

**Corso di formazione  
teorico-pratico  
per la diagnosi  
corretta della  
malattia  
di Hansen**



**25-26  
OTTOBRE  
2024**

**NAPOLI**

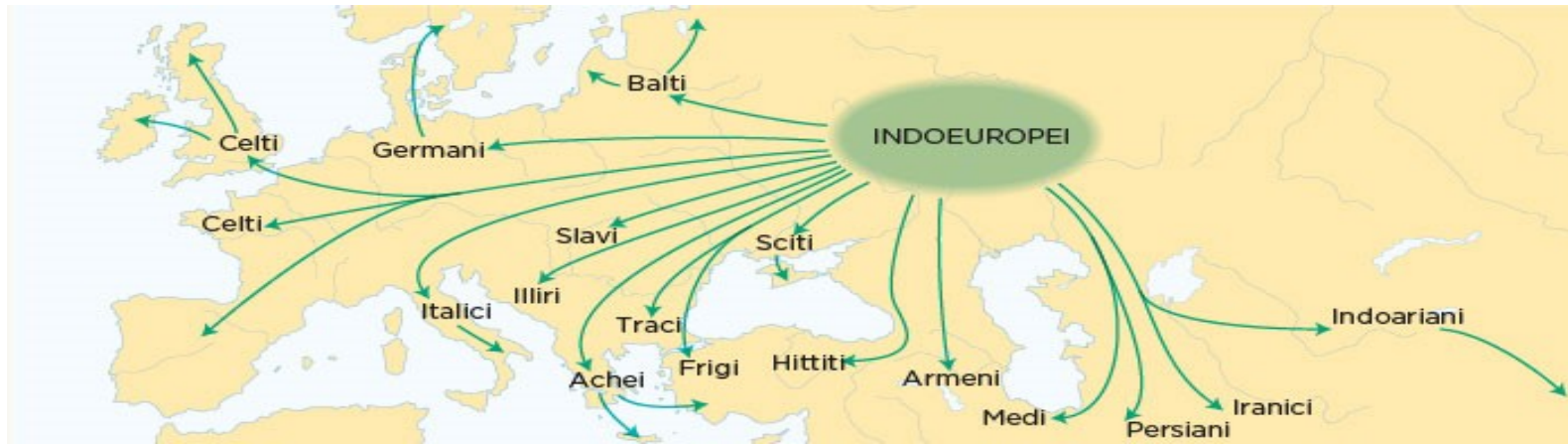
P.O. dei Pellegrini  
Asl Napoli 1 Centro



*Il Mycobacterium leprae:  
microbiologia e risposta immune*

*Biagio Pinchera*





*Λέπρα "squamoso"*







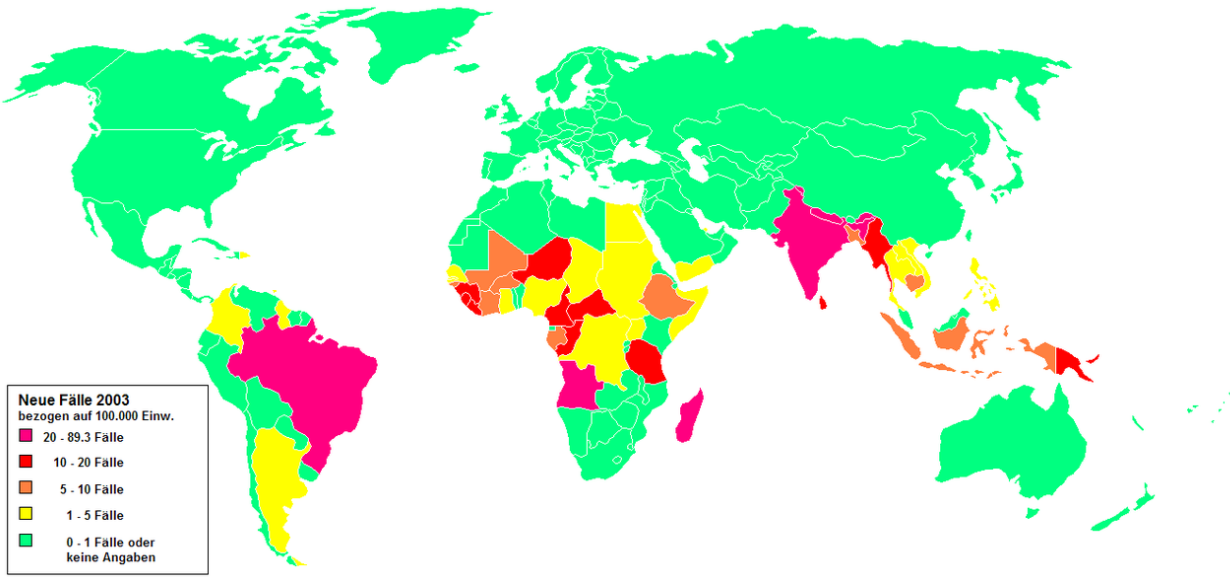
*Il Mycobacterium leprae fu scoperto da Gerhard Armauer Hansen in Norvegia nel 1873.*

*Primo batterio ad essere identificato come causa di malattia nell'uomo*

*Nel 1919 il medico giapponese Kensuke Mitsuda descrisse l'intradermoreazione alla lepromina.*

*Nel 1959, Piero Sensi e Maria Teresa Timbal scoprirono le rifamicine e, da queste, nel 1969 svilupparono la rifampicina, antibiotico attivo contro le micobatteriosi.*





Neue Fälle 2003  
bezogen auf 100.000 Einw.  
■ 20 - 89.3 Fälle  
■ 10 - 20 Fälle  
■ 5 - 10 Fälle  
■ 1 - 5 Fälle  
■ 0 - 1 Fälle oder  
keine Angaben

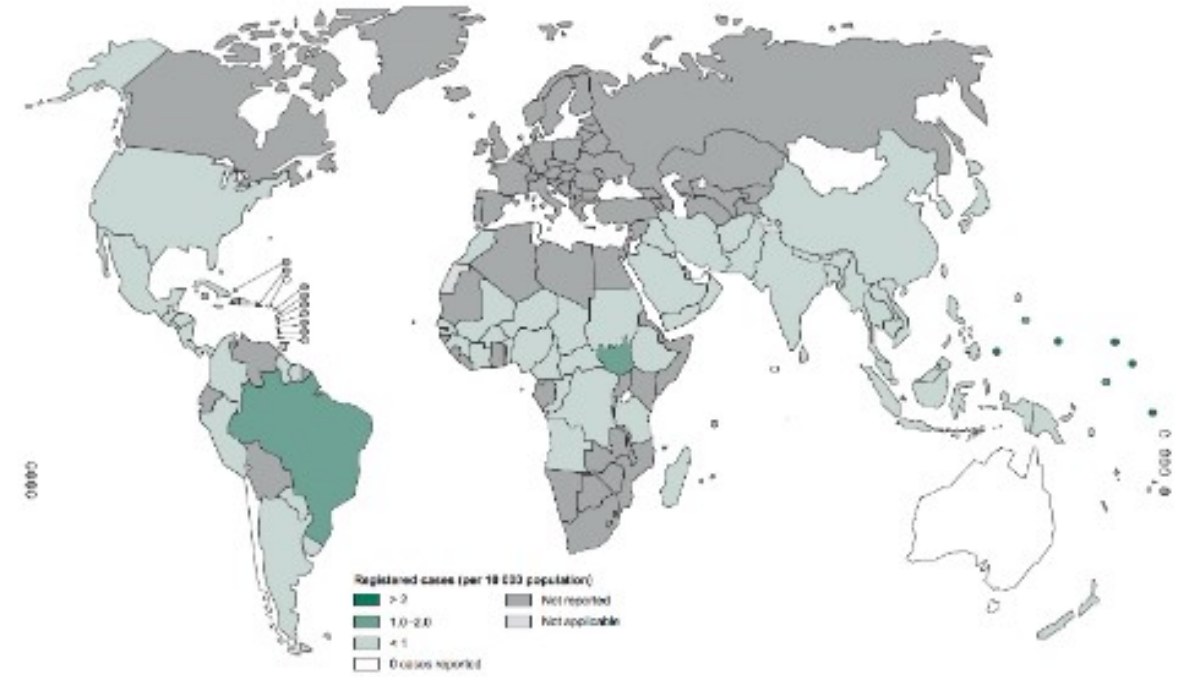
1980...

15.000.000-20.000.000

1990...

2.500.000

200.000



Registered cases (per 100,000 population)  
■ >2  
■ 1.0-2.0  
■ <1  
■ 0 cases reported  
■ Not reported  
■ Not applicable





*In addition, the Global Leprosy Strategy for the years 2021–2030 entitled*

*“Towards zero leprosy”*

*has begun*

The goals of this strategy include:

- (a) no new autochthonous cases in 120 countries,
- (b) a 70% reduction of annual new cases,
- (c) a 90% reduction in the incidence of new Grade-2 disability (G2D) cases, and
- (d) a 90% decrease in the incidence of paediatric leprosy cases



► [Virulence](#). 2022 Nov 3;13(1):1985–2011. doi: [10.1080/21505594.2022.2141987](https://doi.org/10.1080/21505594.2022.2141987) [↗](#)

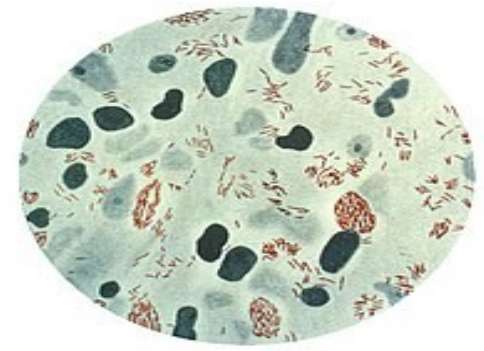
## **Pathogenicity and virulence of *Mycobacterium leprae***

[Mariko Sugawara-Mikami](#)<sup>a,b</sup>, [Kazunari Tanigawa](#)<sup>c</sup>, [Akira Kawashima](#)<sup>a</sup>, [Mitsuo Kiriya](#)<sup>a</sup>, [Yasuhiro Nakamura](#)<sup>c</sup>,

[Yoko Fujiwara](#)<sup>a</sup>, [Koichi Suzuki](#)<sup>a</sup>, [✉](#)



# Microbiologia



## ***Mycobacterium leprae:***

- un batterio intracellulare obbligato
- alcol acido-resistente
- sottile, di forma bastoncellare, aerobio obbligato,
- immobile che replica molto lentamente (14 – 43 gg)
- la lunghezza varia tra 1 e 8  $\mu\text{m}$  con un diametro di circa 0.3  $\mu\text{m}$
- predilige temperature tra i 27 ed i 30 °C

The taxonomic classification of this bacillus comprises:

- the class Schizomycetes,
- order Actinomycetales,
- family Mycobacteriaceae,
- genus Mycobacterium

*La parete cellulare di Mycobacterium leprae possiede una struttura complessa di cere e lipidi, responsabile delle particolari proprietà tintoriali e dell'alta impermeabilità a nutrienti e metaboliti. Dall'interno verso l'esterno troviamo:*

- *La membrana cellulare, formata da un doppio strato lipidico*
- *La parete cellulare, costituita da uno spesso strato di peptidoglicano, uno di arabinogalattano ovvero un polisaccaride legato covalentemente a residui di acido muramico del peptidoglicano. Peptidoglicano e arabinogalattano formano un macro polimero posizionato tra la membrana citoplasmatica e lo strato esterno di acidi micolici a la cui porzione più esterna troviamo legati residui zuccherini (Mannosio, Trealosio) e lipidici (Lipomannano).*



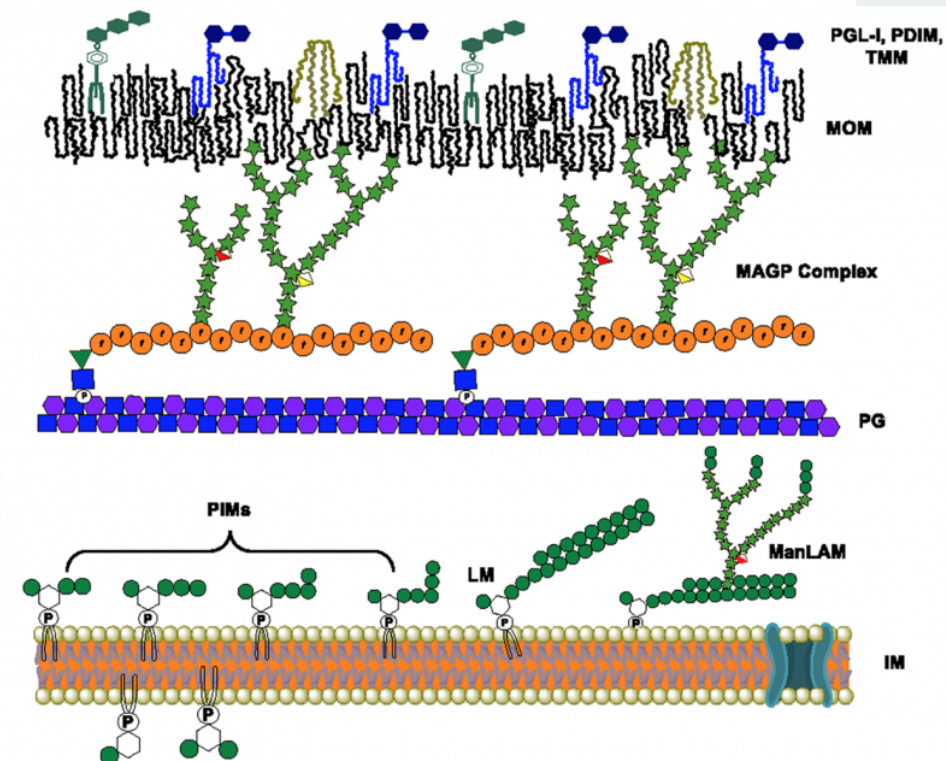
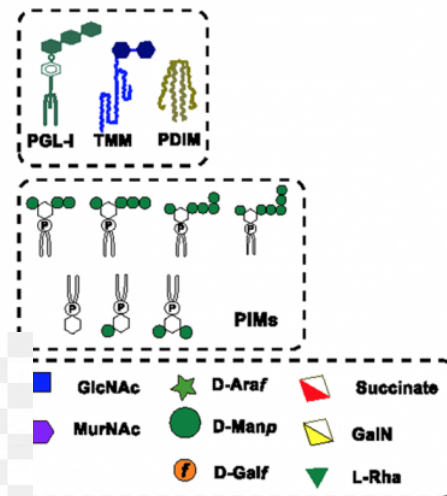
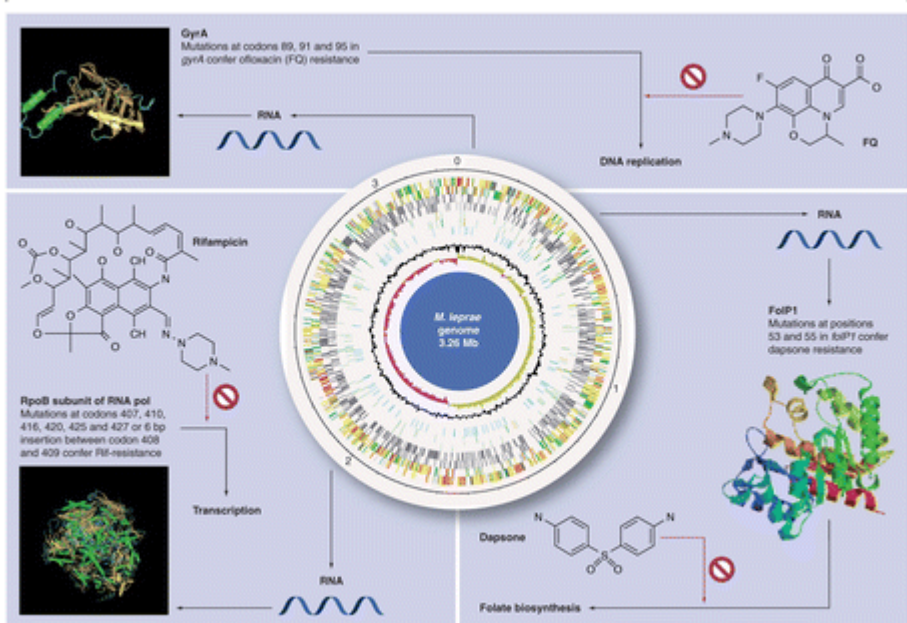
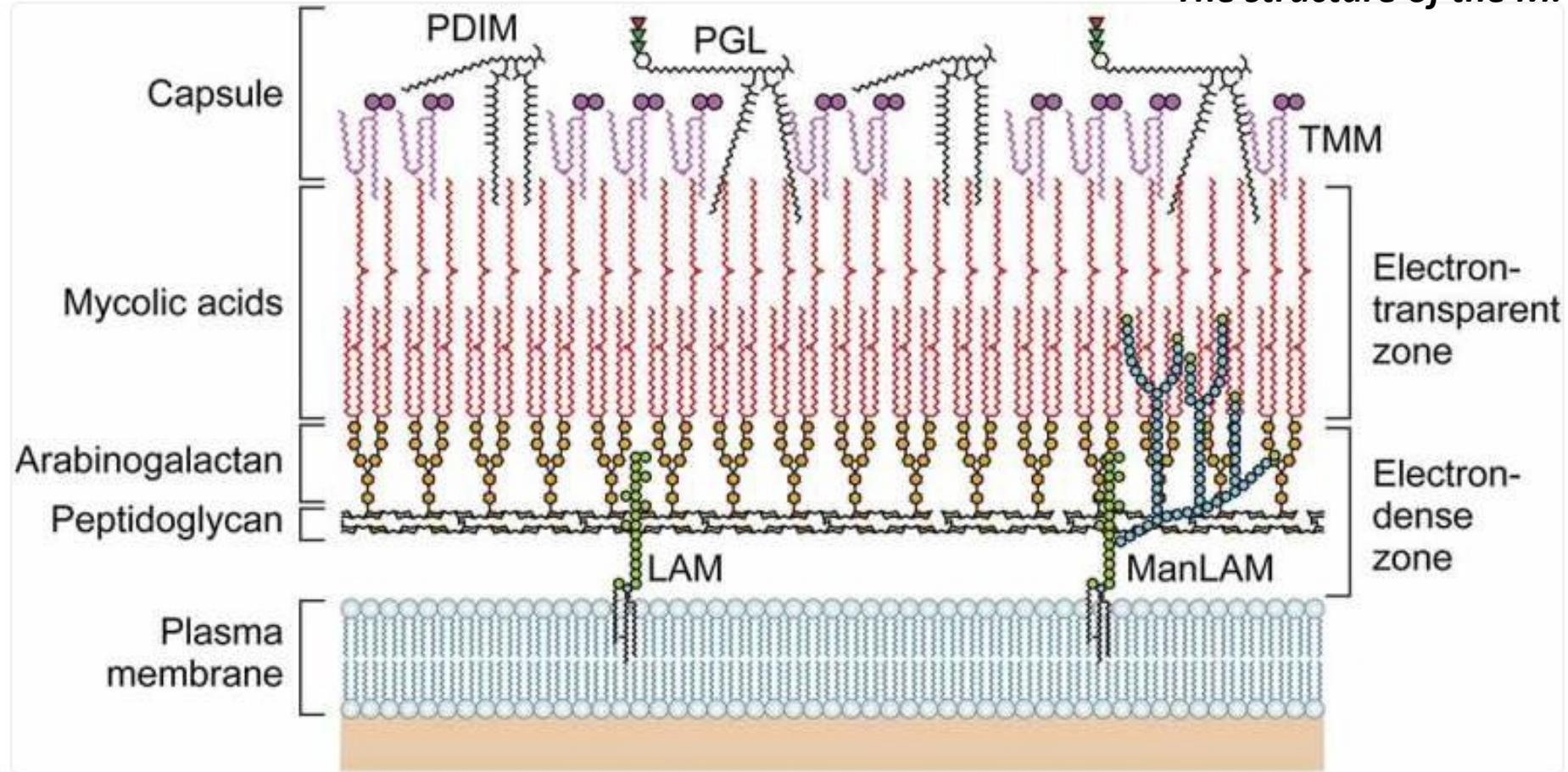


Figura 1. Representação esquemática da parede celular do *Mycobacterium tuberculosis*. Modificado de Park e Bendelac, 2000.





### *The structure of the M. leprae cell wall*

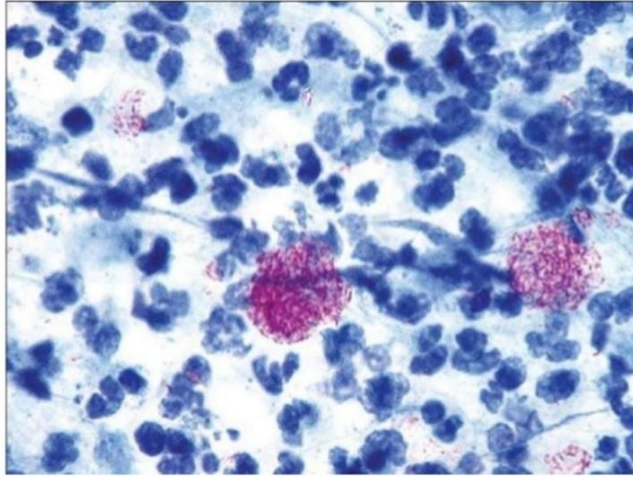


*Eichelmann K et al. An update: definition, pathogenesis, classification, diagnosis, and treatment. Actas Dermosifiliogr. 2013*

*Brennan PJ. Structure, function, and biogenesis of the cell wall of Mycobacterium tuberculosis. Tuberculosis. 2003*



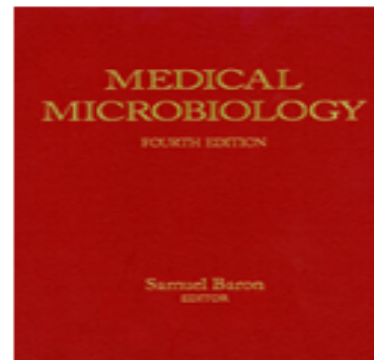
*Mycobacterium leprae* (Acid Fast bacilli with modified Z-N stain)



# Filogenesi



*Nel peptidoglicano della parete cellulare di M. leprae, inoltre, la glicina sostituisce costantemente la lisina presente negli altri micobatteri. In base a questi dati alcuni studiosi suggeriscono che M. leprae dovrebbe essere classificato insieme ai membri del genere Nocardia.*



## Medical Microbiology, 4th edition

Editor: Samuel Baron.

► [Editor Information](#)

Galveston (TX): [University of Texas Medical Branch at Galveston](#); 1996.  
ISBN-10: 0-9631172-1-1

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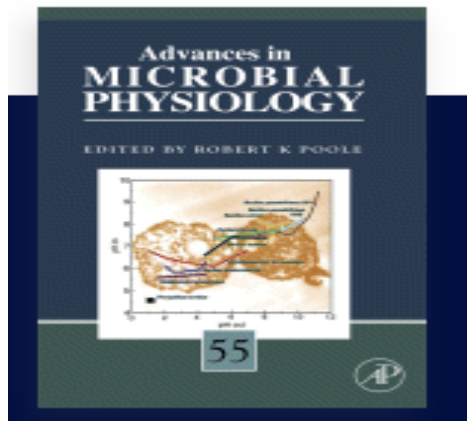
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# *Mycobacterium leprae* vs *Mycobacterium tuberculosis*

*Il confronto tra il genoma di M. leprae e quello di M. tuberculosis rivela un caso estremo di “evoluzione riduttiva” in base al quale circa la metà del suo genoma è rappresentato da pseudogeni.*

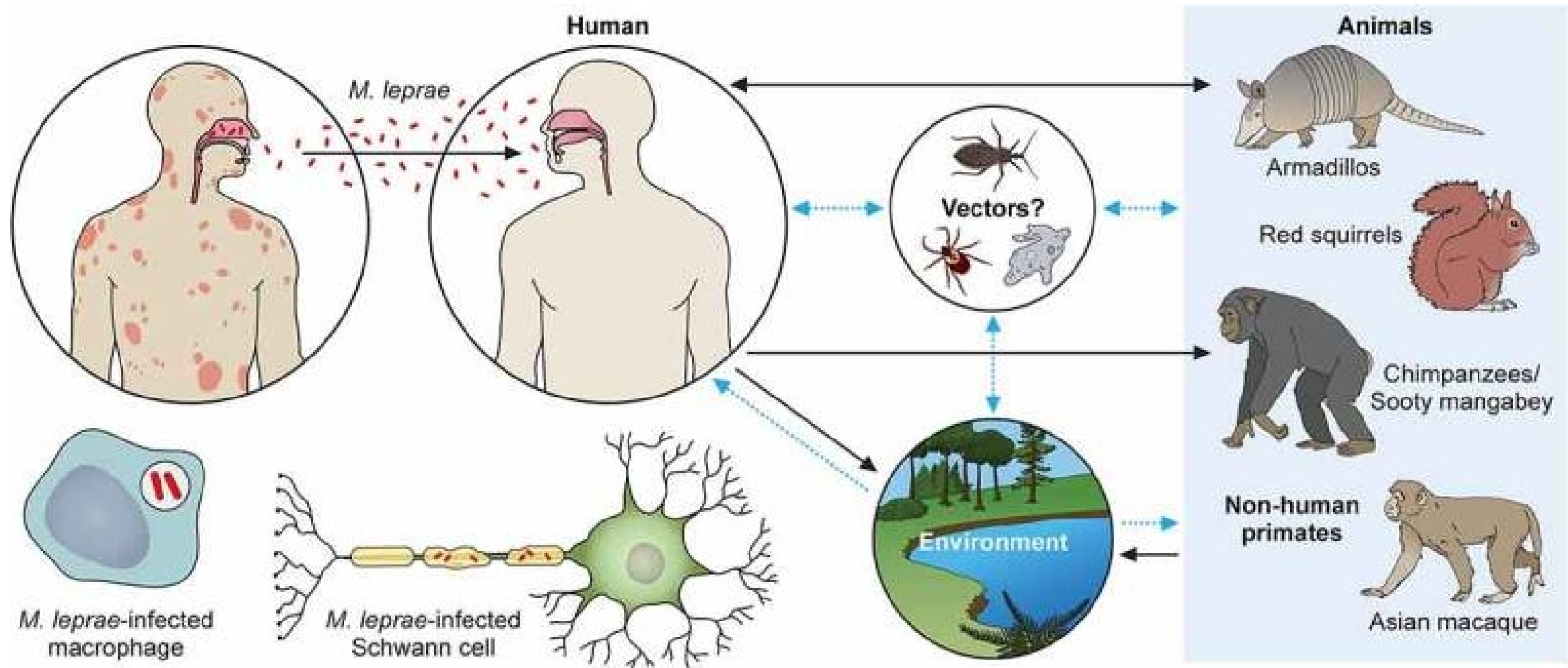


Advances in Microbial Physiology

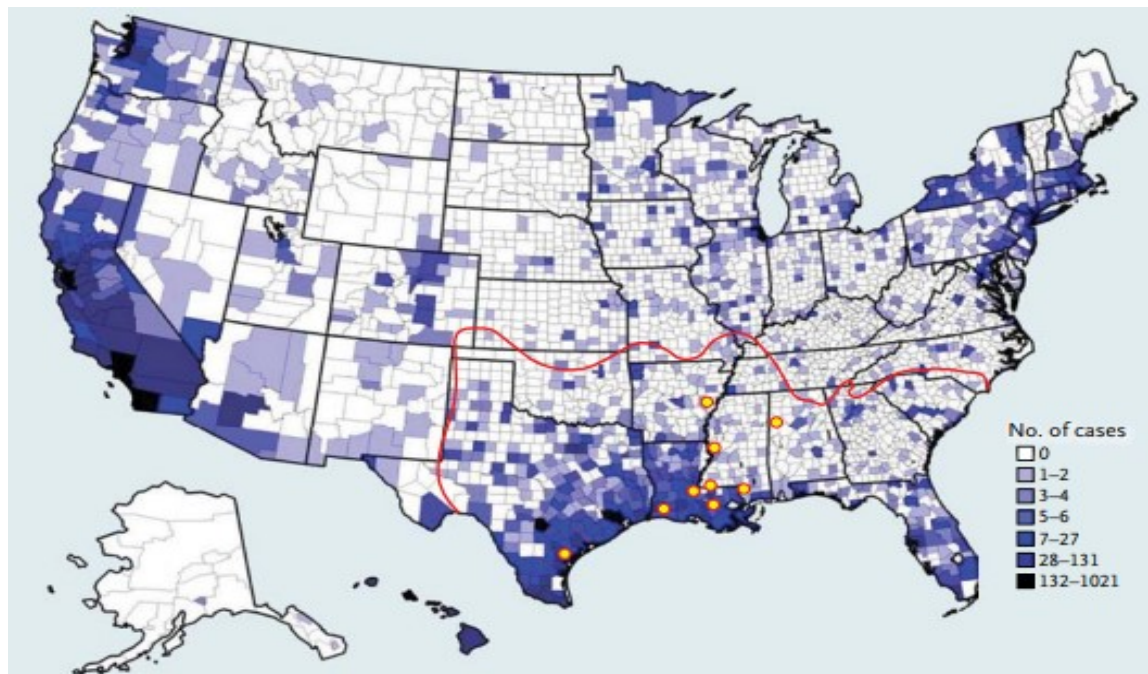
Volume 55, 2009, Pages 81-182, 318-319

## Physiology of Mycobacteria

Gregory M. Cook<sup>1</sup>, Michael Berney<sup>1</sup>, Susanne Gebhard<sup>1</sup>, Matthias Heinemann<sup>2</sup>,  
Robert A. Cox<sup>3</sup>, Olga Danilchanka<sup>4</sup>, Michael Niederweis<sup>4</sup>







*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

# 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.

frontiers | Frontiers in Medicine

ORIGINAL RESEARCH  
published: 23 June 2022  
doi: 10.3389/fmed.2022.879097



# The Armadillo as a Model for Leprosy Nerve Function Impairment: Preventative and Therapeutic Interventions

Maria Teresa Pena<sup>1\*</sup>, Ramanuj Lahiri<sup>1†</sup>, Gigi J. Ebenezer<sup>2</sup>, Stephen W. Wheat<sup>3</sup>, John Figarola<sup>1</sup>, Richard W. Truman<sup>1</sup> and Linda B. Adams<sup>1</sup>







[Nature](#). 2021; 598(7882): 652–656.

Published online 2021 Oct 13. doi: [10.1038/s41586-021-03968-4](https://doi.org/10.1038/s41586-021-03968-4)

PMCID: PMC8550970

PMID: [34646009](https://pubmed.ncbi.nlm.nih.gov/34646009/)

## Leprosy in wild chimpanzees

[Kimberley J. Hockings](#)<sup>1,2</sup>, [Benjamin Mubemba](#)<sup>#3,4</sup>, [Charlotte Avanzi](#)<sup>#5,6,7,8</sup>, [Kamilla Pleh](#)<sup>#3,9</sup>, [Ariane Dux](#)<sup>#3</sup>,  
[Elena Bersacola](#)<sup>#1,2</sup>, [Joana Bessa](#)<sup>#2,10</sup>, [Marina Ramon](#)<sup>#1</sup>, [Sonja Metzger](#)<sup>3,9</sup>, [Livia V. Patrono](#)<sup>3</sup>, [Jenny E. Jaffe](#)<sup>3,9</sup>,  
[Andrej Benjak](#)<sup>11</sup>, [Camille Bonneaud](#)<sup>1</sup>, [Philippe Busso](#)<sup>5</sup>, [Emmanuel Couacy-Hymann](#)<sup>12</sup>, [Moussa Gado](#)<sup>13</sup>,  
[Sebastien Gagneux](#)<sup>7,8</sup>, [Roch C. Johnson](#)<sup>14,15</sup>, [Mamoudou Kodio](#)<sup>16</sup>, [Joshua Lynton-Jenkins](#)<sup>1</sup>, [Irina Morozova](#)<sup>17</sup>,  
[Kerstin Mätz-Rensing](#)<sup>18</sup>, [Aissa Regalla](#)<sup>19</sup>, [Abilio R. Said](#)<sup>19</sup>, [Verena J. Schuenemann](#)<sup>17</sup>, [Samba O. Sow](#)<sup>16</sup>,  
[John S. Spencer](#)<sup>6</sup>, [Markus Ulrich](#)<sup>3</sup>, [Hyacinthe Zoubi](#)<sup>20</sup>, [Stewart T. Cole](#)<sup>5,21</sup>, [Roman M. Wittig](#)<sup>9,22</sup>,  
[Sebastien Calvignac-Spencer](#)<sup>3</sup> and [Fabian H. Leendertz](#)<sup>3,23</sup>



Case Reports

> [Vet Rec.](#) 2014 Sep 20;175(11):285-6. doi: [10.1136/vr.g5680](https://doi.org/10.1136/vr.g5680).

## Leprosy in red squirrels in Scotland

[Anna Meredith](#)<sup>1</sup>, [Jorge Del Pozo](#)<sup>1</sup>, [Sionagh Smith](#)<sup>1</sup>, [Elsbeth Milne](#)<sup>1</sup>, [Karen Stevenson](#)  
[Joyce McLuckie](#)<sup>2</sup>

## Red squirrels in the British Isles are infected with leprosy bacilli

[CHARLOTTE AVANZI](#), [JORGE DEL-POZO](#), [ANDREJ BENJAK](#), [KAREN STEVENSON](#), [VICTOR R. SIMPSON](#), [PHILIPPE BUSO](#), [JOYCE MCLUCKIE](#), [CHLOÉ LOISEAU](#), [COLIN LAWTON](#), [...].

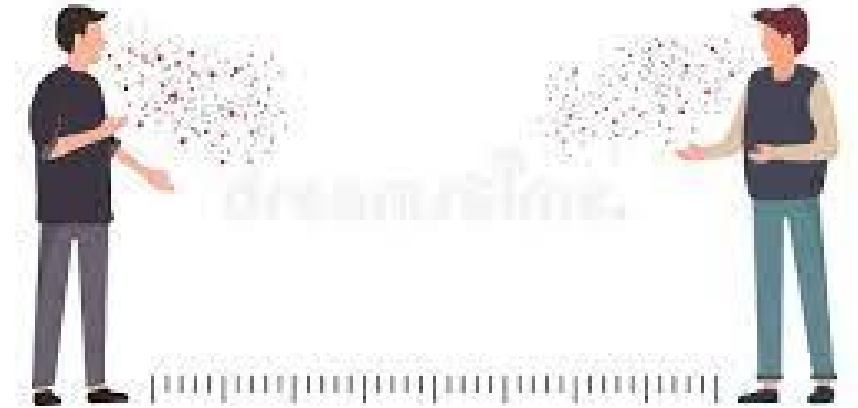
AND [ANNA L. MEREDITH](#)

+8 authors

[Authors Info & Affiliations](#)



*Respiratory secretions are likely the most common route of transmission*



*Skin contact and vertical transmission are also possible infection mechanisms*



*The incubation period is quite broad, with estimates ranging from three to five years for tuberculoid leprosy up to 9 to 12 years for lepromatous leprosy. Longer incubation periods have been described.*





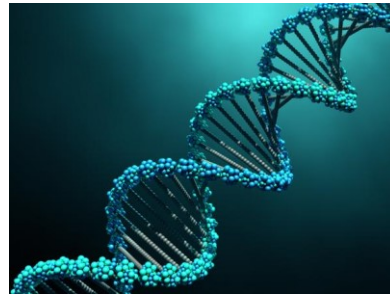


# Risk factors

## RESEARCH ARTICLE

### Evidence of zoonotic leprosy in Pará, Brazilian Amazon, and risks associated with human contact or consumption of armadillos

Moises B. da Silva<sup>1</sup>, Juliana M. Portela<sup>2</sup>, Wei Li<sup>3</sup>, Mary Jackson<sup>3</sup>, Mercedes Gonzalez-Juarrero<sup>3</sup>, Andrea Sánchez Hidalgo<sup>3</sup>, John T. Belisle<sup>3</sup>, Raquel C. Bouth<sup>1,4</sup>, Angélica R. Gobbo<sup>1</sup>, Josafá G. Barreto<sup>1,5</sup>, Antonio H. H. Minervino<sup>2</sup>, Stewart T. Cole<sup>6</sup>, Charlotte Avanzi<sup>6</sup>, Philippe Busso<sup>6</sup>, Marco A. C. Frade<sup>7</sup>, Annemieke Geluk<sup>8</sup>, Claudio G. Salgado<sup>1,4</sup>, John S. Spencer<sup>3</sup>\*

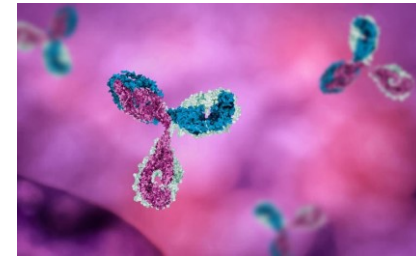


- *exposure to individuals with lepromatous/multibacillary leprosy*

- *exposure to armadillos*



- *immunosuppression/immunodeficiency*



- *genetic predisposition (which is poorly understood)*

SCIENCE OF MEDICINE | FEATURE SERIES

## Leprosy (Hansen's disease): An Update and Review

by Andrea Gilmore, MD, James Roller, MD & Jonathan A. Dyer, MD

Missouri Medicine | January/February 2023 | 120:1 | 39

A recent review noted that the World Health Organization (WHO) program targeting elimination of leprosy is based solely around eliminating human to human transmission and does not account for the potential of spread via zoonotic vectors.

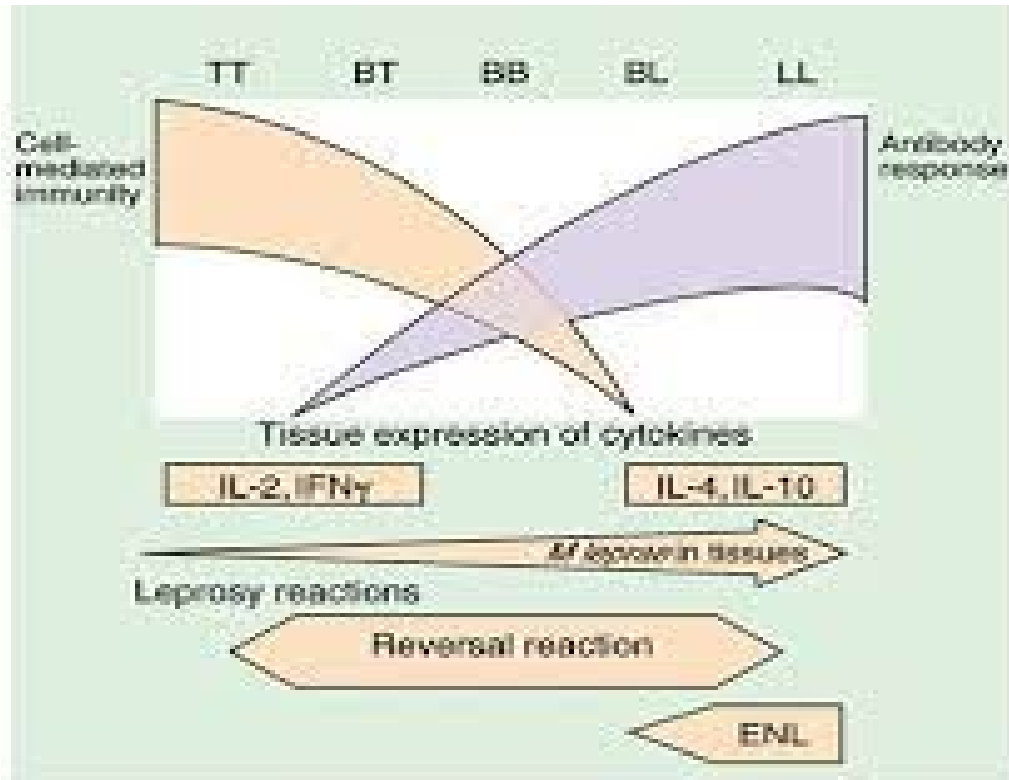


Fig. 4: The Ridley-Jopling Classification and the relationship with host immunity. From: Walker SL, Lockwood DNJ. *Leprosy: Clinics in Dermatology* 2007; 25: 165-72

SCIENCE OF MEDICINE | FEATURE SERIES

## Leprosy (Hansen's disease): An Update and Review

by Andrea Gilmore, MD, James Roller, MD & Jonathan A. Dyer, MD

Missouri Medicine | January/February 2023 | 120:1 | 39

*Importantly, most individuals (up to 90% of the population) appear immune or resistant to *M. leprae* such that most who are exposed do not acquire the infection.*

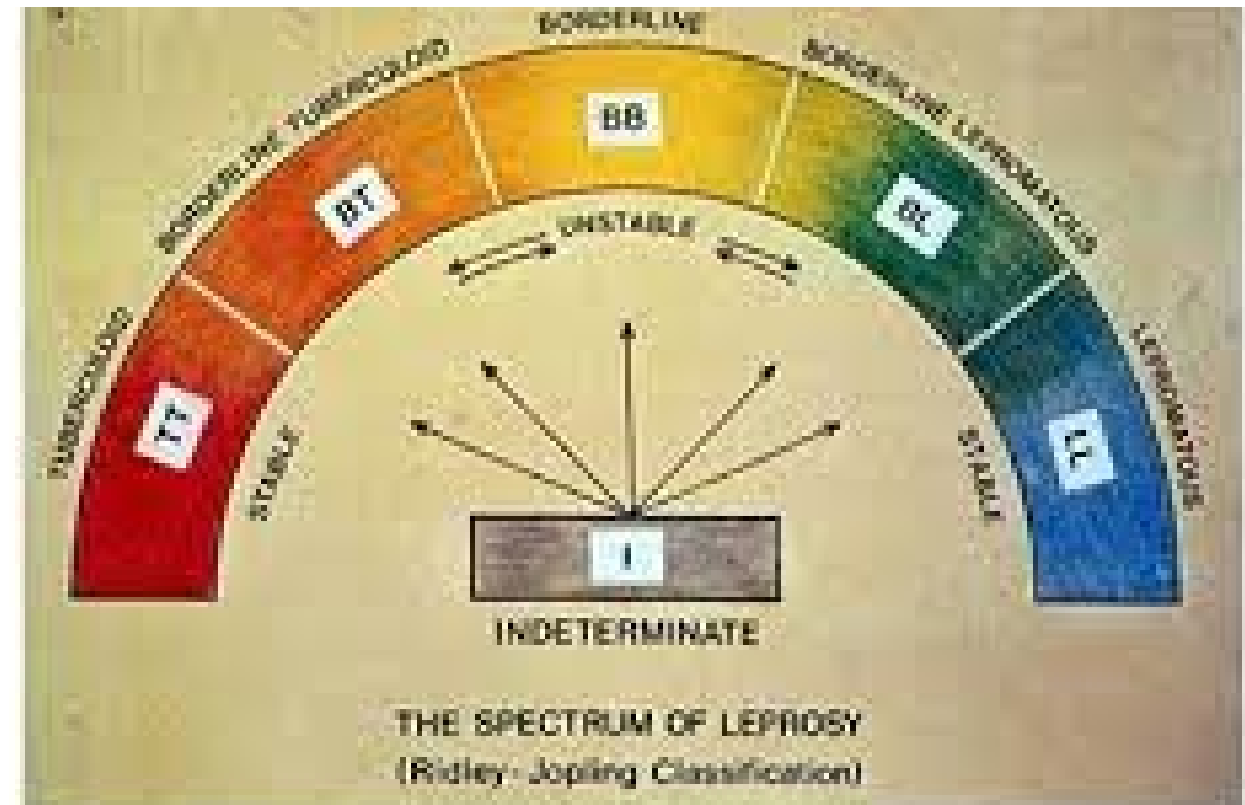


Fig. 3: The spectrum of leprosy (Ridley-Jopling Classification). From: Leiker DL, Nuzi E. *Leprosy in the light skin: an illustrated manual*. Bologna OCSI, 1985.

# ***Pathogenicity and infection of M. leprae***

## ***Microbiology***

M. leprae mainly infects and invades skin macrophages and Schwann cells in the peripheral nerves  
***to produce a chronic infection*** in humans.

Using the Gram strain, M. leprae tests as invisible, producing negatively stained representations known as “ghosts,”  
or as rod-shaped Gram-positive bacilli

*Due to its higher lipid content, M. leprae does not become discoloured by acid-alcohol with the Ziehl-Neelsen stain,  
a red stain that contains fuchsin.*

Thus, it appears as characteristic acid-alcohol-resistant bacilli using a slit skin smear test





Leprosy has been classified into five types using the Ridley-Jopling classification:

*tuberculoid (TT),*

*borderline tuberculoid (BT),*

*mid-borderline (BB),*

*borderline lepromatous (BL)*

*and lepromatous (LL).*



TT is associated with strong cellular immunity and low humoral immunity with granulomatous local skin lesions, whereas LL is characterized by strong humoral immunity

Nerve damage affected by this bacillus induces neuropathy with sensory and motor neuronal impairment.

Moreover, the leprosy reaction is an intense immune reaction of the host against *M. leprae*. It is also a major factor that leads to disabling neurological disorders.



# Classification of leprosy according to immunity. A five-group system

D S Ridley, W H Jopling

## Classificazione della lebbra secondo Ridley e Jopling

Ridley-Jopling		Lebbra tubercoloide (LT)	Lebbra borderline tubercoloide (BT)	Lebbra borderline (BB)	Lebbra borderline lepromatosa (BL)	Lebbra lepromatosa (LL)
	Bacilli acido-alcol resistenti nelle lesioni cutanee	-	-/+	+	+++	+++
	Reazione di Mitsuda	+++	++	+/-	-	-
	Anticorpi anti-M. leprae	-/+	-/++	++	+++	+++
		++	Immunità cellulomediata			

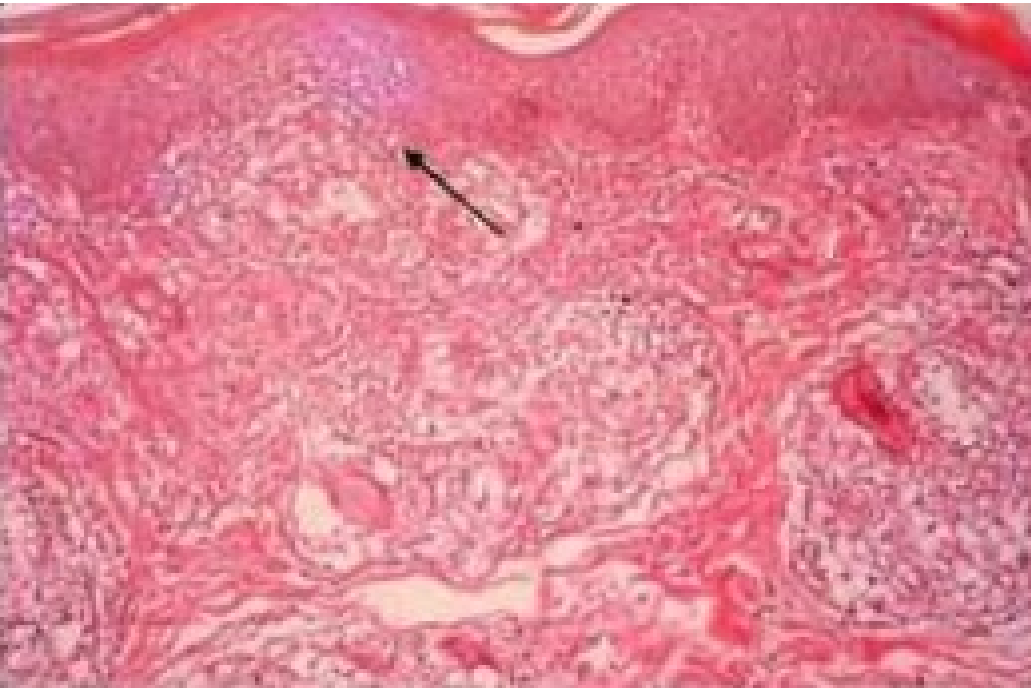
## Classificazione della lebbra secondo l'OMS

OMS		Paucibacillare	Multibacillare
	Lesioni cutanee	> 2 ≤ 5	> 5

> World Health Organ Tech Rep Ser. 1982;675:1-33.

Chemotherapy of leprosy for control programmes

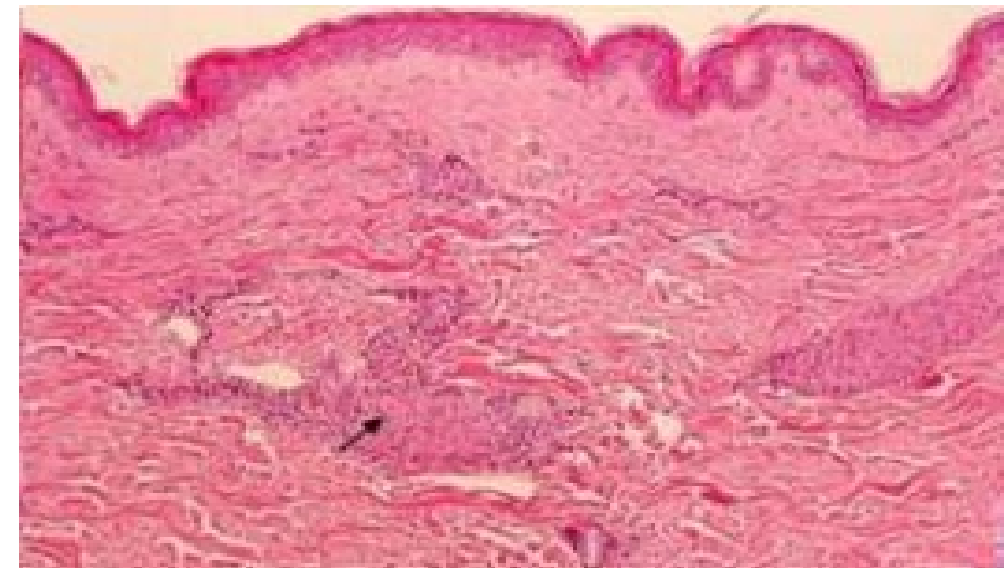
## ***Histopathology of leprosy***



***TT is characterized by granulomas with lymphocyte infiltration.  
These are multiple, well-formed granulomas  
with multinuclear Langhans giant cells.  
Erosion of the basal layer of epidermis is observed, with lymphocytes (→).  
(HE stain, 40×)***

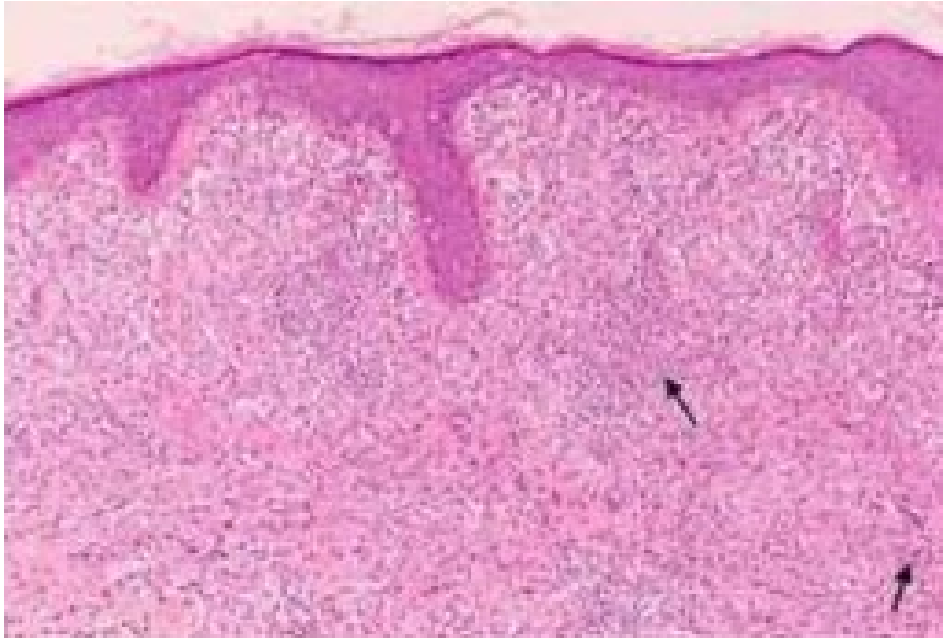


***in BT lesions a granulomatous appearance can be observed (→),  
similar to TT lesions, with the presence of a grenz zone.  
Lymphocytic infiltration is less than in TT.  
(HE stain, 40×)***

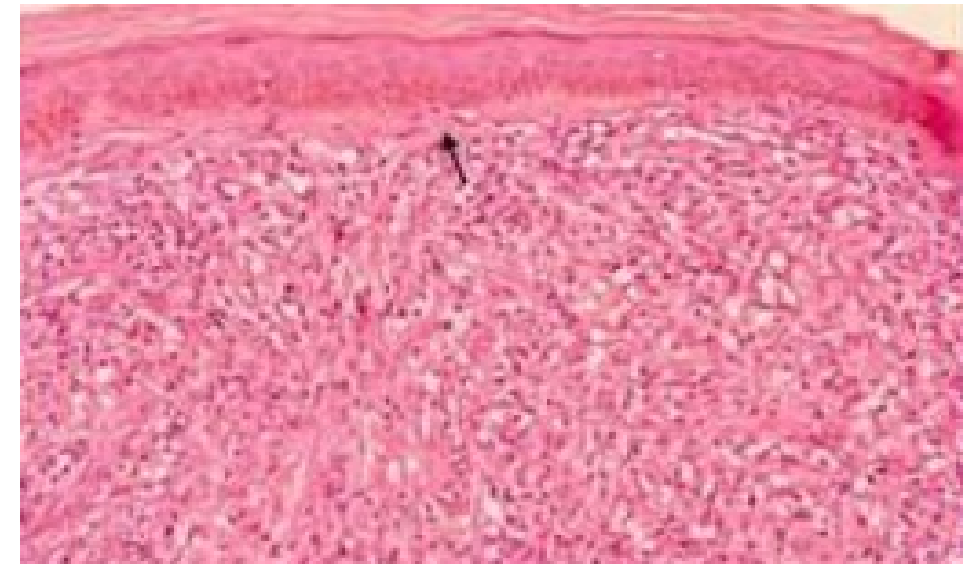




## ***Histopathology of leprosy***



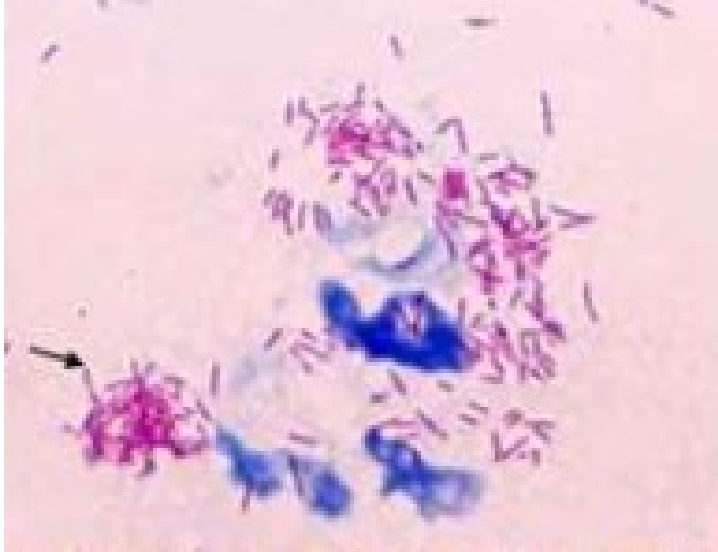
***in BL cases, lymphocytic infiltration and histiocytes (→)  
with granular to foamy cytoplasm are observed.  
(HE stain, 40×)***



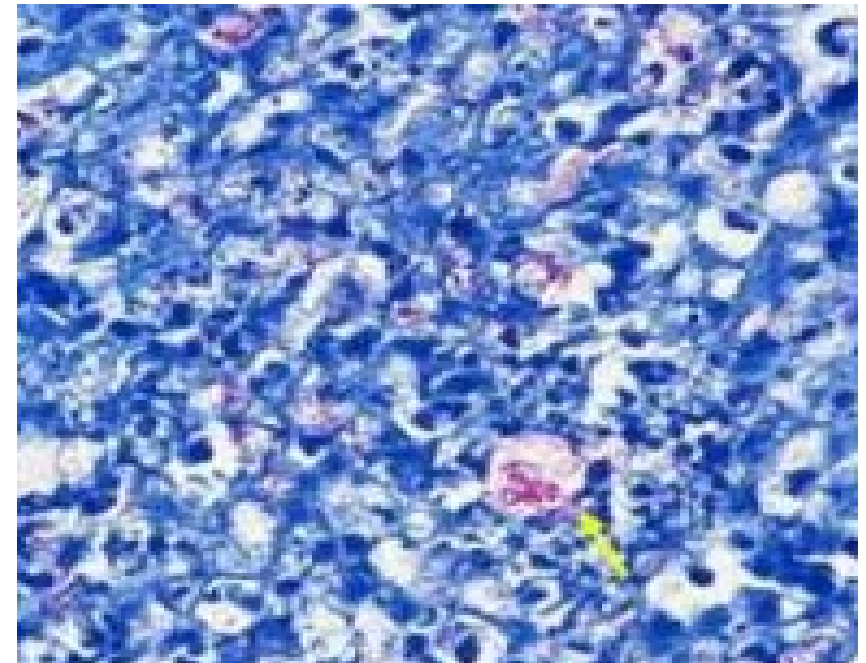
***LL is characterized by foamy histiocytes with a grenz zone  
below the epidermis. (→)  
(HE stain, 40×)***



## ***Histopathology of leprosy***



***the slit skin smear test shows the acid fast bacilli. (→)  
(Ziehl- Neelsen stain, 1000×)***



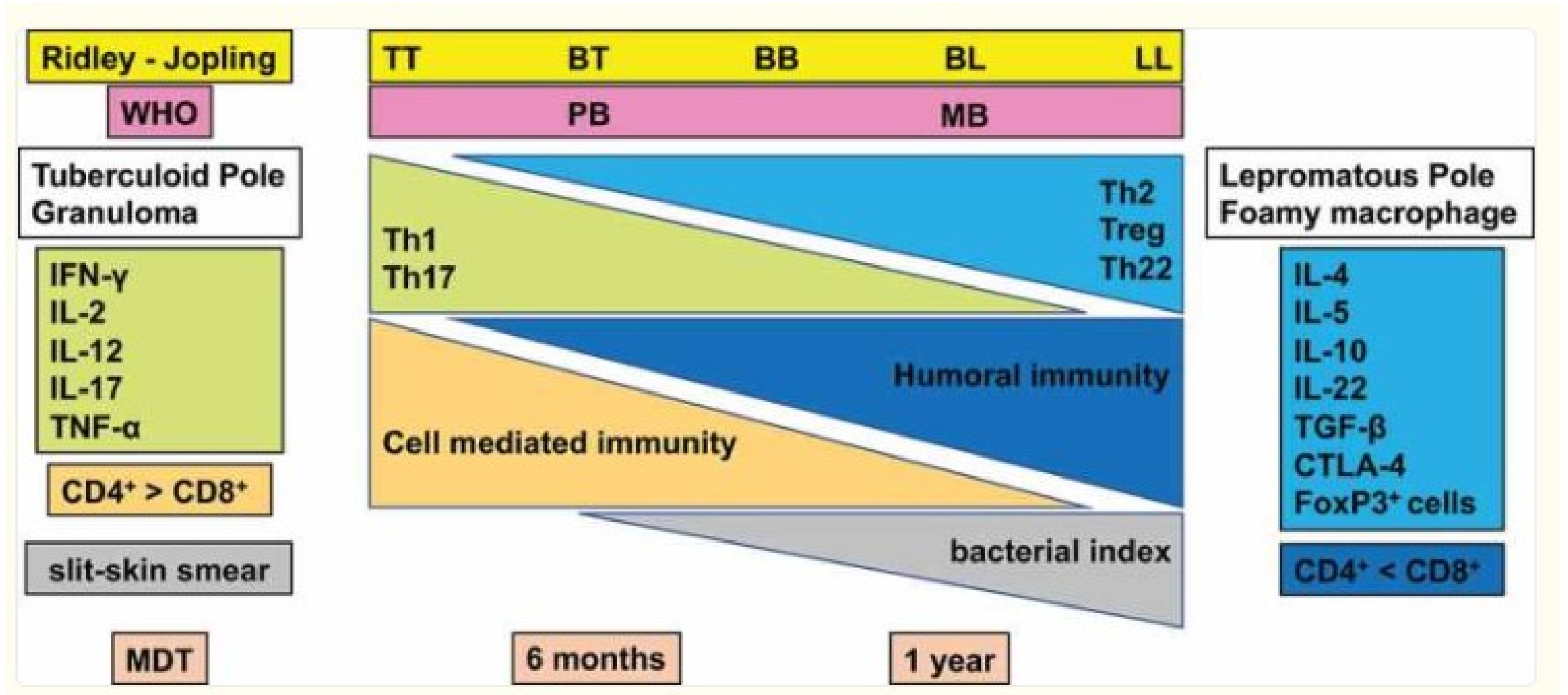
***a large number of bacilli are observed within foamy histiocytes  
with LL lesions. (→)  
(Ziehl- Neelsen stain, Wade-Fite, 400×)***



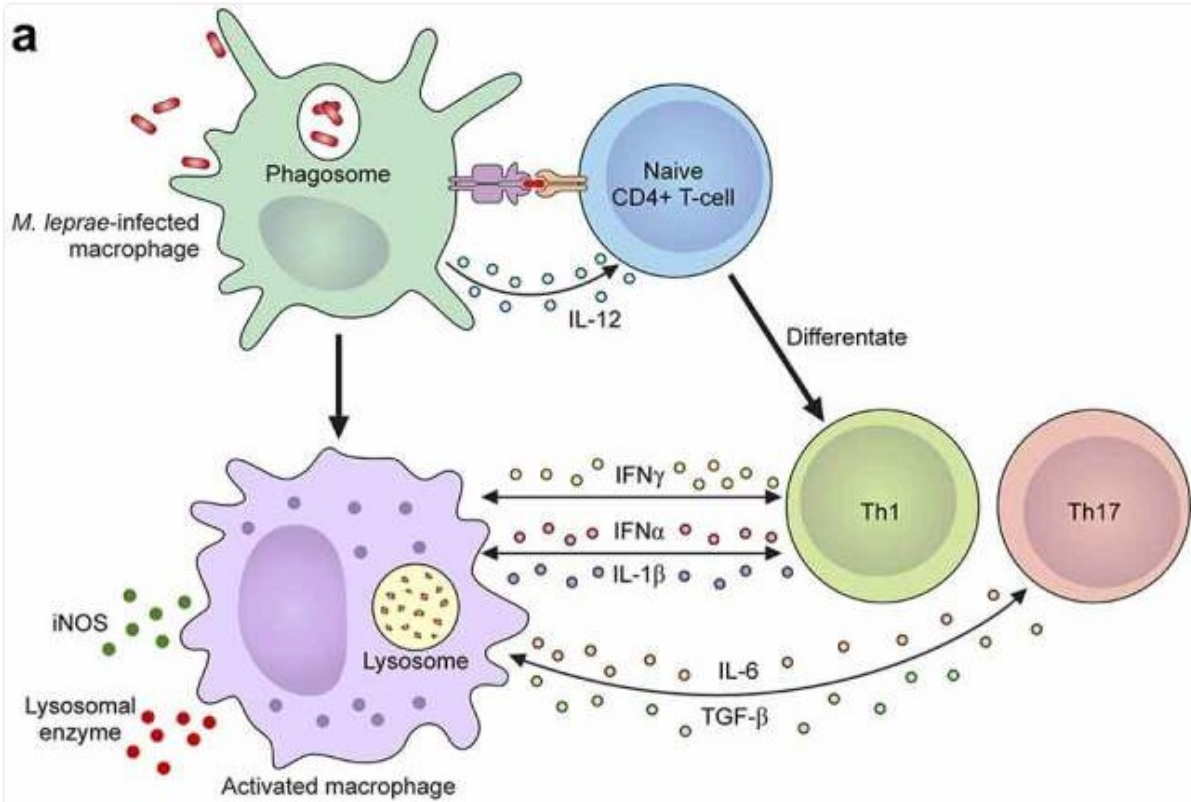


# Immune response

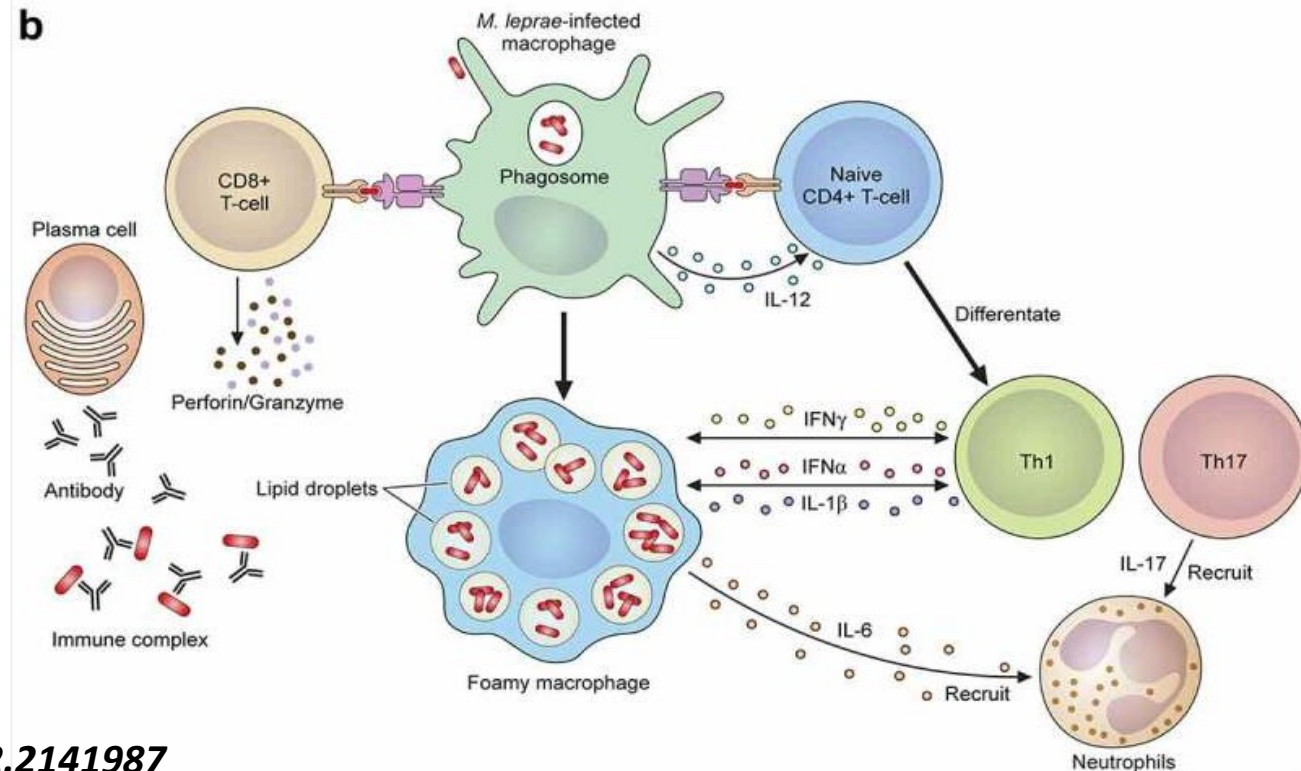
## Innate and acquired immune responses







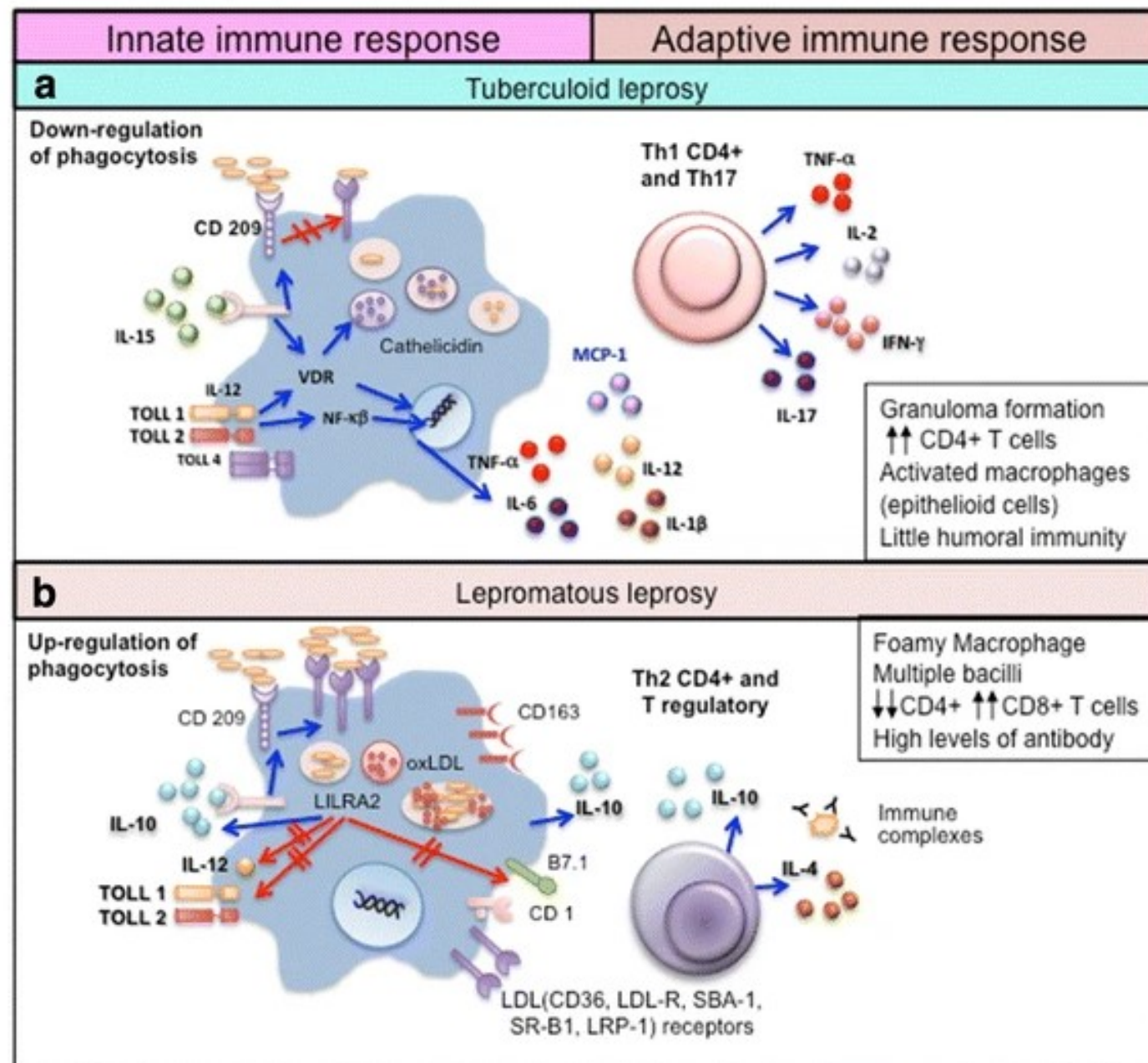
## *The mechanism of the leprosy reaction*





# The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy

[Adriana Barbosa de Lima Fonseca](#), [Marise do Vale Simon](#), [Rodrigo Anselmo Cazzaniga](#), [Tatiana Rodrigues de Moura](#), [Roque Pacheco de Almeida](#), [Malcolm S. Duthie](#), [Steven G. Reed](#) & [Amelia Ribeiro de Jesus](#) 







The NEW ENGLAND  
JOURNAL of MEDICINE

December 23, 1982

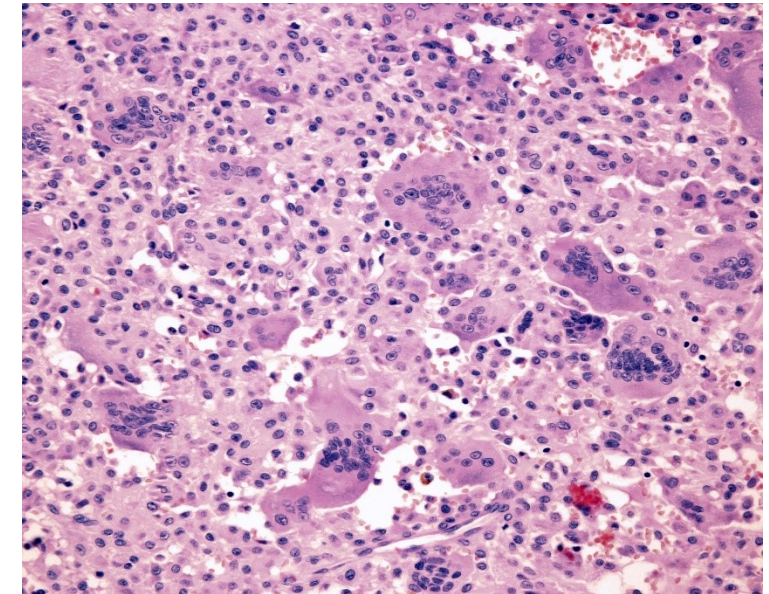
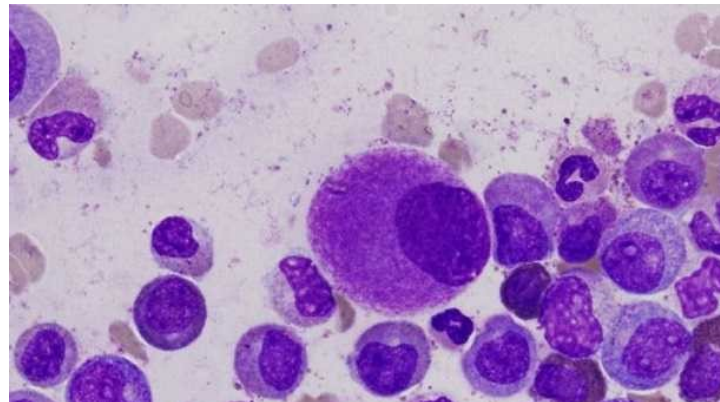
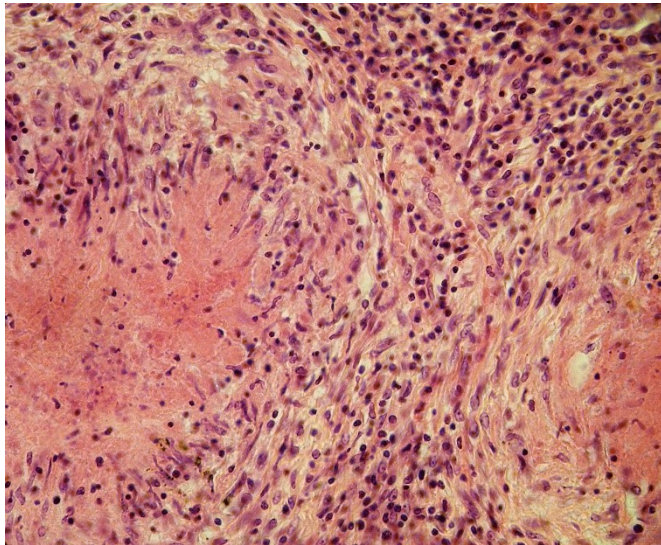
N Engl J Med 1982; 307:1593-1597

DOI: 10.1056/NEJM198212233072601

ORIGINAL ARTICLE **ARCHIVE**

# The Cutaneous Infiltrates of Leprosy — Cellular Characteristics and the Predominant T-Cell Phenotypes

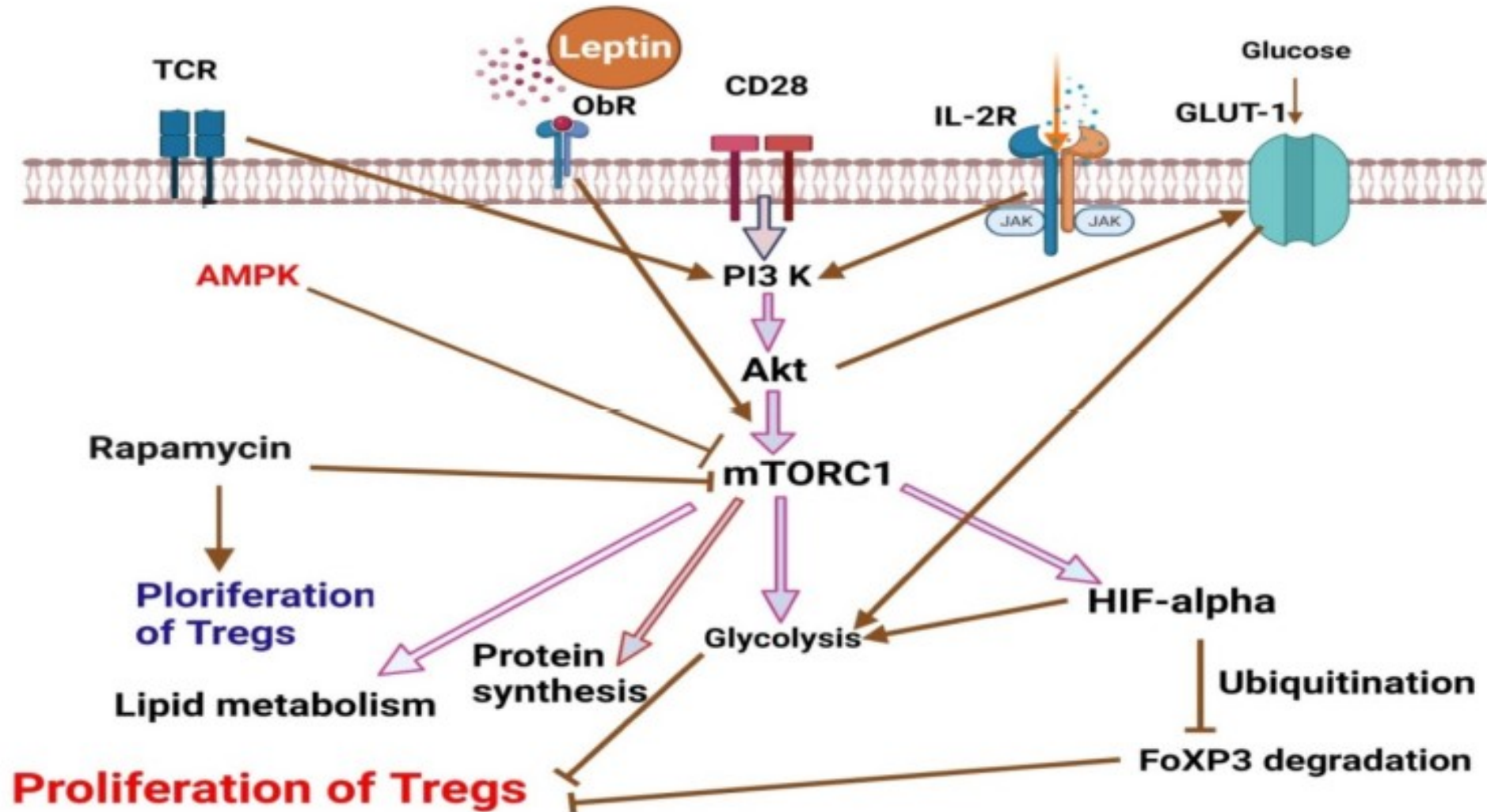
Wesley C. Van Voorhis, S.B., Gilla Kaplan, Ph.D., Euzenir Nunes Sarno, M.D., Marcus A. Horwitz, M.D., Ralph M. Steinman, M.D., William R. Levis, M.D., Nadia Nogueira, M.D., Ph.D., Laura S. Hair, B.A., Cerli Rocha Gattass, Ph.D., Bradley A. Arrick, B.A., and Zanjil A. Cohn, M.D.







# *The Role of T Helper 17 in Pathogenesis of Leprosy*



## *Immune Reactions*

*Immune reactions to the M. leprae bacilli are one of the major causes of morbidity and even mortality in leprosy patients.*

*The sudden activation of a more pronounced immune response can lead to significant inflammatory reactions, often involving infected nerves and worsening existing nerve damage.*

*In severe cases it can lead to great morbidity or even death.*

*Development of these immune reactions may prompt patients to seek medical care, often for the first time.*

*Clinicians should be aware of how such reactions can manifest.*

SCIENCE OF MEDICINE | FEATURE SERIES

## **Leprosy (Hansen's disease): An Update and Review**


*by Andrea Gilmore, MD, James Roller, MD & Jonathan A. Dyer, MD*

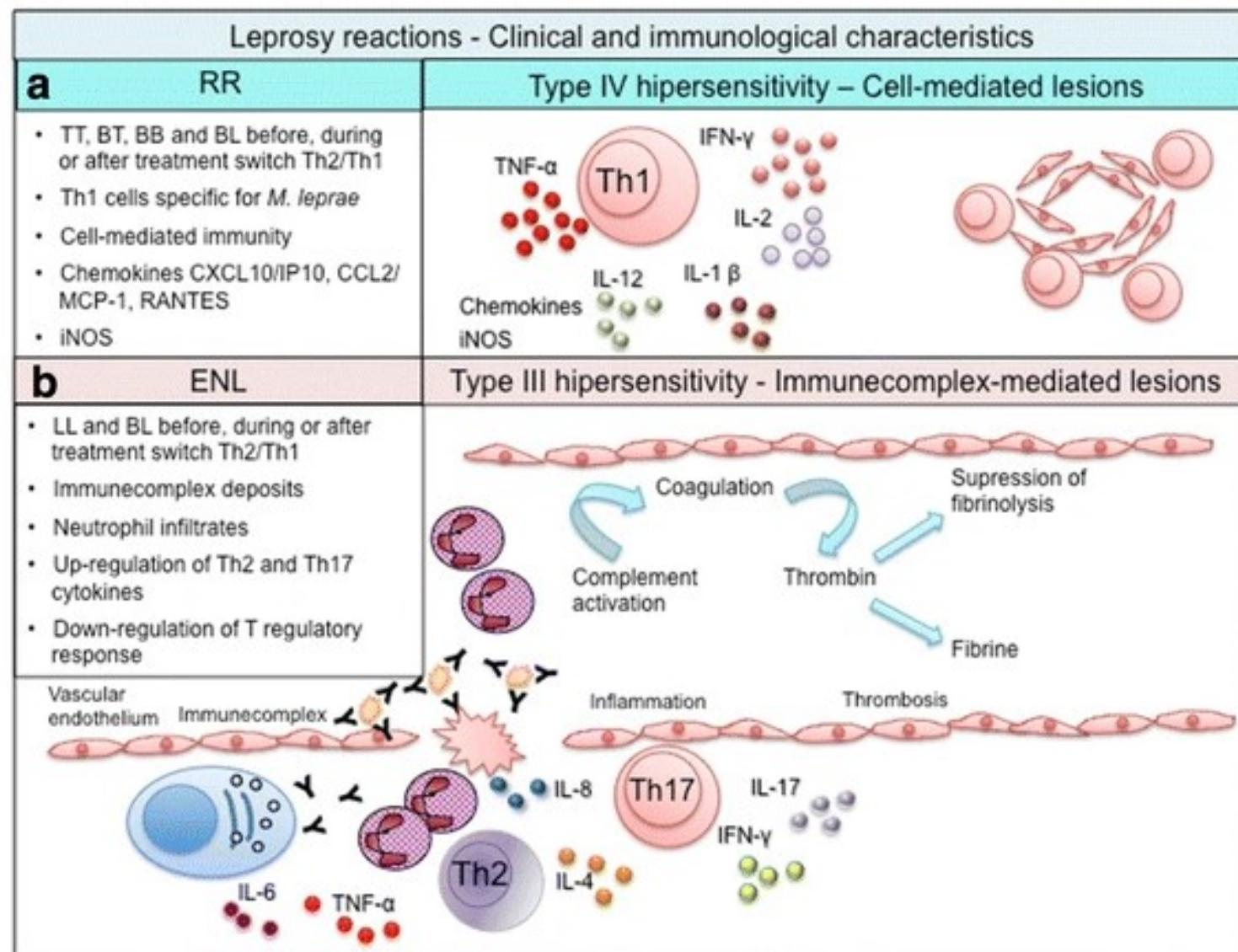
Missouri Medicine | January/February 2023 | 120:1 | 39





# The influence of innate and adaptative immune responses on the differential clinical outcomes of leprosy

[Adriana Barbosa de Lima Fonseca](#), [Marise do Vale Simon](#), [Rodrigo Anselmo Cazzaniga](#), [Tatiana Rodrigues de Moura](#), [Roque Pacheco de Almeida](#), [Malcolm S. Duthie](#), [Steven G. Reed](#) & [Amelia Ribeiro de Jesus](#) 







# Lucio phenomenon

*Lucio phenomenon is rare in the U.S., occurring in patients with diffuse LL.*

*It is a thrombotic reaction characterized by the development of purpuric and discolored skin lesions that become necrotic and heal with atrophic scars.*

*Histopathology can be helpful in the diagnosis*

 **JAAD** Journal of the American Academy of Dermatology

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## Leprosy: Treatment and management of complications

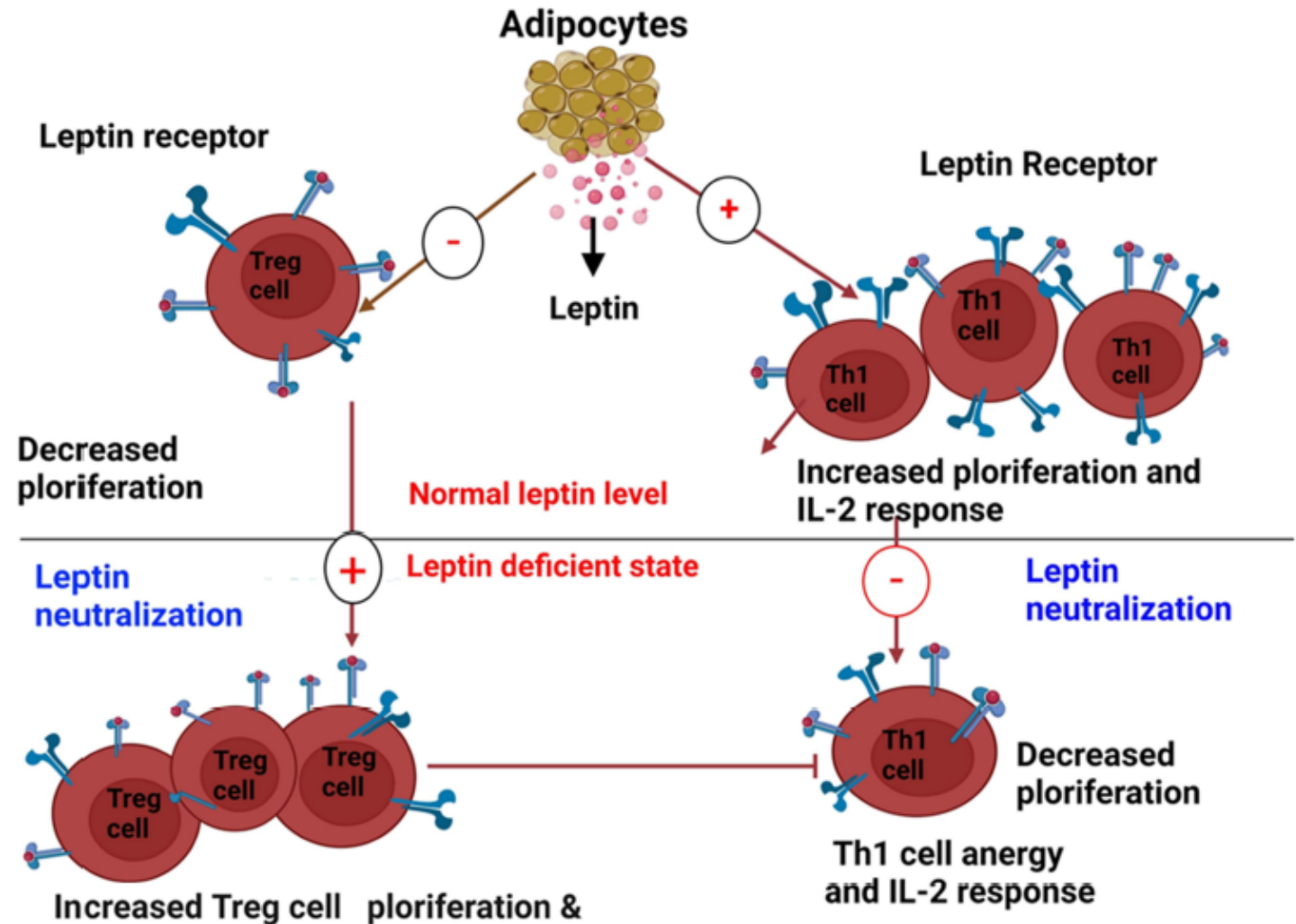
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# Leptin Deficiency May Influence the Divergence of Cell-Mediated Immunity Between Lepromatous and Tuberculoid Leprosy Patients

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