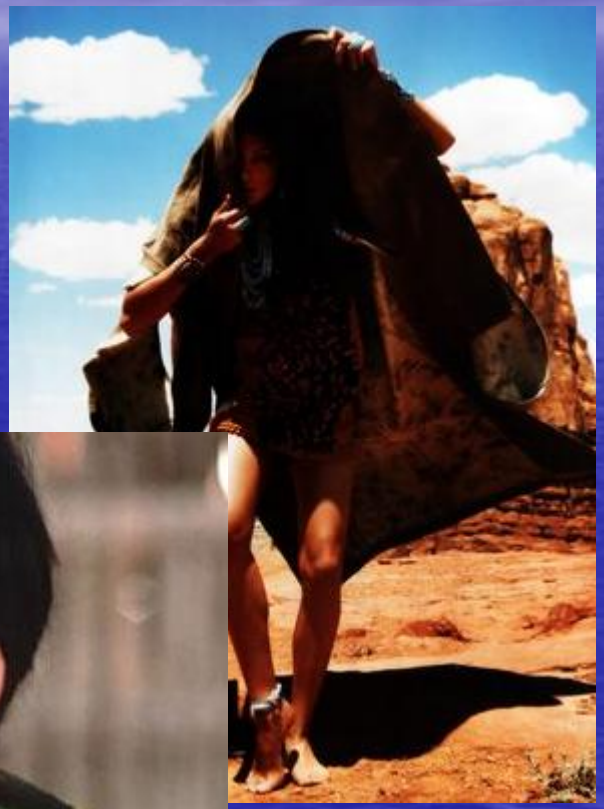
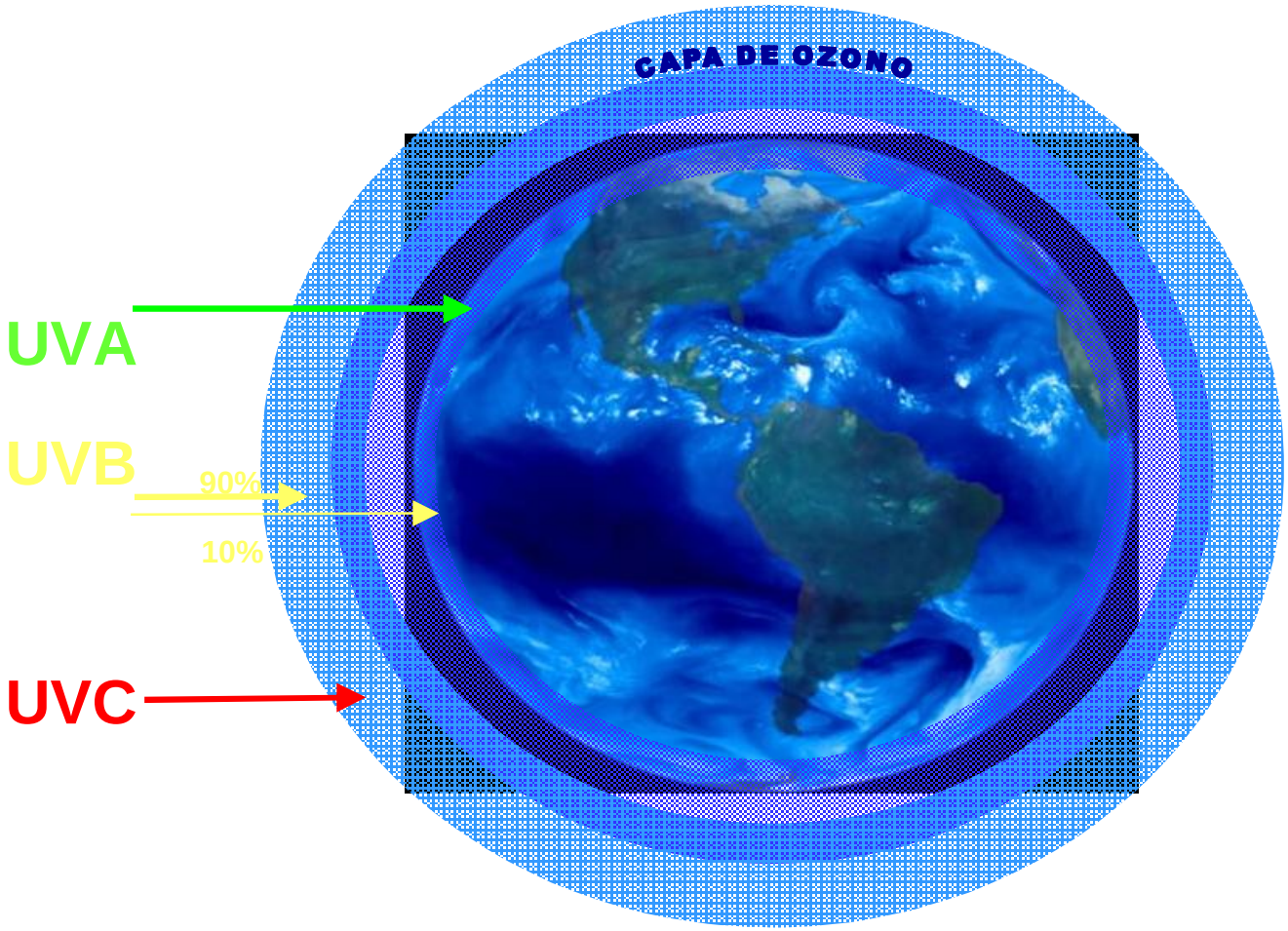
El Maravilloso Viaje al centro de La Piel

Antonio Rondón Lugo

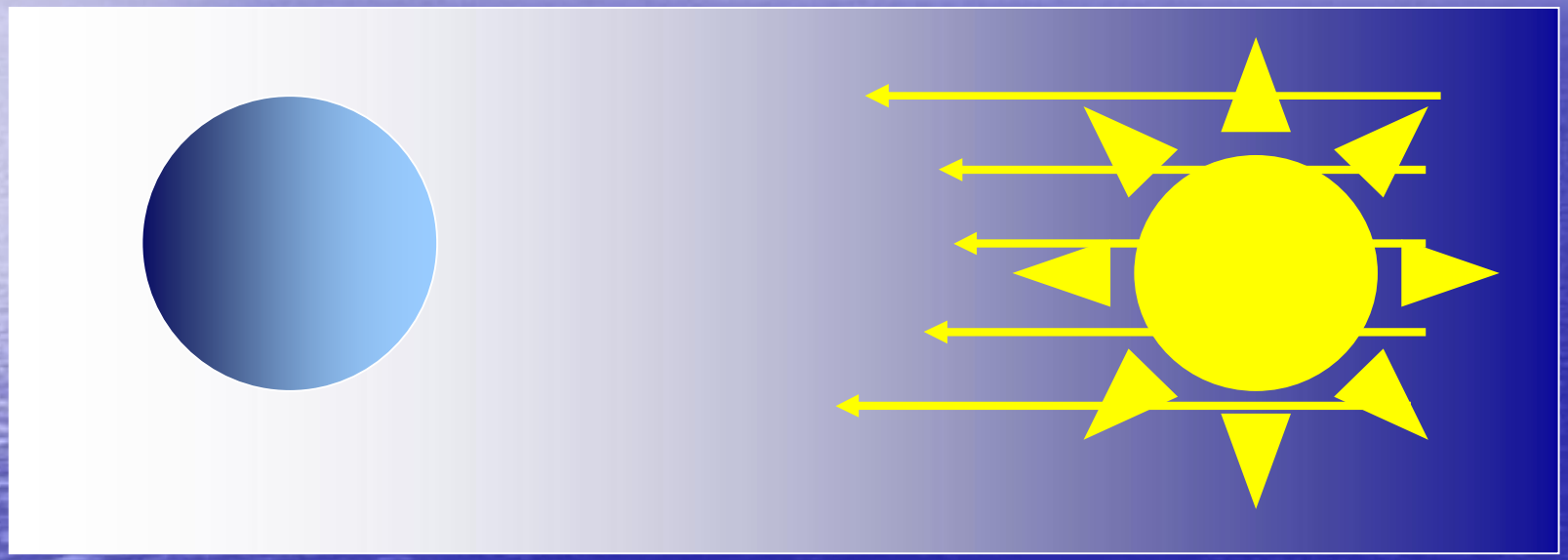
Coordinador comité de Bioética Instituto de Biomedicina

rondonlugo@yahoo.com
www.antoniorondonlugo.com




CAPA DE OZONO
UVA
UVB
90%
10%
UVC

La radiación solar es mas intensa cerca del Ecuador puesto que incide verticalmente sobre la tierra



- La cantidad de radiación UV que llega a la Tierra aumenta un 4% al aumentar 300 mts. la altitud.

Fotoprotección endógena

Pigmentación

Fototipos de Fitzpatrick

I

II

III

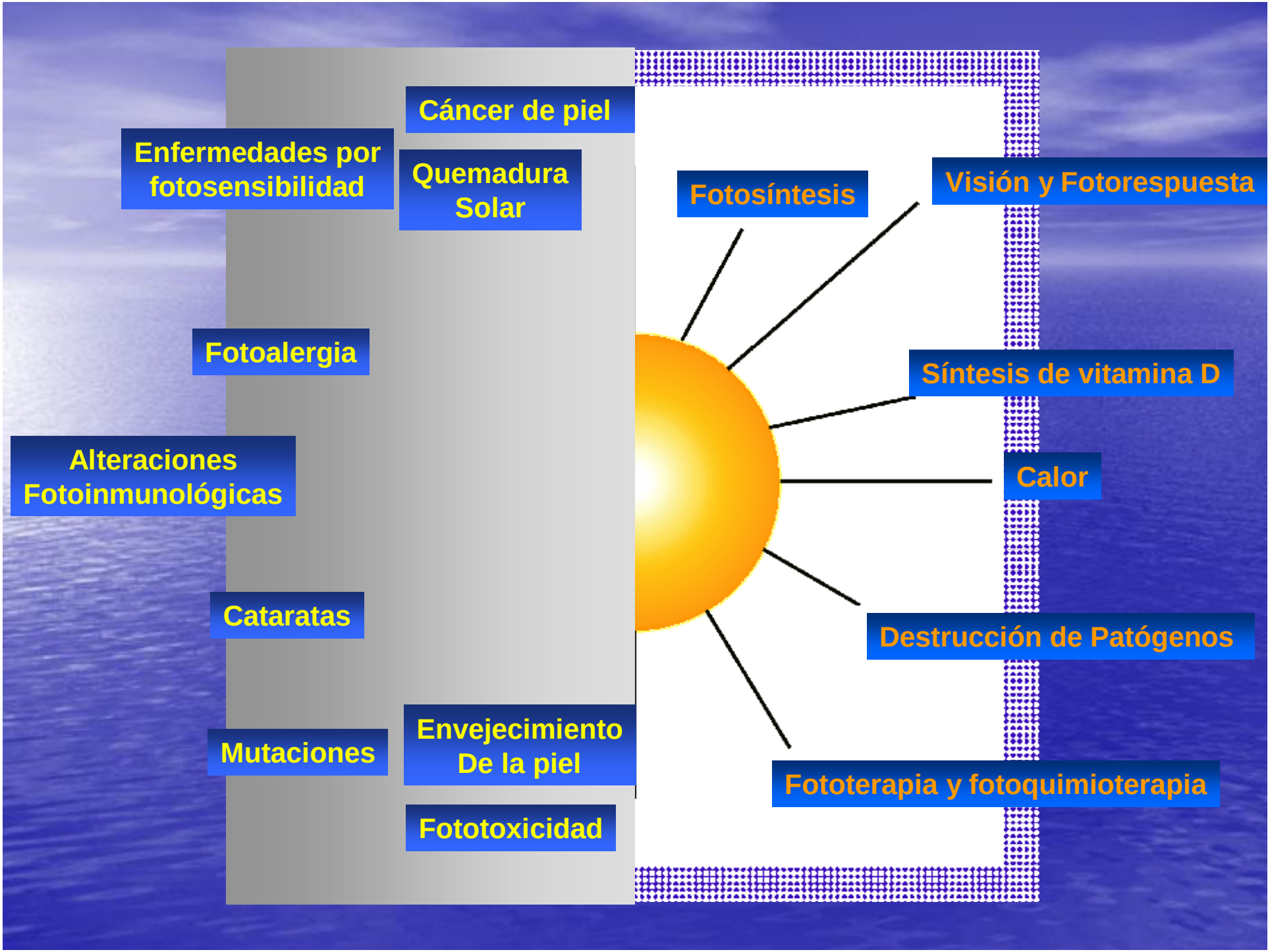
IV

V

VI

§ Pigmentación disminuye 10% por década

§ Melanogénesis disminuye después de los 50 años (piel más blanca- canas)


Cáncer de piel
Enfermedades por fotosensibilidad
Quemadura Solar
Fotosíntesis
Visión y Fotorespuesta
Fotoalergia
Síntesis de vitamina D
Alteraciones Fotoinmunológicas
Calor
Cataratas
Destrucción de Patógenos
Mutaciones
Envejecimiento De la piel
Fototerapia y fotoquimioterapia
Fototoxicidad

Efectos de las Radiaciones UV Diarias

- El conjunto de las radiaciones UV, recibidas diariamente, poseen un efecto acumulativo que induce:

  - Fotoenvejecimiento cutáneo.
  - Fotoinmunosupresión.
  - Fotocarcinogénesis.

Necesidad de una fotoprotección diaria óptima, reforzada en UVA

FILTROS SOLARES - historia

- § Antiguo Egipto : Maquillaje de los constructores de pirámides
- § Índios: tintura
- § Primer filtro solar: USA 1928 (combinación de benzil salicilato y benzil cinamato)
- § 1930: Australia
- § 1936: Francia
- § 1944: Brasil

FILTROS SOLARES - historia

- § 1950: determinación de FPS (Alemania y Suíza)
- § 1969: síntesis de filtros UVA y UVB
- § 1970: aprobación del FPS por FDA
- § 1978: FDA Monografía

Índices de protección UVA

IPD = Inmediate Pigment darkening

PPD = Persistent Pigment darkening

$$\text{IPD} = \frac{\text{Dosis IPD con fotoprotección}}{\text{Dosis IPD sin fotoprotección}}$$

$$\text{PPD} = \frac{\text{Dosis PPD con fotoprotección}}{\text{Dosis PPD sin fotoprotección}}$$

David Fisher del Dana-Farber Cancer Institute y John D'Orazio de University Of Kentucky College of Medicine en Lexington.

Determinaron que el p53 además de reparar los daños causados en el ADN por los UV, controla el inicio de la cascada en el proceso del bronceado

Barsh G, Attardi L. A Healthy tan? N Engl J 2007;356:2208-9.
Fisher D, Cui R, Windlund H, Feige E, Lin J, Wilensky D, et al.Central role of p53 in the suntan response and
Pathologic Hyperpigmentation. Cell 2007;128:853-64.

Calentamiento global y aumento incidencia MM

Fotoeducación

Reducción: Exposición / absorción UV total (piel)

- §Evitar la exposición solar / fuentes artificiales
- §Respetar los horarios más peligrosos
- §Proveerse de sombra: Portátil / estática
- §Promover la protección diaria / cotidiana
- §Uso correcto de cremas fotoprotectoras 20 min.previos

Fotoeducación

- § Telas de poliester o mezclas protegen mas que telas de algodón.
- § Telas oscuras protegen mas .
- § Tejidos mas "intrincados "y densos protegen mas.Int.J.Der 1997;36:374-9
- § Mensajes confusos: sol sin riesgo broncearse sin problemas, bronceado seguro , camas solares .

Fotoeducación

- § Mejora el nivel de información después de campañas Arch. Pediat. Adolesc. Med. 1998 13:445-487. Robinson,Olson . Buendía. Editorial : Piel 2000;15: 247-9
- § Hábitos erróneos
- § Falta de información a necesidad y forma de aplicación


Mad Hare

LEISHMANIASIS
Leishmaniasis Tegumentaria en la América precolombina

Nazca 200 AC – 600 DC

Mochica Siglos I-VIII DC

Lesiones naso-palatinas demostradas por análisis de rayos X de cráneos de momias Incas.

Lesiones destructivas craneana por leishmaniasis en Markat-Tampu durante el Imperio Inca: S XV-XVI, Valle de Bajo Rimac, Peru.

Altamirano AJ, Moreira JS, Marzochi MCA.

Rev Archaeol Etnol Museum Univ São Paulo 2001

Inca Siglo
XV-XVI

Historia

- 1855 .Cunningham . India.Observó parásitos de leishmania.(ulcera de Delhi)
- 1891 Firth :* denomina Sporozoa furunculosa *.
- 1898 Borovsky En Asia central estudia foco de Botón de Oriente.
- 1903 Leishman observa los parásitos en vísceras de casos de Kala-azar.
- 1003 Donovan observa los parásitos y los diferencia deTrypanosoma.

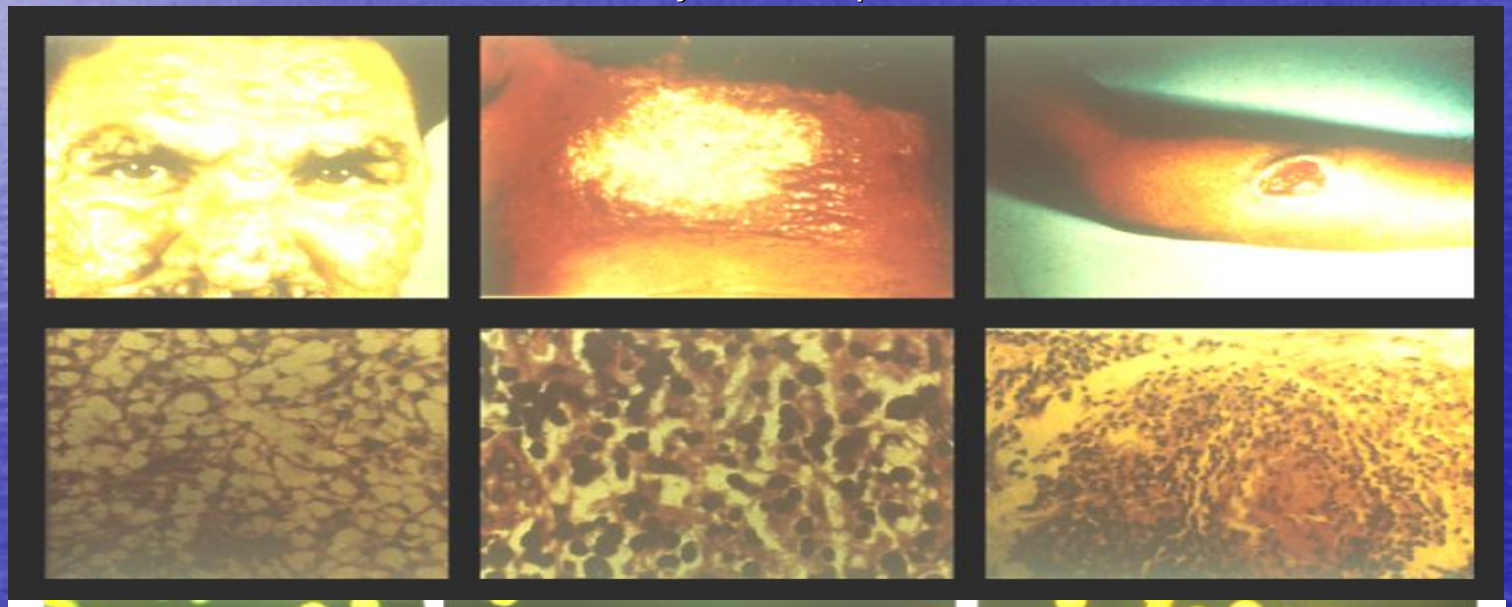
Epidemiología

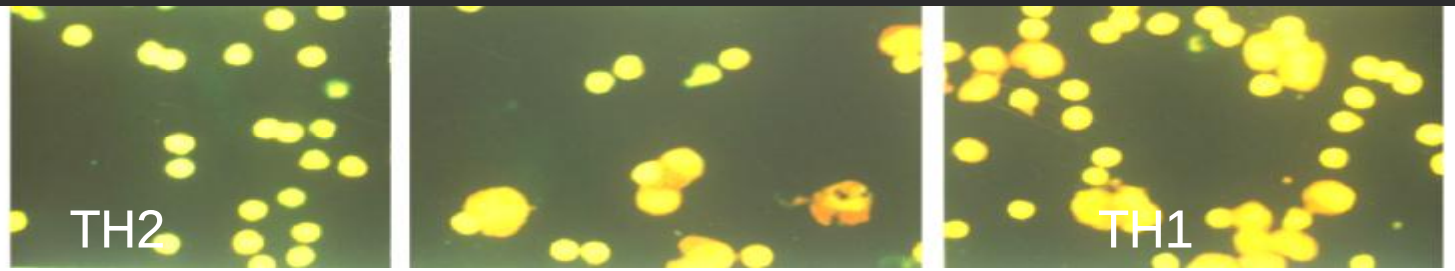
Ocurren dos millones anuales de nuevos casos de leishmaniasis en el mundo (1.5 millones de leishmaniasis cutánea y 500.000 de leishmaniasis visceral) aunque se estima que la cifra pueda llegar hasta 12 millones , ya que de los 88 países donde se presenta, 78 se encuentran en vías de desarrollo y solo en 32 es obligatorio su reporte. La población en riesgo es de 350 millones

Espectro: Clínico-HP-Inmunológico

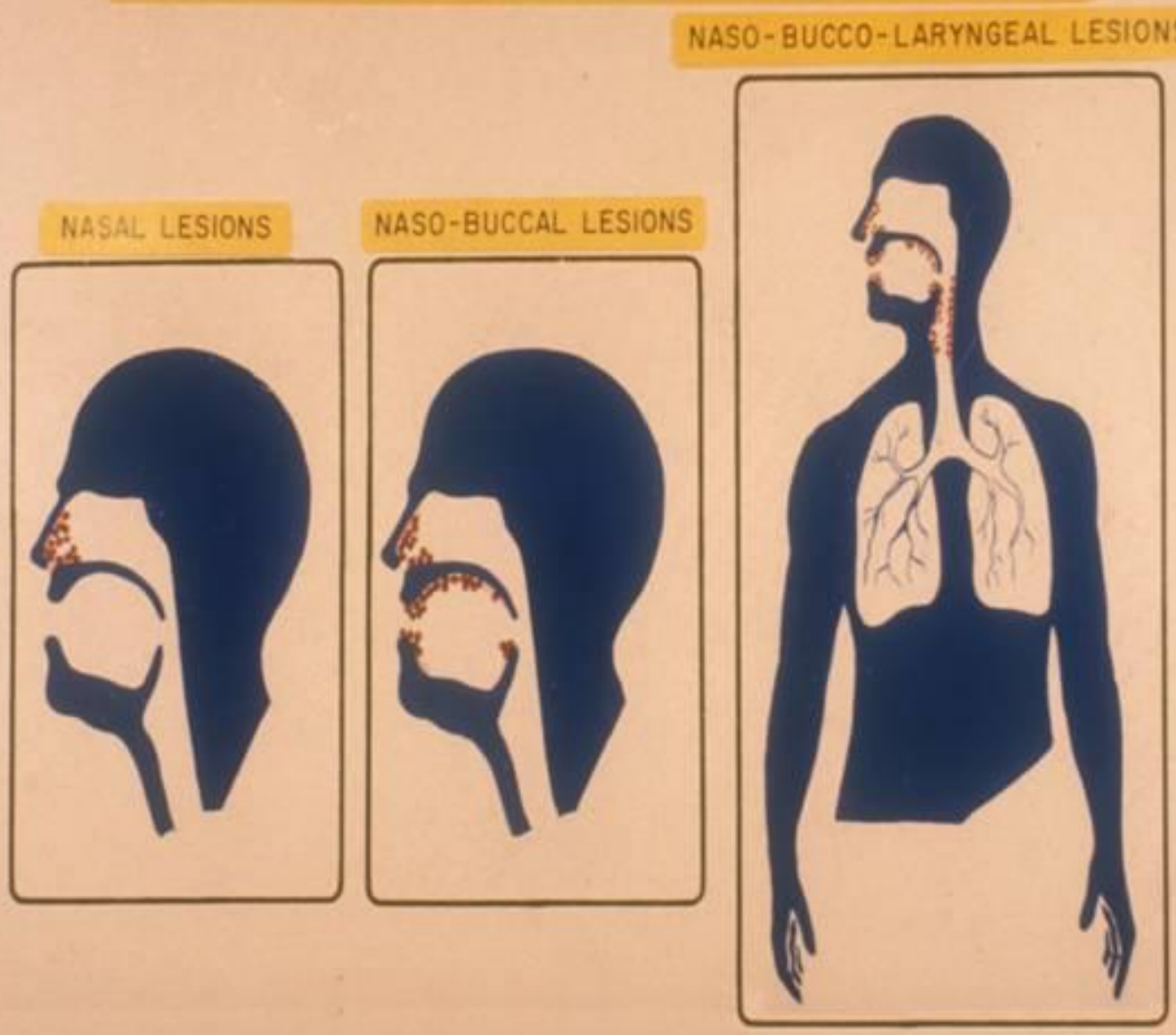
Convit J,Pinardi ME .
Cutaneous Leishmaniasis :the clinical and immunopathological Spectrum .Ciba Foundation Symposium
Rondón Lugo AJ., Convit J.
Spectrum of American Cutaneous Leishmanisis". Dermatology
in five Continents Springler Verlag. Berlin 1988; 789-792

Convit J., Ulrich M., Tapia FJ., Castes M., Rondón Lugo AJ
The Clinical and Immunological Spectrum of American
Cutaneous Leishmanisis". Trans. Roy. Soc. Trop. Medic. 1993. 87: 444-8



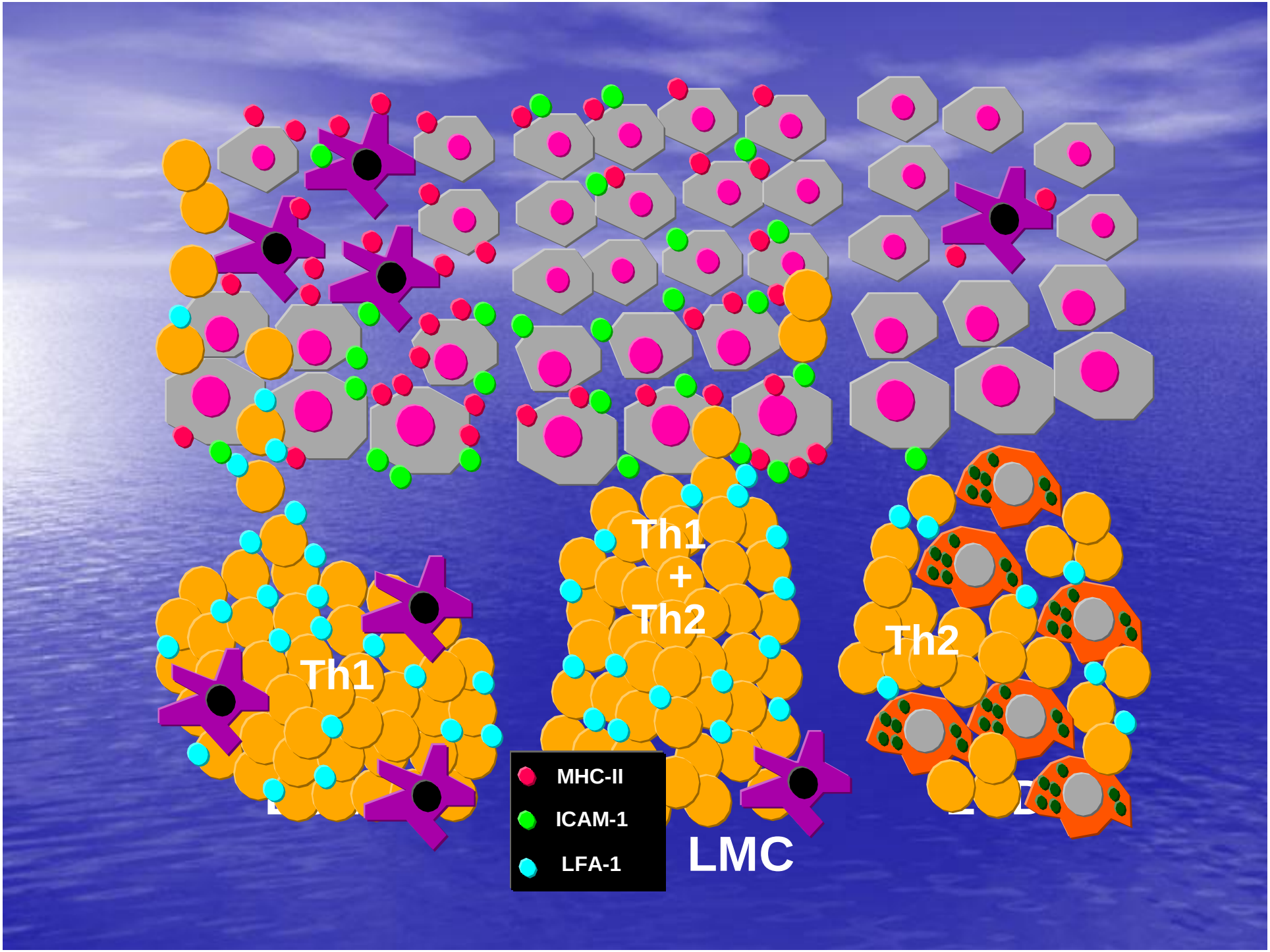


MUCO-CUTANEOUS LEISHMANIASIS



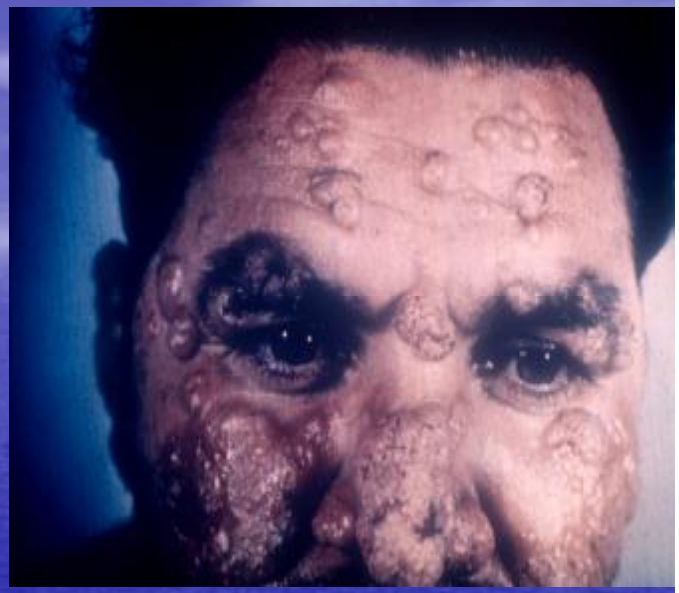
Espectro de la Leishmaniasis

- PARASITOS
- CONDICIONES INMUNOLOGICAS
- CONDICIONES AMBIENTALES
- NUMERO Y LOCALIZACION DE PICADURAS
- CONDICIONES NUTRICIONALES
- INFECCION BACTERIANA


Th1
Th1
+
Th2
Th2
MHC-II
ICAM-1
LFA-1
LMC

Leishmaniasis Difusa anérgica. Primer caso en Venezuela

Convit J., Lapenta P. 1948



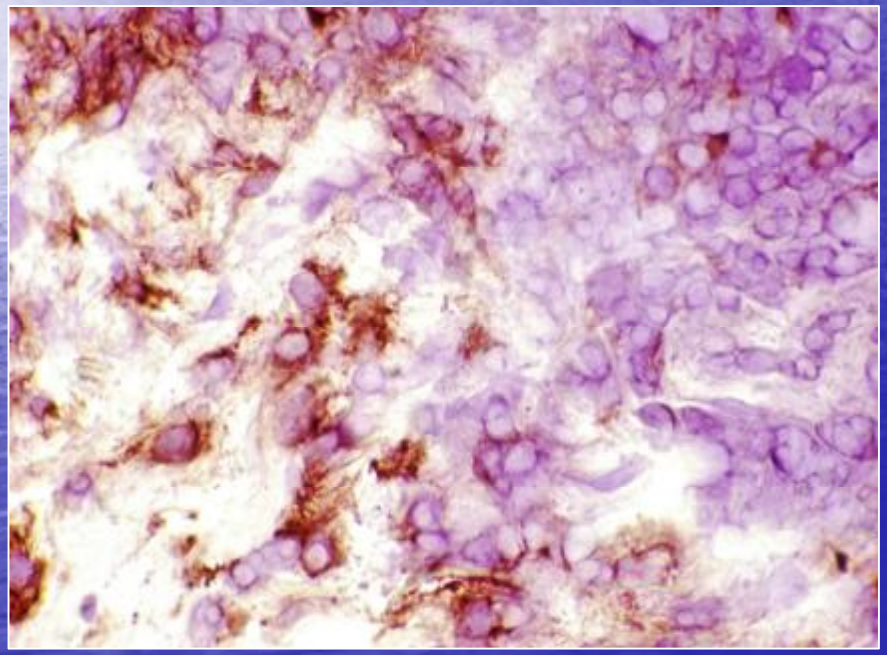
Reprinted from
TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.
Vol. 66. No. 4. pp. 603-610, 1972.

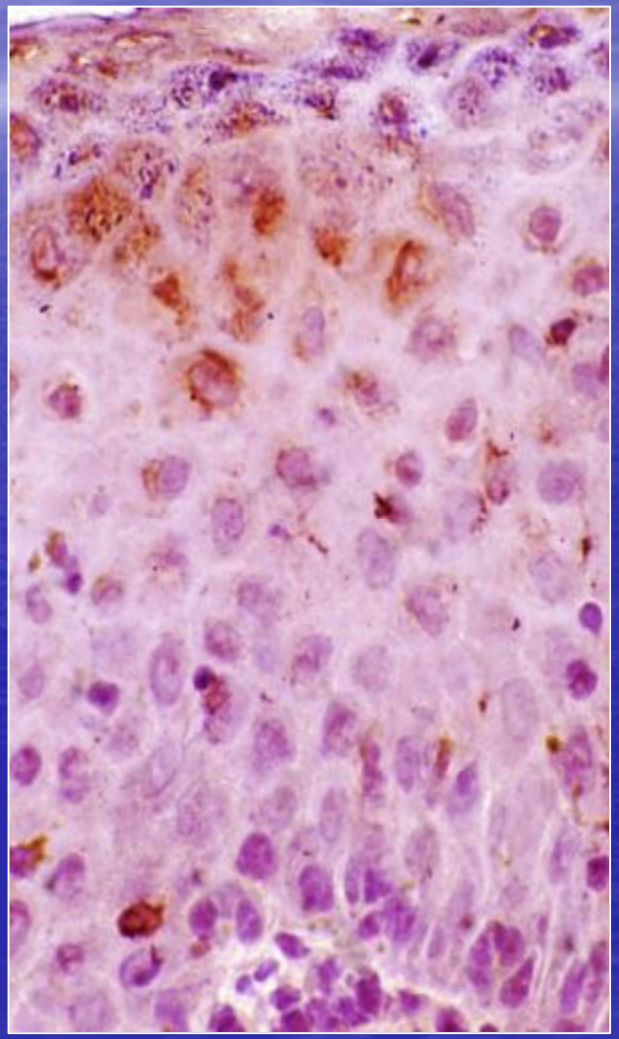
DIFFUSE CUTANEOUS LEISHMANIASIS: A DISEASE DUE TO AN IMMUNOLOGICAL DEFECT OF THE HOST

J. CONVIT, M. E. PINARDI AND A. J. RONDÓN
Division de Dermatologia Sanitaria (M. S. A. S.) and Department of Dermatology, Escuela de Medicina Vargas, Universidad Central de Venezuela, Caracas

Citocinas en LCL

IFN-g LCI





IL-10 LCI

Genes que regulan la diferenciación

- § Cisteine preoteinases
- § Thermal shock proteins
- § gp63 glycoprotein
- § Proteophosglycan
- § Amastine
- § MAPK
- § LPG

Moleculas relacionadas con la virulencia de leishmanias

- § Invasive/Evasive determinantes
- § Glycophosfatidil inositos - Glycoprotein - GP63
- § Glycosil phospholipids - Cisteine proteases
- § Lipophosphoglicans - Histones
- § Phosphoglicans – ATphases
- § Proteophosphoglicans

Determinantes inmunopatológicos

- Cytoskeletal proteins (kinesins and tubulins)
- Chaperons (Histones: HSP 60, 70, 83)
- Ribosomal proteins
- Nuclesomes
- Proteosomes

Tratamientos

- Antimoniales
- Anfotericina B
- Anfo.. Liposomal
- Pentamidina
- Inmunoterapia
- Miltefosina
- Ketoconazol
- Terbinafina
- Itraconazol
- Termoterapia
- Crioterapia
- Interleuquinas
- Interferon
- Laser CO2
- Rifampicina
- Trimetropin

Miltefosine

- Miltefosine for New World Cutaneous Leishmaniasis
  J. Soto, B. A. Arana,J. Toledo, N. Rizzo, J. C. Vega, A. Diaz,M. Luz, P. Gutierrez,M. Arboleda,J. D. Berman, K. Junge, J. Engel,5and H. Sindermann.
  Clinical Infectious Diseases 2004:38 (1 May)
- **Diffuse cutaneous leishmaniasis responds to miltefosine but then relapses**

  Zerpa, O.; Ulrich, M.; Blanco, B.; Polegre, M.; Avila, A.; Matos, N.1; Mendoza, I.2; Pratlong, F.3; Ravel, C.3; Convit, J.
  British Journal of Dermatology, Volume 156, Number 6, June 2007, pp. 1328-1335(8)

Nuevas terapias

- § Paromomicina tópica y parenteral
- § imiquimod tópico
- § Bifosfonatos como risidranote y pamidronato
- § Plantas como licochalcone A y alcaloide de quinolina

Steven G. Reed

IDRI

Leish-111f + MPL-SE Vaccine

Current Regulatory Strategy

PROPHYLAXIS

- U.S. IND Filed
- Phase 1 Trial (CCLV001-01)
- Dose-Escalation in Healthy Subjects
  Patients
- 20 ug & Immungenicity
  Immungenicity

10 ug

THERAPEUTIC

- U.S. IND Filed
- Phase 1 Trial (CCLV001-02)
  - Dose Escalation in
  with CL or ML
  - Safety &

5 ug

10 ug

The Lancet · Saturday 21 February 1987

IMMUNOTHERAPY VERSUS CHEMOTHERAPY IN LOCALISED CUTANEOUS LEISHMANIASIS

JACINTO CONVIT, PEDRO L. CASTELLANOS, ANTONIO RONDON, MARIA E. PINARDI, MARIAN ULRICH, MARIANELLA CASTES, BARRY BLOOM*, LEONARDO GARCIA

*Instituto de Biomedicina (Ministerio de Sanidad y Asistencia Social/Universidad Central de Venezuela), Caracas, Venezuela; and Albert Einstein College of Medicine of Yeshiva University, Bronx, NY 1046, USA**

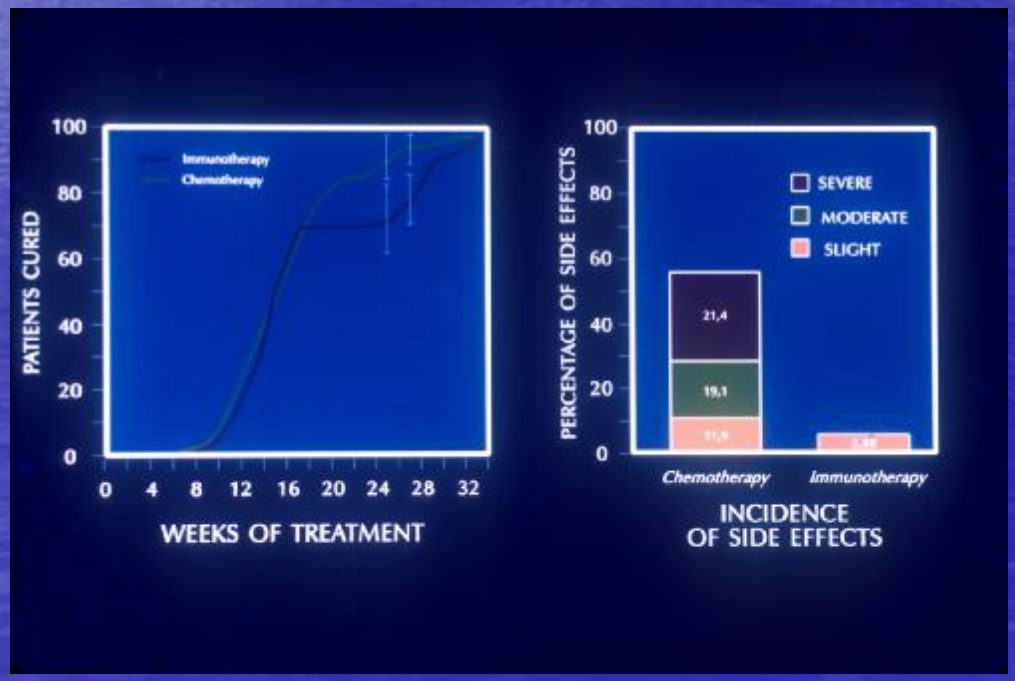
THE JOURNAL OF INFECTIOUS DISEASES • VOL. 160, NO. 1 • JULY 1989

Immunotherapy of Localized, Intermediate, and Diffuse Forms of American Cutaneous Leishmaniasis

Jacinto Convit, Pedro L. Castellanos, Marian Ulrich, Marianella Castés, Antonio Rondón, Maria E. Pinardi, Noris Rodríguez, Barry R. Bloom, Santina Formica, Lourdes Valecillos, and Antonio Bretaña

From the Instituto de Biomedicina, Caracas, Venezuela, and Albert Einstein College of Medicine, Bronx, New York

The clinical efficacy of immunotherapy for localized American cutaneous leishmaniasis with a combination of heat-killed *Leishmania mexicana amazonensis* promastigotes and viable BCG (bacille Calmette Guérin) has been compared with meglumine antimoniate chemotherapy and with BCG alone in a controlled clinical study in 217 patients. The results in the first two groups were comparable, with >90% clinical cures with an average time of 16–18 w required for healing. The cure rate was considerably lower (42%) and more prolonged in the group receiving BCG alone. Secondary effects were observed in <5% of the patients receiving combined immunotherapy or BCG alone. In contrast, 49% of the patients receiving chemotherapy showed side effects. High therapeutic efficacy was also observed using combined immunotherapy in patients with intermediate and diffuse cutaneous leishmaniasis who were previously unresponsive to chemotherapy. Cure or clinical improvement was seen in all 11 patients with intermediate forms of the disease, and marked clinical improvement was observed in 9 of 10 patients with diffuse disease. The results on the efficacy of the combined vaccine in immunotherapy for American cutaneous leishmaniasis provide a strong rationale for studying its effectiveness in prophylactic trials.



Vacuna Ideal

- Induce respuesta efectiva tipo I , con apropiados antígenos celulares
- Segura
- Reproducible ,trasferible y reproducible
- Induzca inmunidad por largo tiempo
- Proteja contra mas de una especie de leishmania .
- Costo razonable

Lepra:

Una Lucha de Siglos entre el Hombre y el Bacilo...

Nacarid Aranzazu

Lev. XIII. 45-46

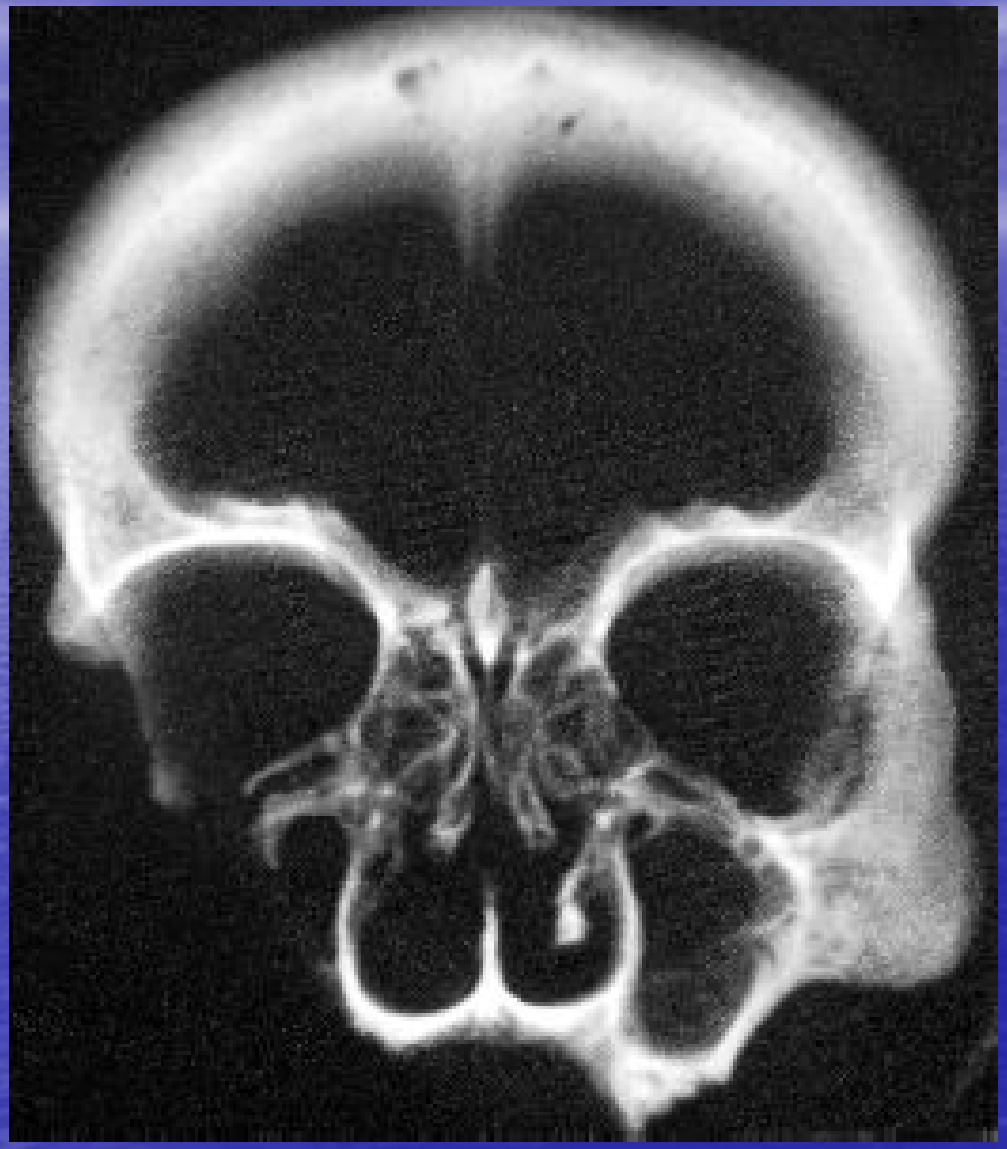
"El afectado por la lepra llevará los vestidos rasgados y desgreñada la cabeza, se cubrirá hasta el bigote e irá gritando: ˇImpuro, impuro! Todo el tiempo que dure la llaga, quedará impuro. Es impuro y habitará solo; fuera del campamento tendrá su morada."

Microbiology and Infectious Disease/Original Article

Detection of Leprosy in Ancient Human Skeletal Remains by Molecular Identification of Mycobacterium leprae

Christian J. Haas, PhD,1,2 Albert Zink, PhD,2 György Pálfi, PhD,3,

4 Ulrike Szeimies, MD,5 and Andreas G. Nerlich, MD, PhD2



Microbiology and Infectious Disease/Original Article

Detection of Leprosy in Ancient Human Skeletal Remains by Molecular Identification of Mycobacterium leprae

evidencias muy sustentables es el hallazgo de 4 esqueletos de posibles enfermos de lepra en las excavaciones arqueológicas realizadas en el desierto de Dakleh en Egipto

Christian J. Haas, PhD,1,2 Albert Zink, PhD,2 György Pálfi, PhD,3, 4 Ulrike Szeimies, MD,5 and Andreas G. Nerlich, MD, PhD2

Key Words: Ancient DNA; Mycobacterium leprae; PCR; Paleopathology; Historic bone samples

Era Presulfónica

SIGLO XIX

Uso de TODOS los tratamientos empíricos imaginables

- Aceite de Chalmougra

Cambios sensoriales sin lesiones de piel
Vat Rakta o Vat Shonita

Sushrata Samhita 600 A.

Con cambios sensoriales

Con lesiones de piel

Con ulceraciones Aruna Kushta

Ridley. D.S. And Jopling W.H. 1962. A Clasification of leprosy for research purpose. Leprosy Review 33.

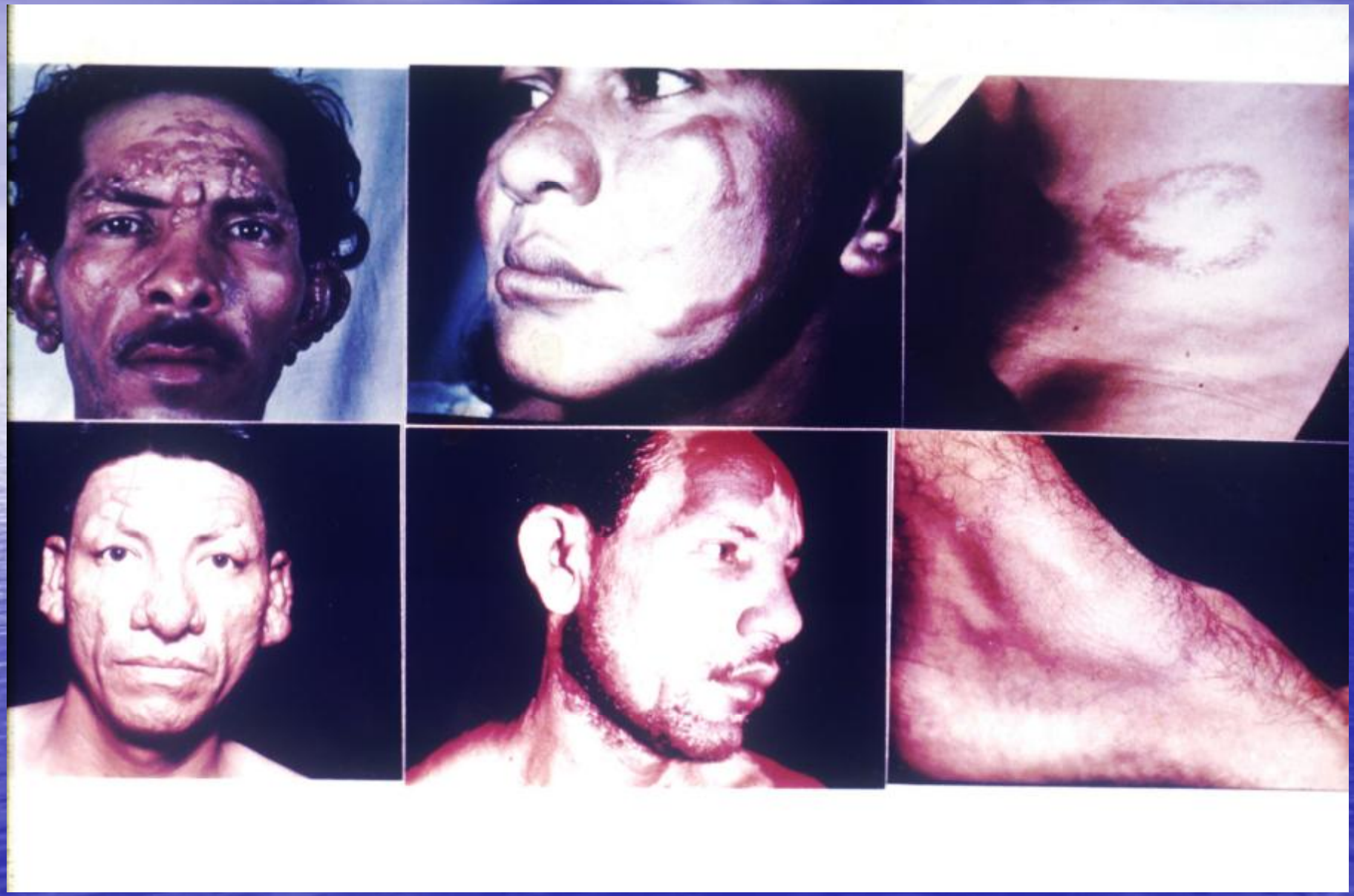
Sugieren una subdivisión basada en una correlación clínica, inmunológica e histopatológica (1962).

Proponen una clasificación que correlaciona el cuadro clínico, bacteriológico e inmunológico (1966).

Tipo lepromatoso (LL)
Tipo Tuberculoide (LT)

<u>Grupo Borderline:</u>

Borderline lepromatoso (BL)
Borderline borderline(BB)
Borderline tuberculoide (BT)



Drogas antileprosas. 1970.

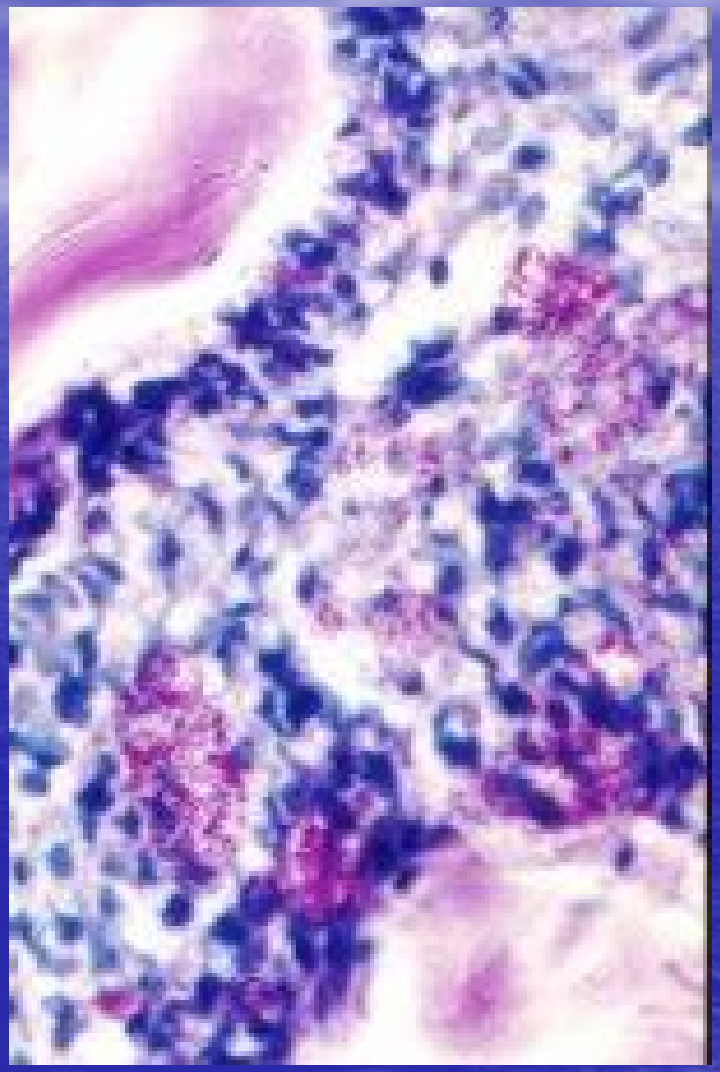
Sulfonas

Dipheniltioureas

Sulfonamidas de acción lenta

Clofazimina **(Sintetizada por Barry y usada en lepra por Browne). 1962**

Globis de Mycobacterium leprae



HANSEN G.H.A.1875. Chirurgical Review 55: 459-489 On the etiology of leprosy

The Nine-Banded Armadillo: A Model for Leprosy and Other Biomedical Research[1, 2]

Eleanor E. Storrs[3]

The nine-banded armadillo (*Dasypus novemcinctus* Linn.), a primitive mammal, has unique potential for use in many areas of medical and biological research. Among characteristics which make this animal a useful research model are: (a) a low body temperature (32° —35° C), (b) regular production of litters of monozygous quadruplet young, (c) possible weak immune responses, (d) susceptibility to some human diseases, (e) long life span, (f) ability to build up an oxygen debt, (g) a complexly structured carapace which appears to mutate readily and (h) a delayed implantation period of the blastocyst of about 14 to 16 weeks duration.

It was because of this first factor, the low body temperature, that I first became interested in the armadillo as an animal model in leprosy studies since it was known that *Mycobacterium leprae* multiplies best in man in the cooler regions of the body. Once set can be used for inoculation, and the others reserved for future breeding if positive results are obtained.

The long life span of the armadillo (estimated at 12 to 15 years) is advantageous for the study of diseases which develop slowly. Also, preliminary results indicate that the immune responses of this animal may be weak ([58]).

In addition to apparent susceptibility to leprosy, the armadillo is susceptible to other diseases of man, including relapsing fever, exanthematic typhus, murine typhus, trichinosis, and schistosomiasis (*vide infra*). Thus the potential of this animal for use in disease transmission and chemotherapy studies could be significant.

DESCRIPTION

Taxonomy and evolution. The nine-banded armadillo, *Dasypus novemcinctus*, Linn., is a mammal of the Subclass Euth-

INTERNATIONAL JOURNAL OF LEPROSY And Other Mycobacterial Diseases

VOLUME 39, NUMBER 3 JULY-SEPTEMBER, 1971

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I. Report of Lepromatoid Leprosy in an Experimentally Infected Armadillo[1]

W. F. Kirchheimer and Eleanor E. Storrs[2]

In October 1965 the Leprosy Panels of the U.S.-Japan Cooperative Medical Science Program issued a "Joint Report on Re-

lepromatous disease. Therefore, search for suitable animal models should be continued.

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Leininger, J.R. Donhan, K. J. and Meyers, W. M. Leprosy in a chimpanzee post-morten lesion. Int J. Lep. 1980. 48, 414-421.

reportan haber diagnosticado lepra lepromatosa en un Chimpancé que nunca había sido inoculado con bacilos de lepra y estaba aislado siendo sometido a estudios para leucemia.

TERNATIONAL JOURNAL OF LEPROSY

Volume 39, Number 2
Printed in the U.S.A.

A. INTRODUCTORY REVIEW OF LEPROSY RESEARCH

The Impact of Experimental Human Leprosy in the Mouse on Leprosy Research

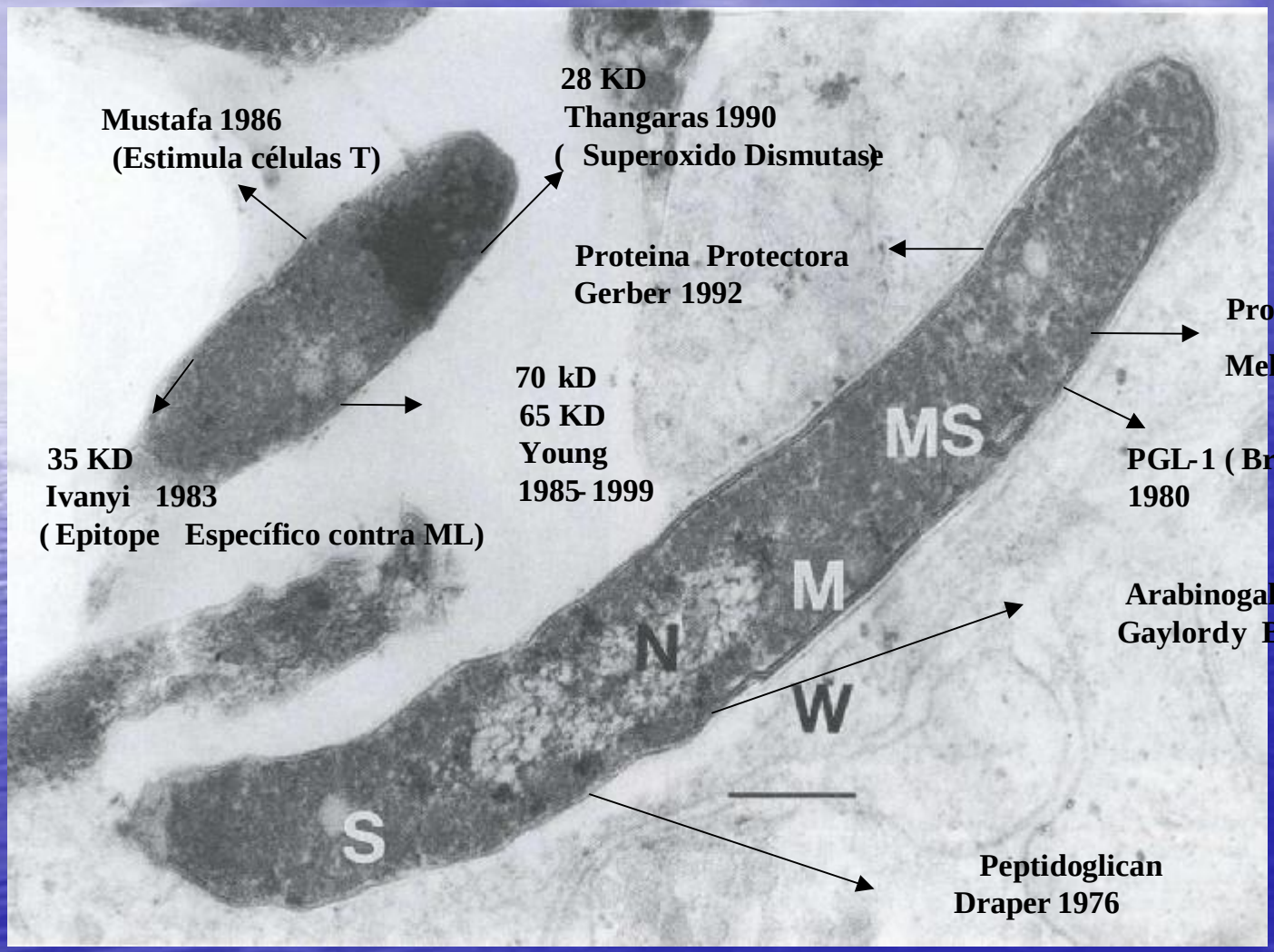
R. J. W. Rees[1]

In no field of medicine has greater progress been made than with the infectious diseases—all within the last hundred years. This has applied to all diseases caused by bacteria and, more recently, many of those caused by viruses. These advances in knowledge, whether they have been on the microbiologic, pathologic, preventive or therapeutic side, have evolved, at every stage, either from studies related to *in vitro* cultivation of the causative organism and/or from infections in experimental animals. Unfortunately the causative organism of human leprosy, *Mycobacterium leprae*

in the last ten years, bearing in mind that all the studies had by necessity to be adapted to *in vivo* conditions.

FIG. 3. Nodular swelling of hind footpad in a thymectomized-irradiated mouse injected locally with 10^7 *M. leprae* 11 months earlier.

Micobacterium leprae



Mustafa 1986
(Estimula células T)

28 KD
Thangaras 1990
(Superoxido Dismutase)

Proteina Protectora
Gerber 1992

Proteína Estimulante TT.
Mehra y Modlin 1989.

70 kD
65 KD
Young
1985- 1999

35 KD
Ivanyi 1983
(Epitope Específico contra ML)

PGL-1 (Brennan)
1980

Arabinogalactan
Gaylordy Brennan 1987

Peptidoglican
Draper 1976

Era post-sulfónica

Nueva clasificación para fines terapéuticos

- **Multibacilares:**
  - -Lepromatosa
  - -Borderline lepromatosa
  - -Borderline Borderline
- **Paucibacilares:**
  - -Borderline tuberculoide
  - -Lepra tuberculoide
  - -Indeterminada

Nuevas Estrategias

44ª Asamblea de la OMS 1991

- **Resolución 44** conmina a los Estados Miembros para promover las medidas de control incluyendo MDT para la eliminación de la lepra como problema de salud pública para el año 2000 (menos de 1 caso por 10000 habitantes)

Nuevas Estrategias

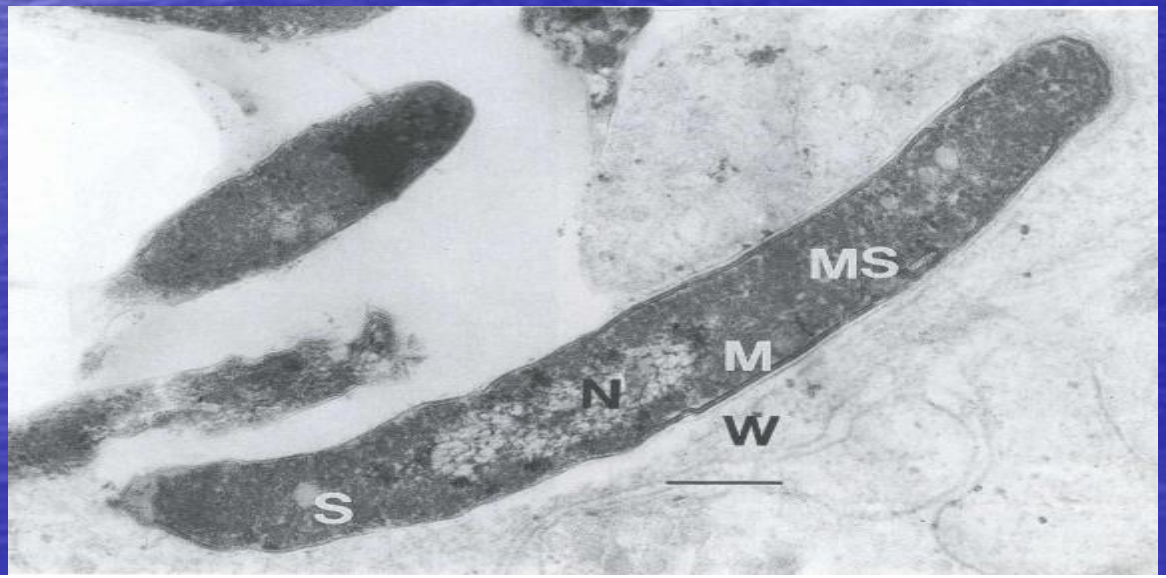
Noviembre 1999

- 122 países que en 1985 eran endémicos bajaron su prevalencia hasta la eliminación del problema como endemia. Sólo 24 países permanecieron con prevalencia alta
- La prevalencia global para 1999 es de l.4 por 10.000 habitantes
- La incidencia persiste estable diagnosticándose para 1998, 805.000 casos nuevos
- **La eliminación de la lepra se prolongó hasta el año 2005**

Draper F. 1976 ***Cells walls of Micobacterium leprae. Int. J. Lep. 44: 95-98.***

Gaylord H. Y Brennan, P.J. 1987 ***Leprosy and the Leprosy bacillus: recent development in characterization of antigens and inmunology of the diseases. Annual review of microbiology, 41, 645-675.***

Brennan, P.J. Barroe. W.W., 1980 ***Evidences for species-specific lipids antigens in Micobacterium leprae. Int. J. of Lep. 48: 382-387.***



Vacunas

Existen 4 vacunas:

BCG

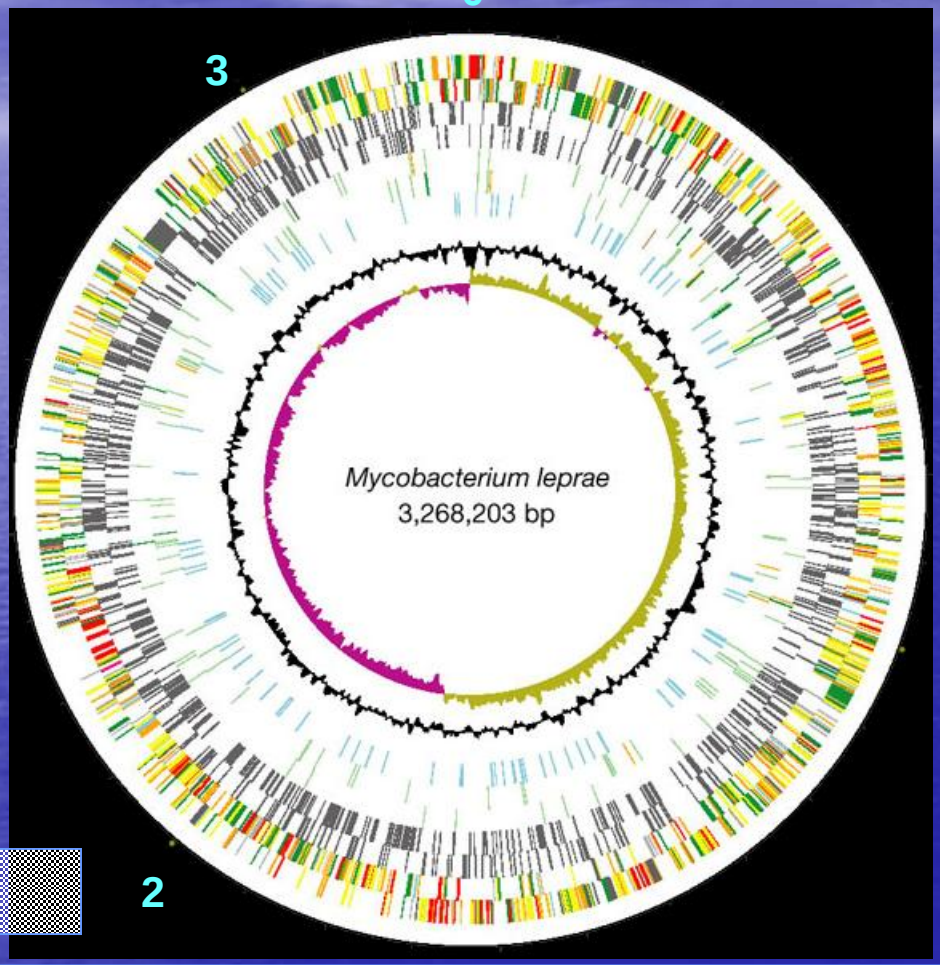
BCG plus Killed M. Leprae

India

Mycobacterium W

Mycobacterium ICRC

Genome and Molecular Biology

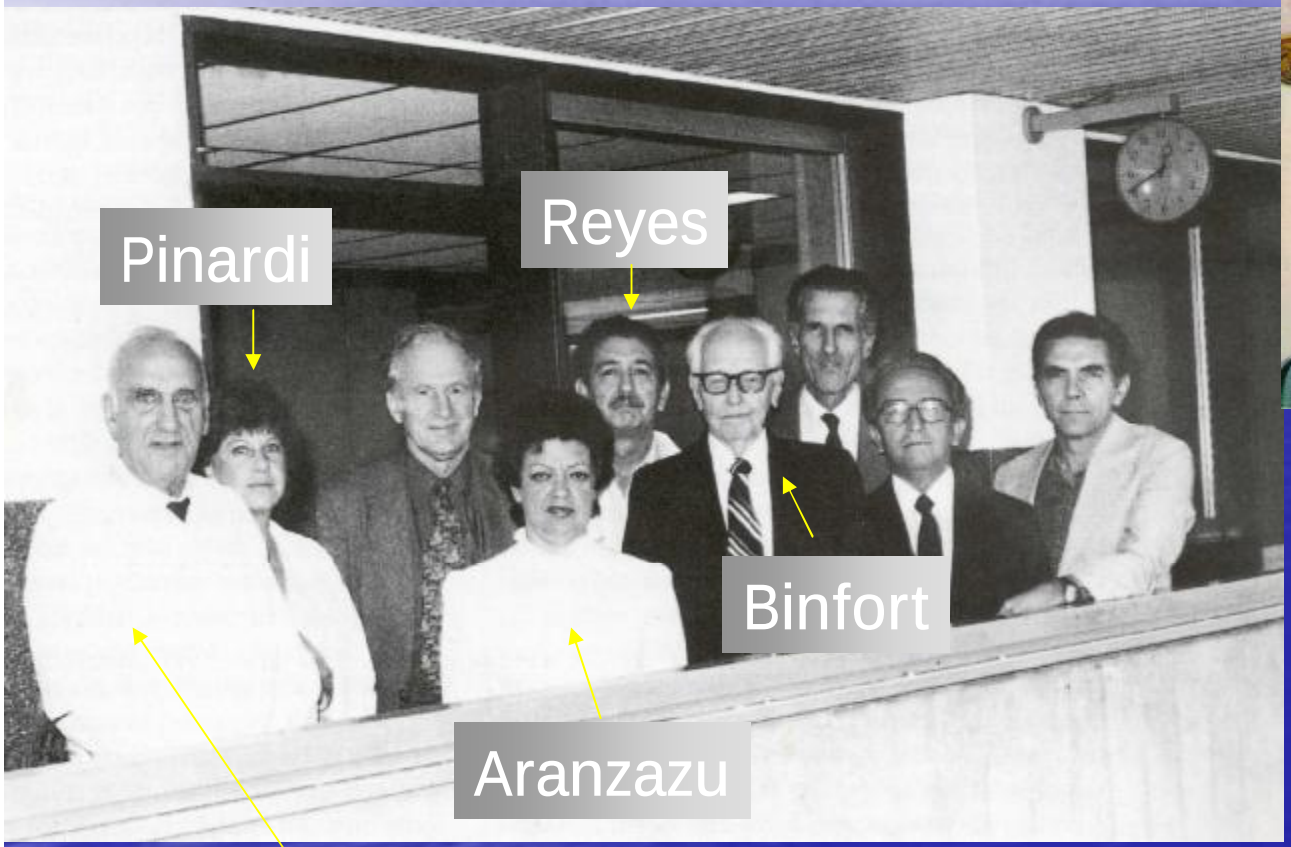


Circular Genome

Nature. 2001:409

1991-2000: Complete sequence of the *M. leprae* Genome *M. leprae*

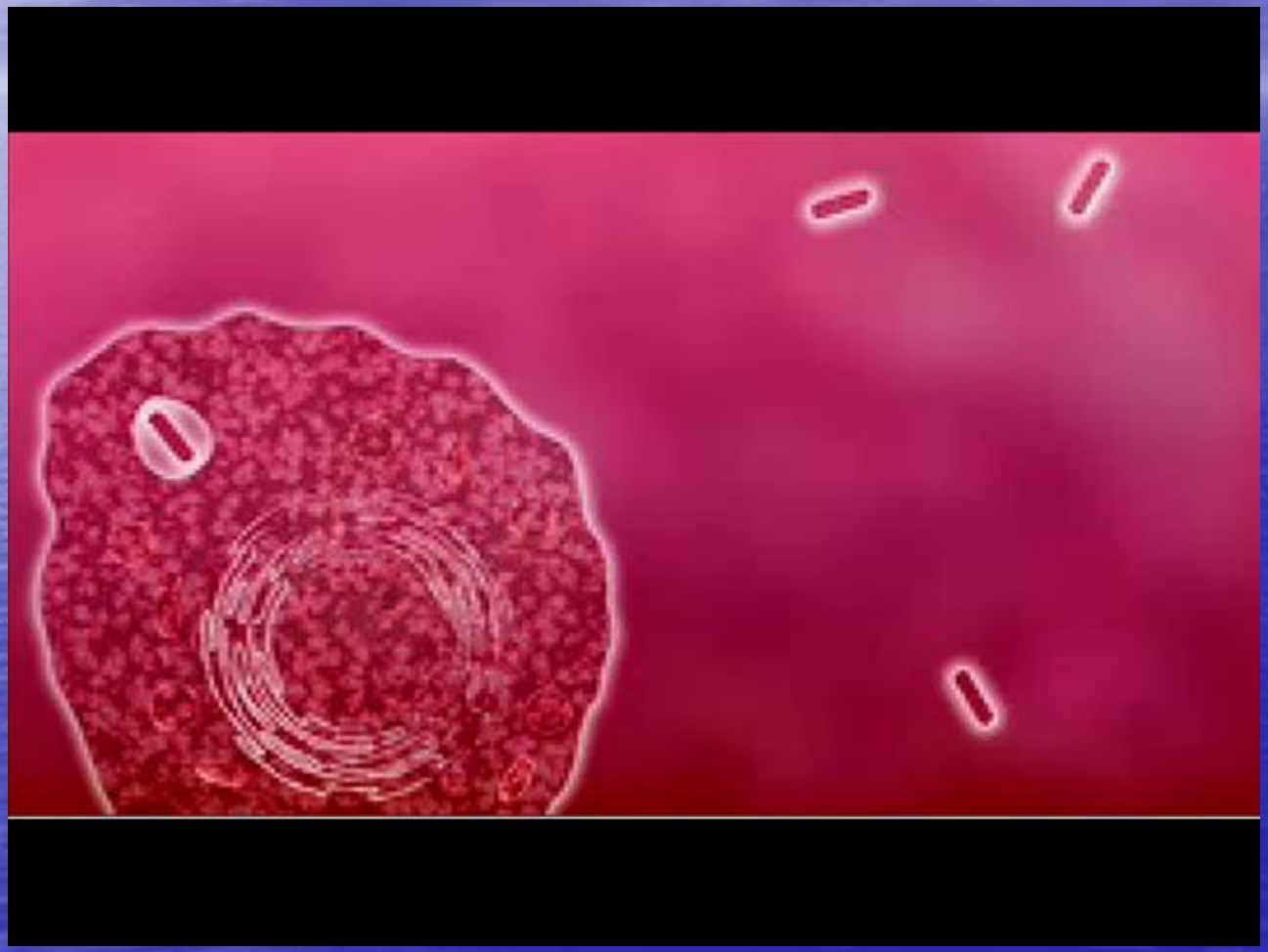
Heroes contra el Hansen



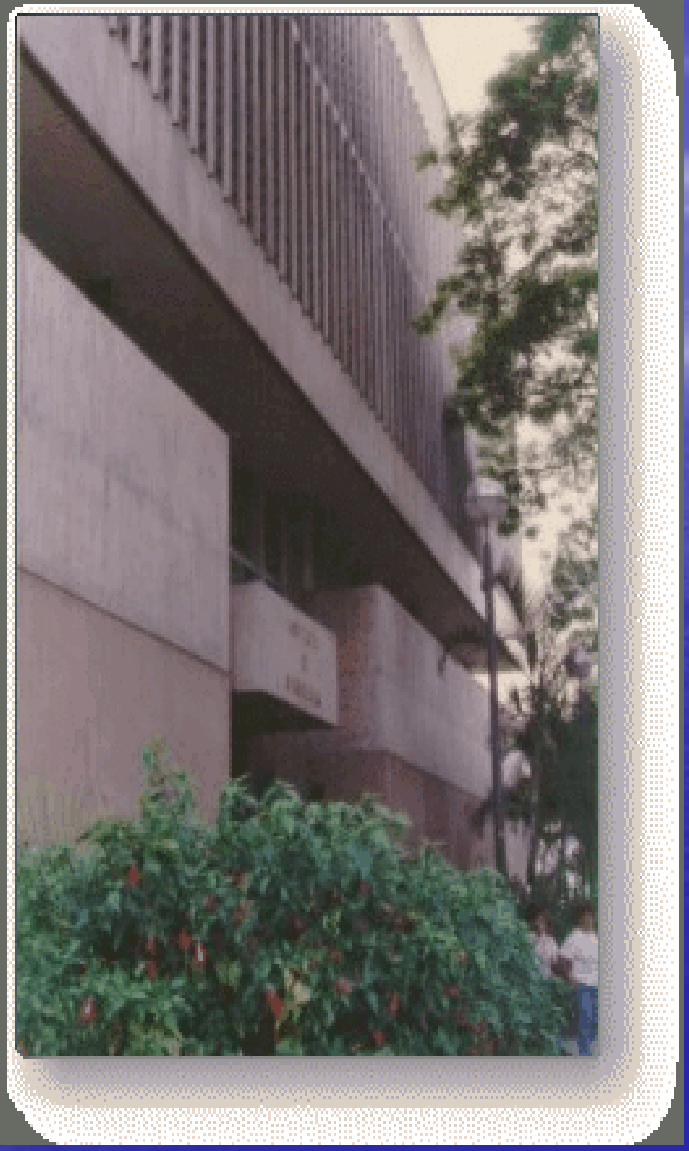
Padre Damian

Madre Teresa de Calcuta

Patogénesis



Gracias



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