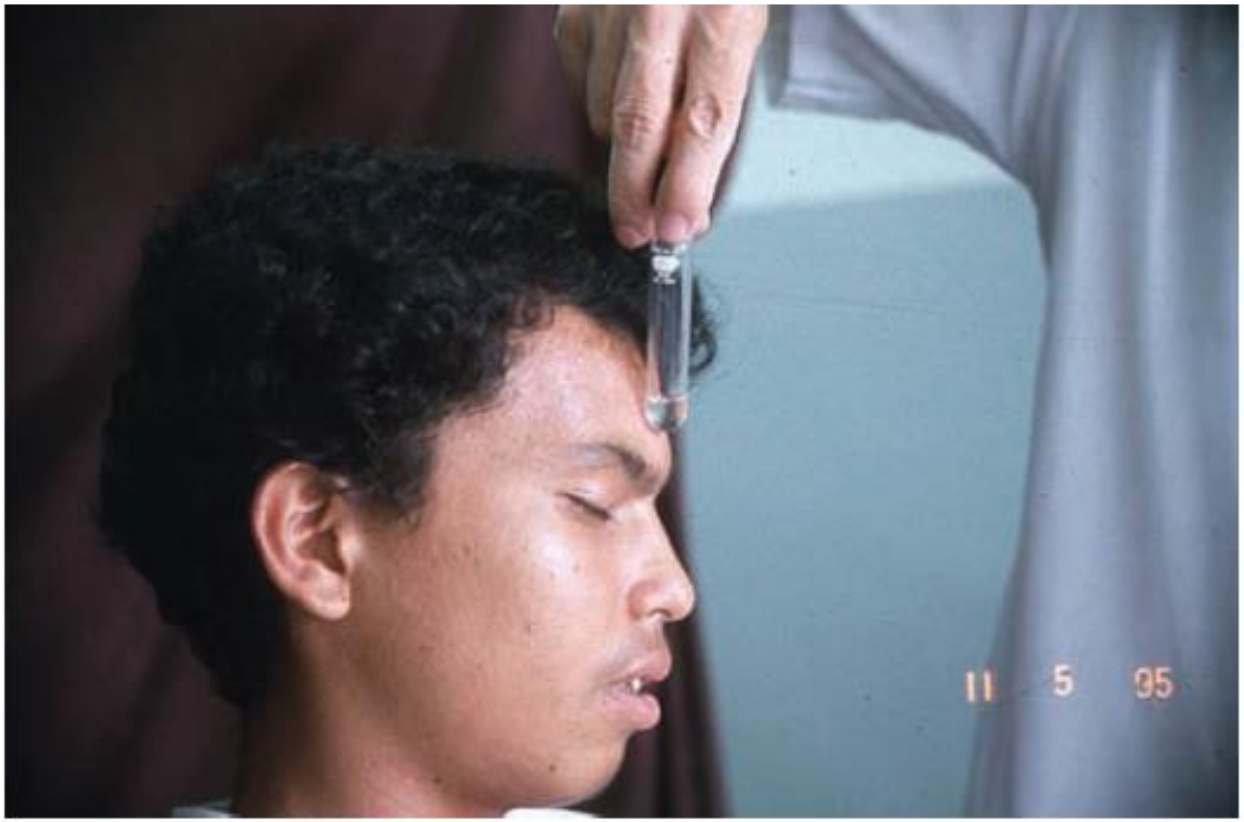



**Figure 13** Loss of thermosensitivity: test tube with warm water.

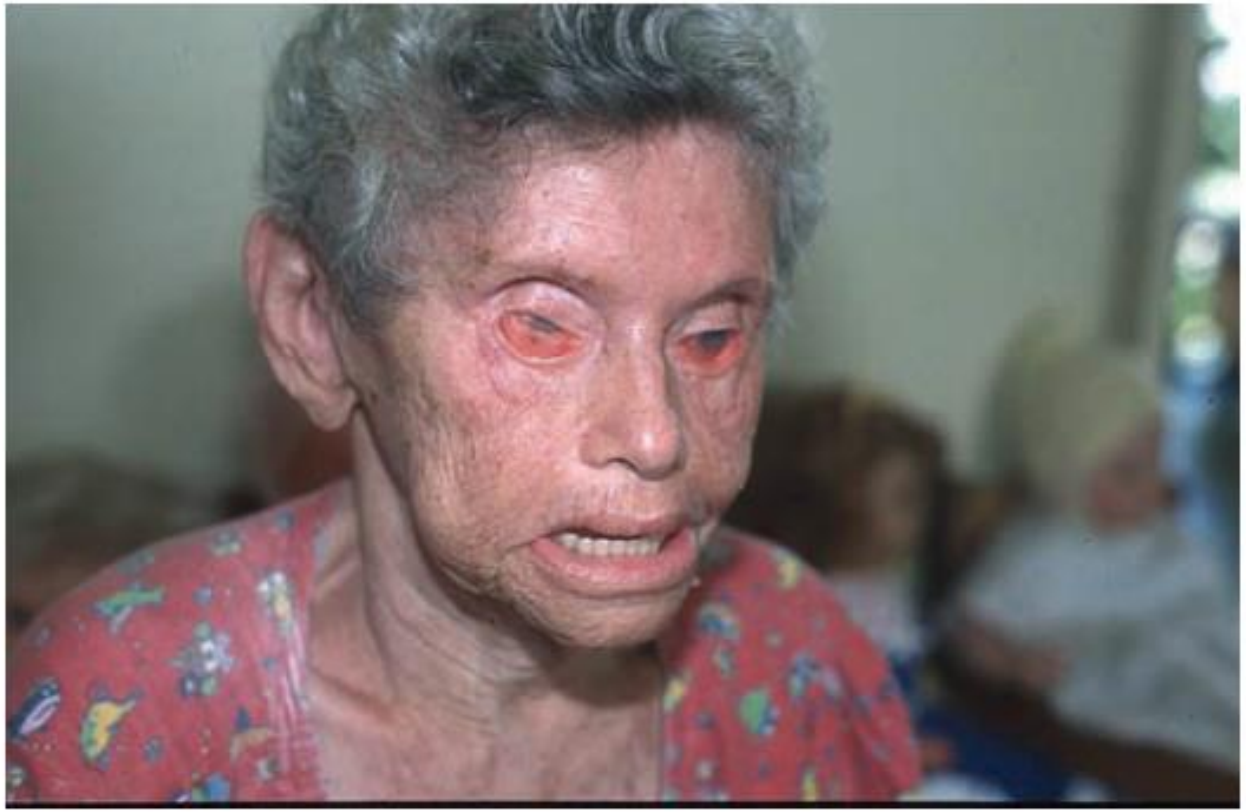


**Figure 14** Lagophthalmos (Bell's palsy). Manaus, Brazil, 2001.

Clinically, the resultant ocular muscle paralysis causes lagophthalmos, subsequently facilitating secondary corneal infections due to incomplete lid closure (Bell's palsy) (Figure 14). The resulting blank facial expression is referred to as antonine facies. Sensory loss of the ophthalmic branch (V1) of the trigeminal nerve, too, results in corneal anesthesia, thus facilitating bacterial corneal ulcerati-

# A Case of Leprosy in Italy: A Multifaceted Disease Which Continues to Challenge Medical Doctors

Martina Maritati[1] · Carlo Contini[1]

We describe the case of a 22 years old man, native from Ghana, who came to Italy after living in Libya in the previous 2 years. He was sent to the service of Rheumatology because of "pain in hands," due to a compression syndrome of the left ulnar nerve (tunnel olecranon). The patient, guest at one local Reception Center for refugees, was found positive to the tuberculin skin test and the QuantiFERON-TB Gold (Chest X-Ray negative); as a consequence, anti-TB prophylaxis with isoniazid was started.

After few months, the patient presented infiltrated and round subcutaneous lesions located on his face, interpreted by dermatologists as urticaria's manifestations. Such lesions, after a further dermatological consultancy, were subsequently described as "infiltrated, fixed, auburn and with irregular borders, associated with arthralgias and arthritis of the hands, ankles and knees". An infectious

Fig. 1 Representative case of ulnar neuropathy involving the fourth and fifth finger of the right hand associated with sensory deficit [4]



J Immigrant Minority Health (2016) 18:490–493

# An inflammatory myopathy unmasks a case of leprosy in an Italian patient

R. Liguori[1,2] · R. Terlizzi[1,2] · M. P. Giannoccaro[2] · A. Amati[3] · M. P. Foschini[2] · A. Parodi[4] · M. L. Valentino[1,2]

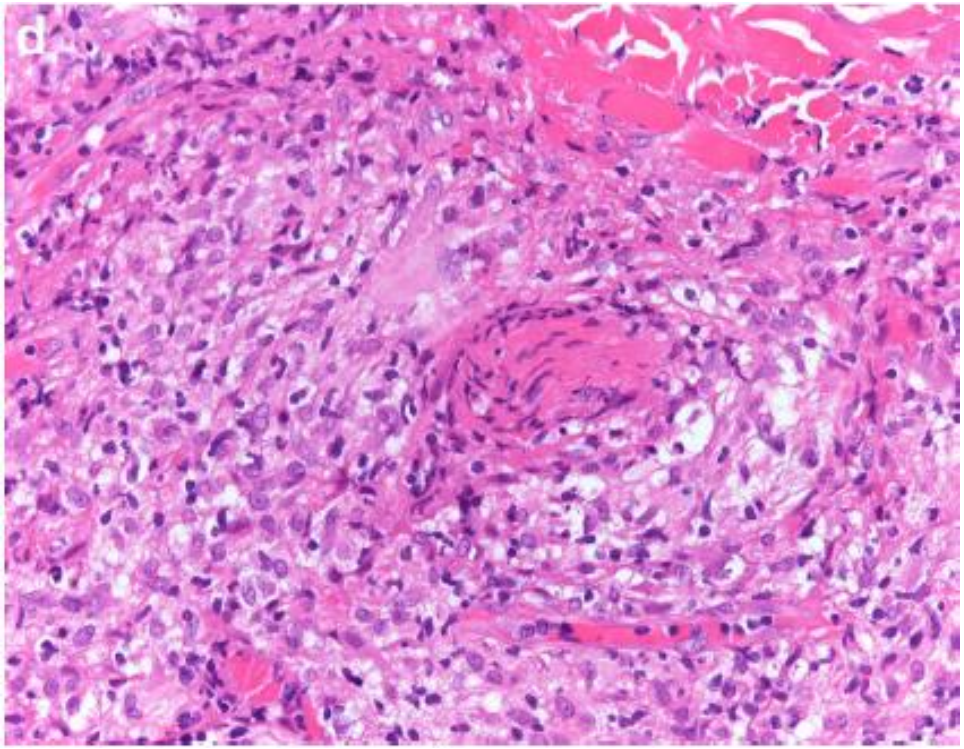
An Italian 61-year-old man presented with a history of diffuse myalgia, limb-girdle muscle weakness and skin lesions. Symptoms started at age 59 with progressive fatigability associated with diffuse arthralgia, prevalent at ankles and wrists, and slight fever followed, after about 6 months, by the appearance of erythematous nodular skin lesions spreading from the arms to the legs, back and trunk over a period of 6 months. After about 1 year from symptom onset, laboratory testing revealed high serum CK levels (up to 1552 U/L, normal values <195 U/L) with normal inflammatory markers. He underwent a muscle biopsy of the biceps brachii, which showed an inflammatory myopathy with endomysial and perivascular cellular infiltrates (Fig. 1a, c). Immunostaining for MHC-class I antigens was positive (Fig. 1b). He was diagnosed with an inflammatory myopathy and started on oral steroid therapy (prednisone 75 mg/day), which led to normalization of CK values, improvement of muscle symptoms and disappearance of skin lesions. After some months, steroid therapy was gradually withdrawn with subsequent relapse of clinical symptoms. At age 61 years, at the time of our evaluation, neurological examination showed paralysis of the left VII cranial nerve, proximal muscle weakness of legs, patchy areas of hypoesthesia of feet and hands, and reduced deep tendon reflexes. On general examination, wrist and ankle joints appeared swollen and multiple maculopapular skin lesions were noted on arms, glutei and trunk.



J Neurol (2015) 262:2179–2181

# An inflammatory myopathy unmasks a case of leprosy in an Italian patient

R. Liguori[1,2] · R. Terlizzi[1,2] · M. P. Giannoccaro[2] · A. Amati[3] · M. P. Foschini[2] · A. Parodi[4] · M. L. Valentino[1,2]



In the meantime, skin biopsy of two different lesions was performed and revealed an inflammatory granulomatous infiltrate around nerves, vessels and annexes, suggestive of tuberculoid leprosy (Fig. 1d). However, histological stainings for acid fast bacilli and PCR analysis for ML and MTB were negative with respect to skin and both muscle biopsies. Because of the suspicion of leprosy, the patient underwent a sural nerve biopsy and the presence of ML was confirmed by PCR analysis. The patient underwent a 6-month therapy with rifampicin (600 mg once a month) and dapsone (100 mg daily) with complete remission of muscle and skin manifestations after 6 months from the end of therapy, but persistence of sensory symptoms. No relapses have been observed to date.



J Neurol (2015) 262:2179–2181

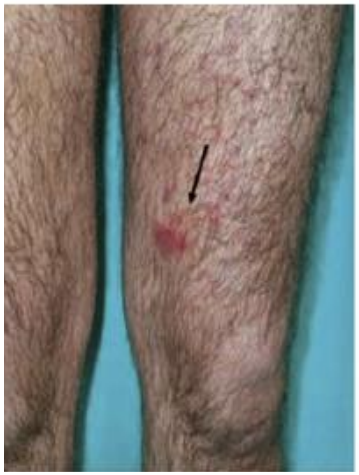
# Leprosy Initially Misdiagnosed as Sarcoidosis, Adult-Onset Still Disease, or Autoinflammatory Disease

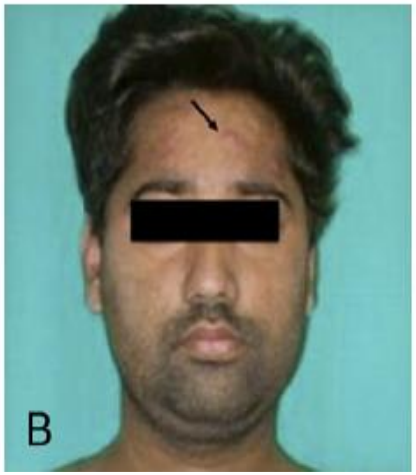
*Sara Simeoni, MD,* Antonio Puccetti, MD,† Elisa Tinazzi, MD,* Orazio Michele Codella, MD,* Michele Sorleto, MD,* Giuseppe Patuzzo, MD,* Chiara Colato, MD,‡ Gianpaolo Tessari, MD,§ and Claudio Lunardi, MD**

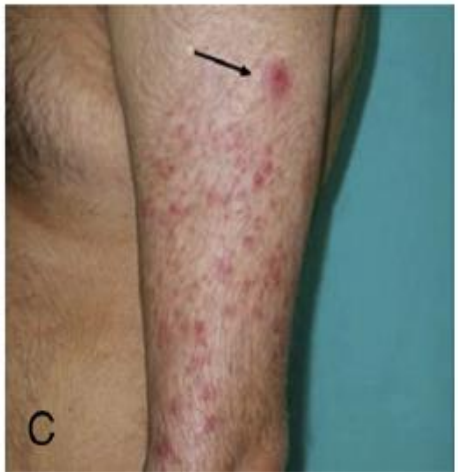
We present a 20-year-old man who moved to Italy from India in 2003; in September 2006, he was admitted to a hospital in northern Italy for the presence of high continuous fever; erythematous papules, macules, and nodules on his arms, legs, and face, with no hypopigmentation or anesthesia; arthritis of the wrists and ankles; and episcleritis in both eyes (Figs. 1A–C). His family history was noncontributory (at first he denied any familiar disease), and his medical history was otherwise unremarkable.

Laboratory investigations showed neutrophilic leukocytosis (white blood cells, 21,400/μL; neutrophils, 87%), very high erythrocyte sedimentation rate (65 mm in the first hour; normal value, <22 mm/hr) and C-reactive protein (300 mg/L; normal value, <5 mg/L), and increased serum angiotensin-converting

(*J Clin Rheumatol* 2011;17: 432–435






Although no skin or transbronchial biopsy was performed on that occasion, "possible sarcoidosis with prevalent extrapulmonary involvement" was diagnosed, and the patient was administered high-dose corticosteroid therapy (1 mg/kg per day) with sudden clinical improvement. After 6 months when the tapering of prednisolone reached 12.5 mg/d, a severe flare of the disease occurred with the same symptoms present at the beginning of the disease. On that occasion, a gallium (Ga) 67

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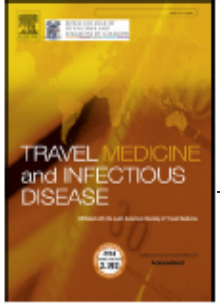



# A case of imported leprosy in Italy: Implications for surveillance by Public Health Services of Local Health Authorities

In April 2017, a 29-year-old Nigerian man referred to the dermatological unit of the city's public hospital, because of non-itchy papulose lesions located on his head and hands. Histopathology of the biopsy material revealed a non-necrotising chronic granulomatous dermatitis with numerous alcohol-acid-resistant bacilli. *Mycobacterium leprae* was identified by 16SrRNA gene sequence analysis. The patient was addressed to the National Leprosy Centre for Hansen's disease (San Martino Hospital, Genoa) which confirmed the diagnosis of Multibacillary Lepromatose Leprosy and started specific therapy. After hospital discharge, the patient was invited to undergo follow-up checks every month at the local infectious disease unit of Rimini and every six months at the national reference centre for a period of almost 5 years. The checks carried out so far (the last in January 2019) evidenced no signs of evolving disease.

*Clinical Infectious Diseases*

PHOTO QUIZ

Anthony Amoroso and Ajit P. Limaye, Section Editor

# A Large Annular Plaque on the Face

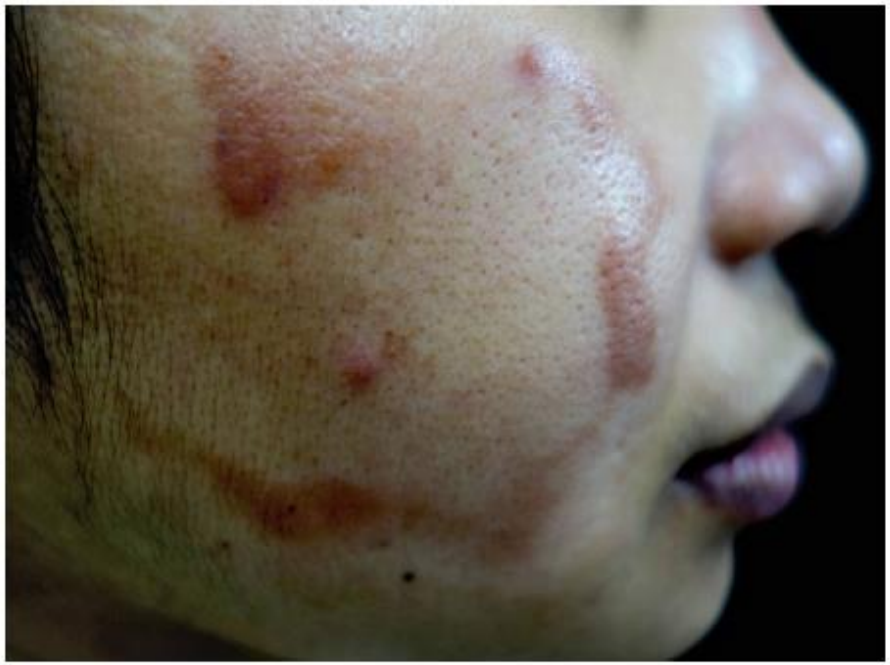


**Figure 1.** A brownish infiltrated plaque with an incompletely annular configuration and irregular border on the right cheek; inside the annular plaque was an area of normal skin with some satellite papules.

A 37-year-old previously healthy woman presented to our clinic with a 5-month history of asymptomatic skin lesions on her face. She was an immigrant worker from Indonesia. On physical examination, a brownish infiltrated plaque with an incompletely annular configuration and irregular border was noted on her right cheek; inside the annular plaque was an area of normal skin with some satellite papules (Figure 1). There was no scaling or erosion. The thermal sensation on the right cheek was diminished compared to the left side. There were no other skin lesions noted, and she denied constitutional symptoms such as fever, malaise, or dyspnea. She had been treated with topical isoconazole cream at an outside facility without significant improvement. A potassium hydroxide test failed to detect any fungal elements, and the result of a subsequent fungus culture was negative. She tested negative on human immunodeficiency virus and syphilis tests and was not immunosuppressed due to use of biologic agents or chemotherapy.

What is your diagnosis?

*Clinical Infectious Diseases*

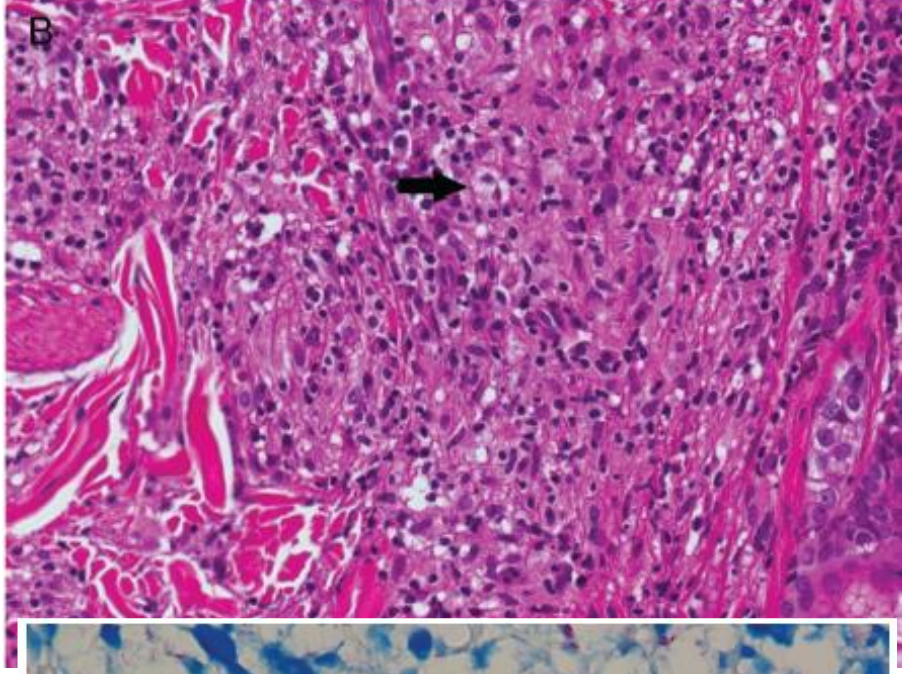
## ANSWER TO THE PHOTO QUIZ

Anthony Amoroso and Ajit P. Limaye, Section Editor

# A Large Annular Plaque on the Face

Diagnosis: Borderline lepromatous leprosy.

The initial differential diagnostic considerations included leprosy, tinea faciei, secondary syphilis, granuloma annulare, annular sarcoidosis, and actinic granuloma. An incisional skin biopsy was performed. The histopathological examination revealed ill-defined granulomas with lymphocytic infiltration in the dermis distributed in a perivascular and periadnexal fashion, a grenz zone of uninvolved area in the papillary dermis, and some macrophages with foamy cytoplasm (Figure 2). Acid-fast stain of the specimen showed acid-fast bacilli in high-power field (Figure 3). The result from a mycobacterial culture performed on the biopsy from the skin lesion was negative. Polymerase chain reaction (PCR) on biopsy detected *Mycobacterium leprae*. The patient returned to her home country for further treatment according to local regulations.



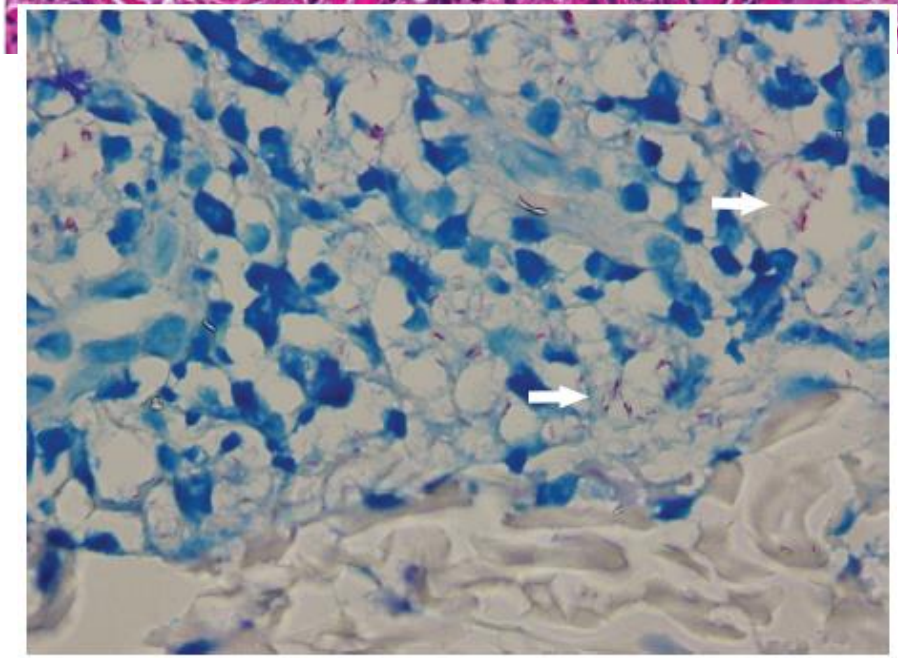



**Figure 3.** Acid-fast stain of the specimen showed acid-fast bacilli distributed in a perineural and periadnexal manner (arrow). Oil immersion, ×1000 magnification.

Standard multidrug therapy regimens for paucibacillary and multibacillary leprosy in adults and children (WHO recommendation, 2013) [33].

*Schémas thérapeutiques préconisés par l'OMS en 2013 dans les lèpres pauci-bacillaire et multi-bacillaire chez les adultes et les enfants [33].*

| Clinical presentations | Population | Agents | Dosing regimen | Treatment duration |
|---|---|---|---|---|
| Paucibacillary leprosy | Adults | Rifampicin | 600 mg/month | 6 months |
| | | Dapsone | 100 mg/day | |
| | Children | Rifampicin | 450 mg/month | 6 months |
| | | Dapsone | 50 mg/day | |
| Multibacillary leprosy | Adults | Rifampicin | 600 mg/month | 12 months |
| | | Clofazimine | 300 mg/month and 50 mg/day | |
| | | Dapsone | 100 mg/day | |
| | Children | Rifampicin | 450 mg/month | 12 months |
| | | Clofazimine | 150 mg/month and 50 mg/day | |
| | | Dapsone | 50 mg/day | |

## Box 1: Reversal Reaction (RR)

- More common in BB and BL patients, as compared to BT patients.
- Acute inflammation of skin and/or nerves: nerve function impairment.
- Erythematous swelling of existing lesions, appearance of new lesions; onset or worsening of neuritis.
- Lesions usually present with increased infiltrates of lymphocytes, epitheloid cells, giant cells, edema, and a decrease in bacterial load. The immune response is characteristic of a delayed-type hypersensitivity (DTH).
- Cell mediated immune process, characterized by an increase in lymphoproliferative response of lymphocytes to *M. leprae,* as well as pro-inflammatory cytokines such as IL-1, IL-2, IL-12, IFN-γ and TNF
- The specific role of T cells in RR is unknown.

## Type 1 reaction

Pathophysiologically, this is a hypersensitivity reaction to *M. leprae* antigens clinically characterized by sudden onset of urticarial swelling of the leprous skin lesions. It may also be associated with acute and very painful neuritides with loss of sensory and motor function (Figures 9, 10). Affected nerves are markedly thickened and exhibit abscesses. The condition may be associated with high fever. It is the most common leprosy reaction and occurs in up to 30 % of patients with borderline tuberculoid (BT), borderline borderline (BB) and borderline lepromatous leprosy (BL), usually within twelve months after treatment initiation. Possible triggers include pregnancy, comorbidities, and therapies.

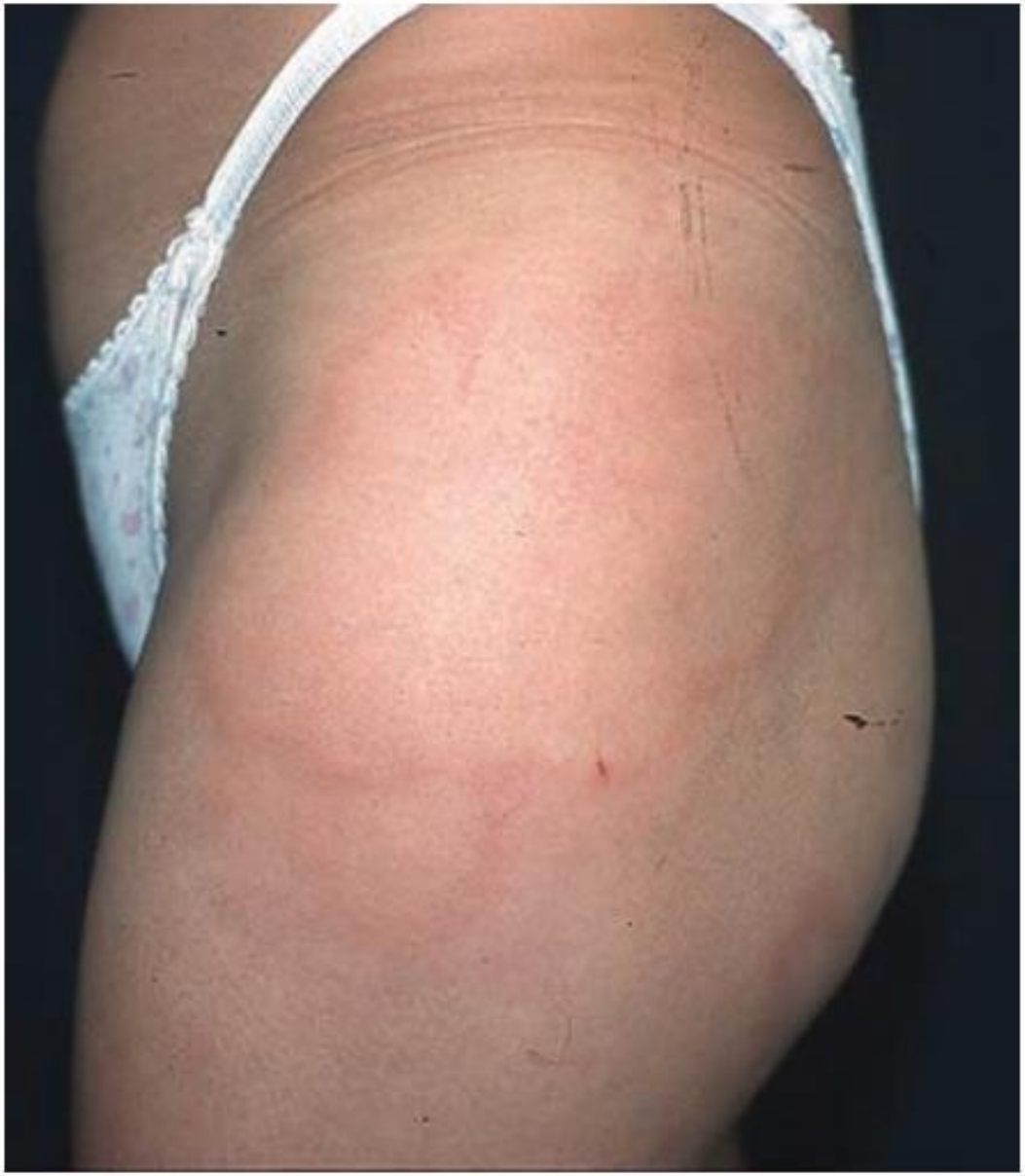


**Figure 9** Four months after treatment initiation, the patient depicted in Figure 8 developed a type 1 leprosy reaction. The figure shows the initial clinical findings.

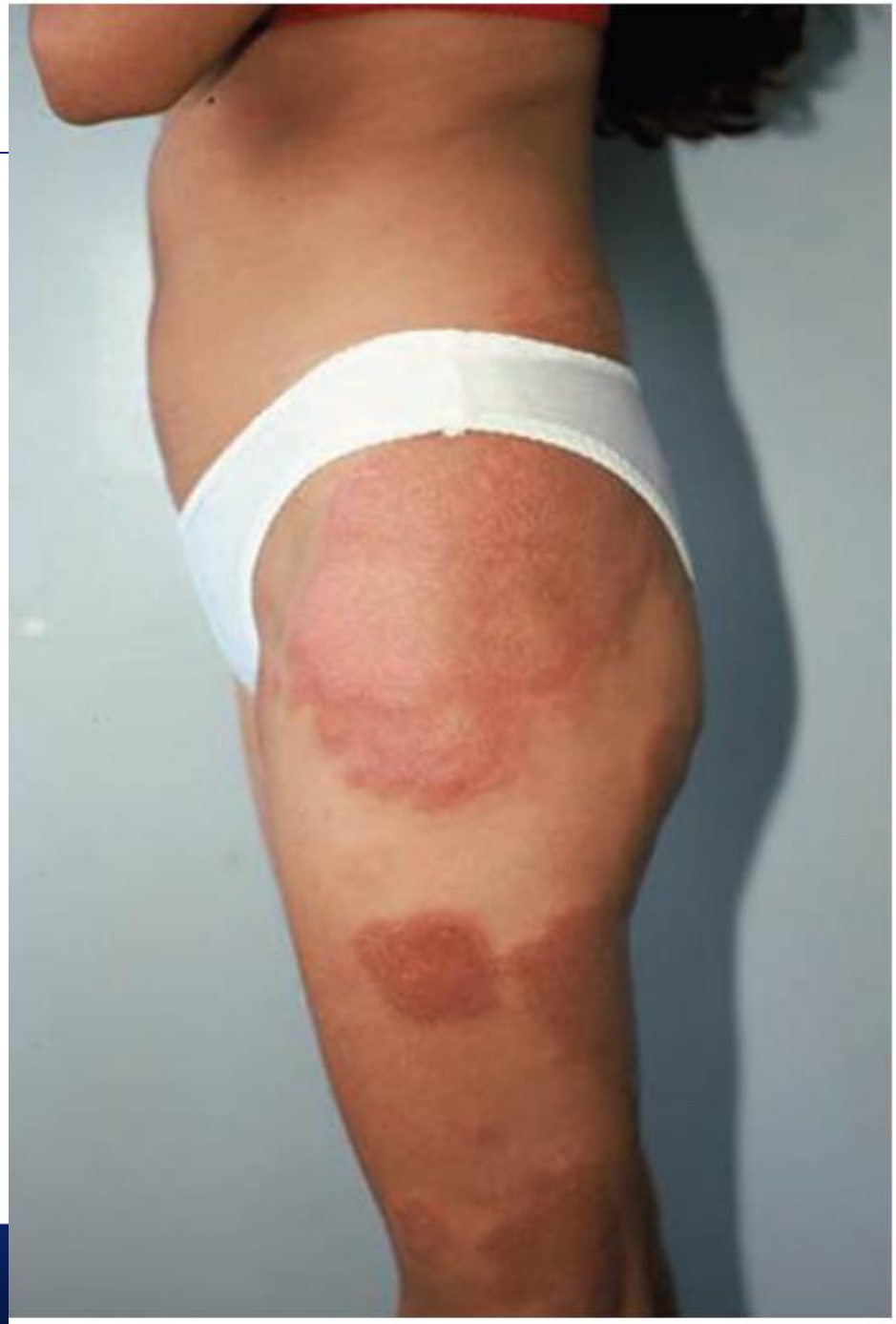


**Figure 10** Prominent urticarial infiltration as a clinical sign of a type 1 leprosy reaction. Manaus, Brazil, 2001.

## Box 2: Erythema Nodosum Leprosum (ENL)

- Afflicts 20% of LL and 10% of BL patients. High bacterial load and greater infiltration of lesions as important risk factors.
- Painful and tender red papules or nodules, which may be accompanied by fever, joint pain, edema of the hands, feet, and face, proteinuria and malaise. Neuritis is usually milder than in RR.
- Immune complex mediated disease with some degree of CMI. Histologically characterized by neutrophils, followed by an increased number of lymphocytes, plasma cells, and histiocytes. Vasculitis appears to be a major pathologic event, along with interstitial edema and necrotizing changes
- Recruitment of immune cells into the lesional sites and their activation is largely effected through the various soluble molecules, such as cytokines, chemokines, and immune complexes.
- The antigen specific function of T cell is ill defined.

## Type 2 reaction (syn. erythema nodosum leprosum)

Clinically, this leprosy reaction is characterized by the occurrence of painful violaceous- erythematous cutaneous or subcutaneous nodules. Unlike classic erythema nodosum, they are found not only on the lower legs but across the entire body. The skin lesions may ulcerate and become necrotic. They occur predominantly on the extensor aspects of the extremities and on the face; the trunk may also be affected. Pathophysiologically, the reaction constitutes an immune complex vasculitis (Coombs and Gell type 3 reaction) with the histological correlate of

Signs and Symptoms of Erythema Nodosum Leprosum.

| Organ or System | Sign and Symptom |
|---|---|
| Skin | Inflamed subcutaneous erythematous nodules or deep or superficial papules. Less of ten vesicles, blisters and pustules. |
| Joints | Polyarthritis or polyarthralgia |
| Lymph nodes | Lymphadenopathy |
| Eyes | Uveitis (iritis and iridocyclitis) that can progress to cataracts, glaucoma and blindness. |
| Liver | Hepatosplenomegaly |
| Testicles | Orchitis and epididymitis |
| Kidneys | Glomerunephritis, tubulo-interstitial-nephritis and amyloidosis which can progress to renal failure. |
| Respiratory system | Rhinitis, epistaxis, laryngitis |
| Bone | Dactylitis, pre-tibialgia |
| Muscles | Myositis |
| Nerves | Neuritis |
| Others | Acrofacial or generalized edema, fever, insomnia and depression. |

Table 3

Classification of ENL according to the severity of the reaction.

| SEVERITY | CHARACTERISTICS |
|---|---|
| MILD | Less than 10 nodules per affected body segment, predominantly in the lower limbs and slightly painful to palpation with absence or mild intensity of systemic signs and symptoms. |
| MODERATE | 10 to 20 nodules per affected body segment, necessarily more than one, accompanied by moderate fever (< 38.4 °C), with mild systemic symptomatology and local and/or regional lymph node involvement. |
| SEVERE | More than 20 nodules per affected body segment, painful even without palpitation, usually involving a large area of the integument, sometimes having ulcerated lesions, accompanied by significant systemic symptoms such as high fever (> 38.5 °C), arthralgia, chills, headache, anorexia and generalized involvement of a lymph node. |

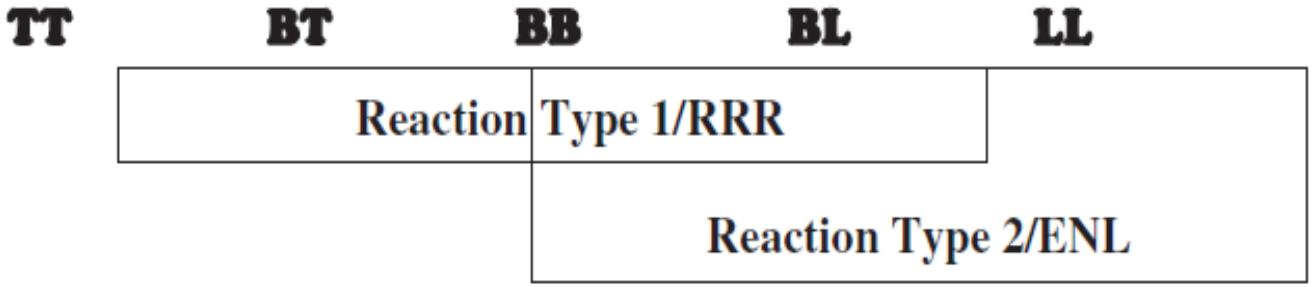
Characteristics of the main treatments available for ENL.

| Drug | Mechanism of action | Regimen of treatment | Most Frequent Adverse Effects |
|---|---|---|---|
| **Prednisone** | Inhibition of leukocyte recruitment and activity, activation of neutrophils and macrophages, and reduction in the production of TNF-α and IL-2, IL-4, IL-6 and IL-8 | 1 to 1.5 mg/kg/day for 15–30 days Reduction of 10 mg every 15 days up to the dose of 20 mg. Then decrease of 5 mg every 15 days. | Dependence, induced Cushing, acne, diabetes, osteoporosis, gastritis, cataract and immunosuppression, which can lead to the risk of opportunistic infections including fungal infections and tuberculosis, among others. |
| **Thalidomide** | Inhibition of the production of TNF-α and IL-6, IL-8, IL-10 and C-reactive protein. | 100–400 mg/day Reduction of 50 mg every 2–4 weeks | Teratogenicity, peripheral neuropathy, thrombosis, drowsiness, dizziness, constipation, rash, edema, neutropenia, bradycardia, dryness, pruritus, headache, hypotension, increased appetite, mood changes, male sexual dysfunction, nausea, tachycardia, weight gain. |
| **Pentoxifylline** | Inhibition of IL-1, IL-6, IL-8 and TNF-α synthesis. | 1200 mg/day No reduction | Dry mouth, constipation, anorexia, cholecystitis, septic meningitis, seizures, confusion, depression, anxiety, hypotension, edema, dyspnea, nasal congestion, nosebleed, breathing difficulty, rash, angioedema, urticaria, pruritus, brittle nails earache, scotoma, conjunctivitis, blurred vision, excessive salivation, malaise, leukopenia, bad taste, weight gain or loss, sore throat, nausea, headache. |
| **Clofazimine** | Inhibition of proliferation of T lymphocytes. | 3-month schedule: 100 mg 3X daily Reduction of 100 mg every month 15-month schedule: Starting dose 300 mg x day for 3 months Reduction of 100 mg over a period from one to six months. | Skin pigmentation and gastrointestinal effects: abdominal pain, nausea, diarrhea, vomiting, gastrointestinal intolerance, bowel obstruction. |

# Type 3 reaction (syn. Lucio's phenomenon)

Recently designated as type 3 reaction, Lucio's phenomenon is distinct from the aforementioned leprosy reactions. Clinically, this frequently afebrile reaction is characterized by extensive violaceous patches and bullous infiltrates; it is observed in untreated patients with lepromatous disease.

Affected areas of the skin may ulcerate and become necrotic. In case of successful treatment, lesions heal with scarring. Histopathology shows extensive vasculitis with endothelial proliferation. At an advanced stage, this is clinically reflected by cutaneous infarctions, thromboses, and hemorrhages. *M. leprae* can be detected in endothelial cells.




T-helper (Th) 1 *M. leprae* specific

- Cytokines: IL-2, IFN-γ, TNF, IL-10+/-
- Cell mediated immune response
- Activate macrophages
- Important against intracellular organisms

T-helper (Th) 2 *M. leprae* specific

- Cytokines: IL-4, IL-5, IL-13, IL-10+/-, IL-6-
- Antibody response
- Not very useful against intracellular organisms

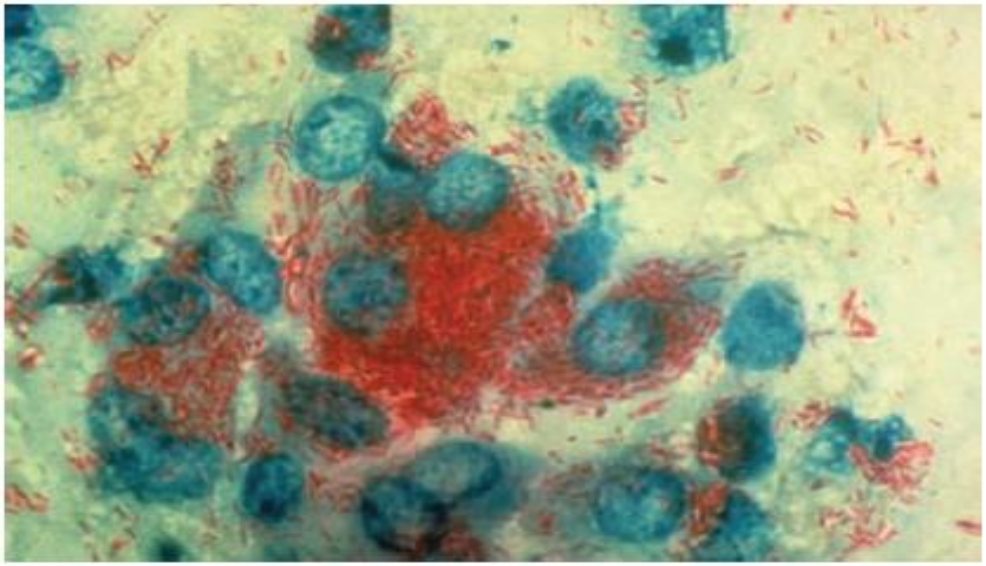


**Figure 15** Lepromatous leprosy with high bacterial load: vast number of *M. leprae* in a skin smear – Ziehl-Neelsen stain (© Deutsche Lepra- und Tuberkulosehilfe e. V. [DAHW]) [3].

| Bacterial count per visual field(s) | Bacterial index (BI) |
|---|---|
| 1–10/100 | 1 + |
| 1–10/10 | 2 + |
| 1–10/1 | 3 + |
| 10–100/1 | 4 + |
| 100–1000/1 | 5 + |
| > 1000/1 | 6 + |

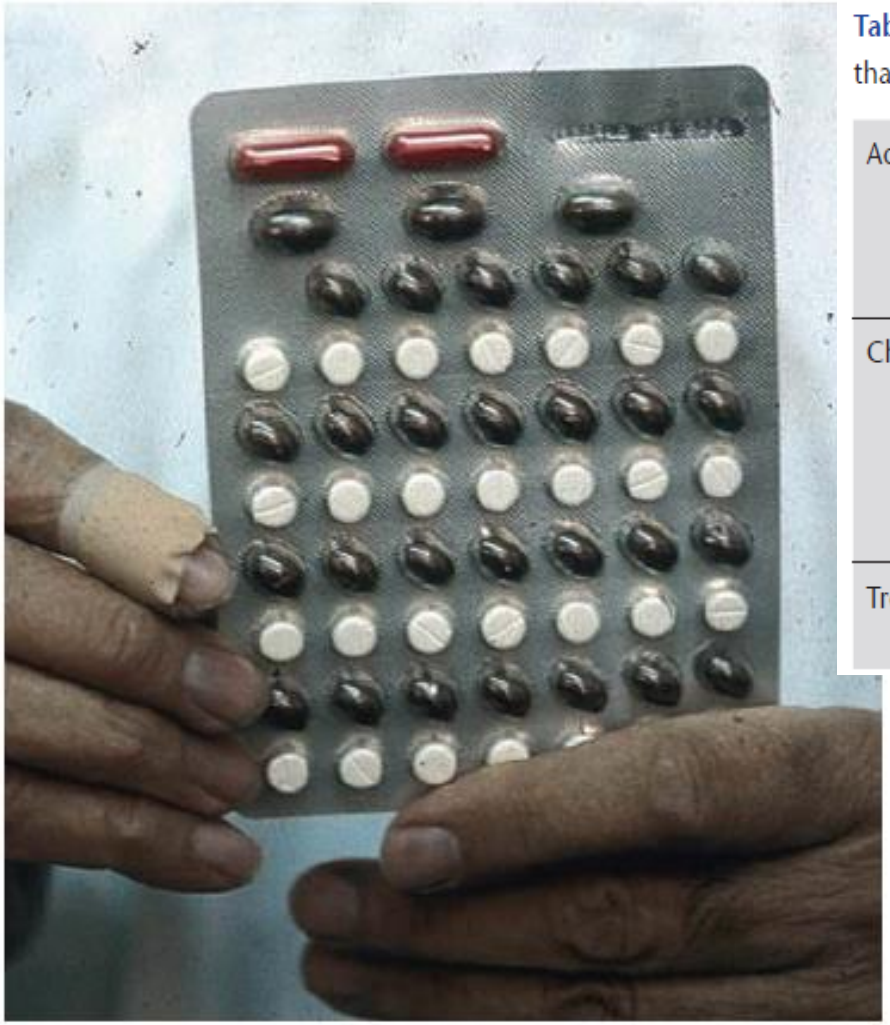


Table 5 WHO recommendation for the treatment of multibacillary leprosy (more than five lesions, bacteria detected).

| | |
|---|---|
| Adults | Once a month (taken under supervision): rifampicin 600 mg, clofazimine 300 mg, dapsone 100 mg.<br>Daily: clofazimine 50 mg and dapsone 100 mg |
| Children | Once a month (taken under supervision): rifampicin 450 mg, clofazimine 150 mg, dapsone 50 mg<br>Every other day: clofazimine 50 mg<br>Daily: dapsone 50 mg |
| Treatment duration | Twelve months or intake of twelve supervised monthly doses within 18 months |

**Figure 17** WHO standard treatment regimen for leprosy: blister pack for multibacillary treatment, including rifampicin, dapsone, and clofazimine.