

Leishmaniasis

WRAIR- GEIS 'OPERATIONAL CLINICAL INFECTIOUS DISEASE' COURSE



WRAIR

Walter Reed Army
Institute of Research

Soldier Health • World Health



Leishmaniasis

- Diverse group of diseases caused by infection from protozoan parasites of the genus *Leishmania*
- Designated one of the five most important diseases worldwide by the WHO
 - 1.5 to 2 million new cases/year
- Leishmaniasis threatens over 350 million individuals in 88 countries, and directly impacts US service members abroad

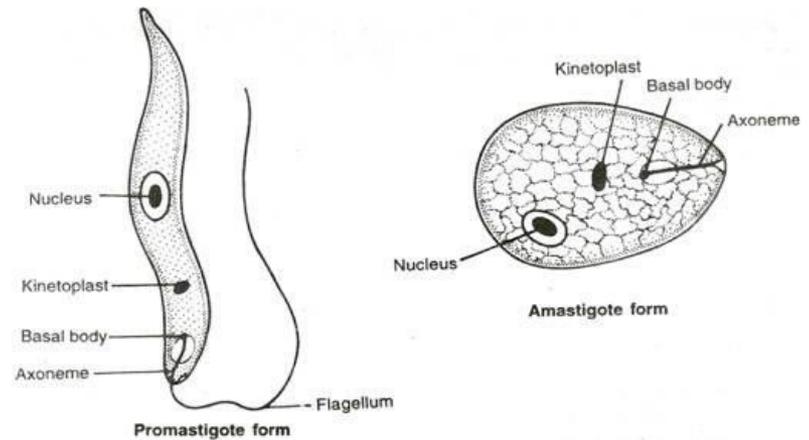
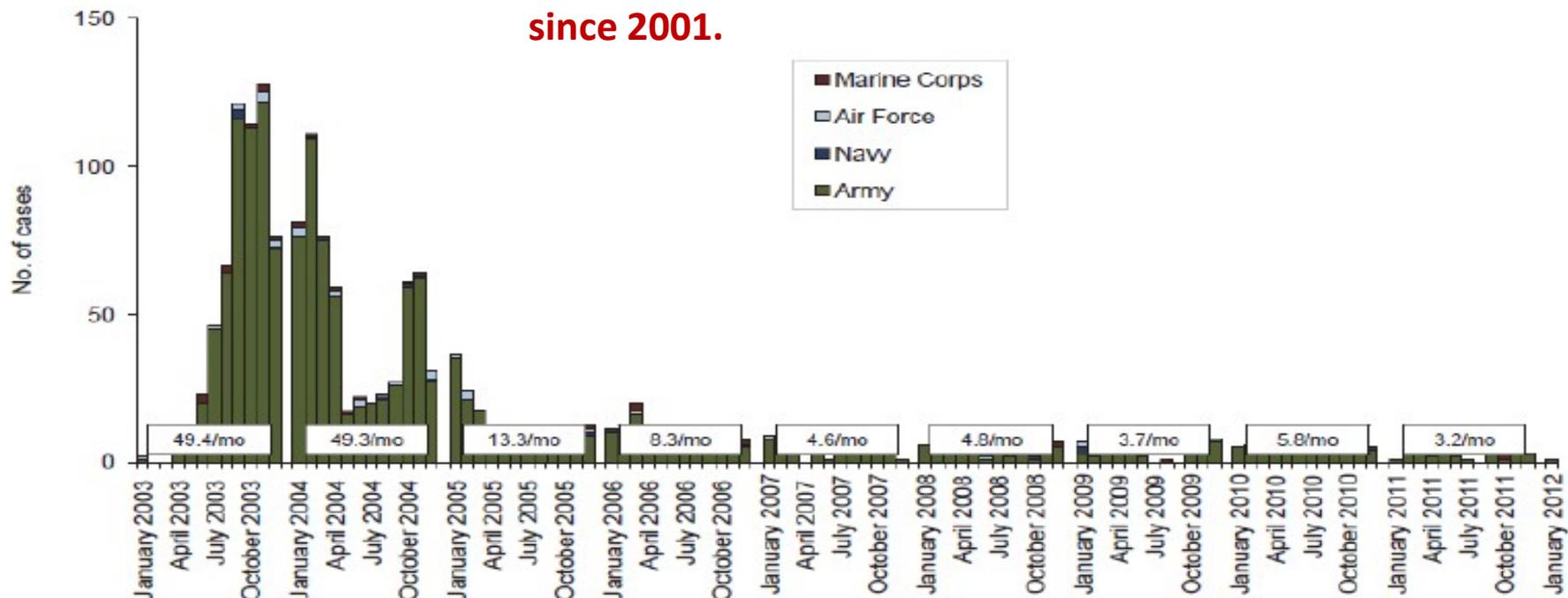


Fig. 178. Morphological forms of *Leishmania donovani*
www.yourarticlelibrary.com

Leishmaniasis among US Armed Forces: 2003-2012

Over 2000 cases of Leishmaniasis have occurred in American troops deployed to Iraq and Afghanistan since 2001.

Leishmaniasis (ICD-9: 085.0 to 085.9)^b



Reference: Army Medical Surveillance Activity. Deployment-related condition of special surveillance interest: leishmaniasis. Leishmaniasis among U.S. Armed Forces, January 2003–November 2004. *MMWR*. Nov/Dec 2004;10(6):2-4.

^bIndicator diagnosis (one per individual) during a hospitalization, ambulatory visit, and/or from a notifiable medical event during/after service in DEF/OIF/OND.

An scourge of many names...

- Aleppo evil
- Baghdad boil
- Biskra nodule
- Jericho button
- Lahore sore
- pian bois (bush yaws)
- chiclero's ulcer
- uta
- sandfly disease
- espundia
- black fever
- Dum-Dum fever
- kala-azar



Sir William Boog Leishman
(1865-1926)

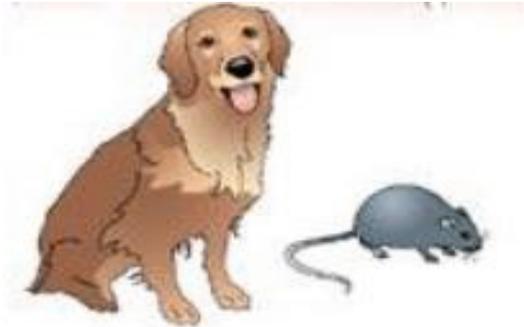
Vector

- Female Sand fly
 - Lutzomyia* in the Americas
 - Phlebotomus* elsewhere
- Poor flyers, remain near ground
- World wide distribution
- Bites at exposed areas and clothing lines

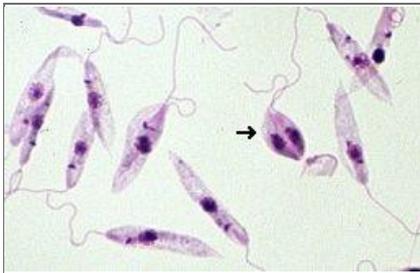


Reservoirs

- Humans
- Dogs
- Rodents



Transmission* and Lifecycle



Promastigotes divide and migrate to the anterior midgut and foregut.

Sand fly injects promastigotes into the skin during a blood meal. ***infective stage**

Promastigotes are phagocytized by neutrophils that are rapidly recruited to the bite site.

Infected neutrophils release the parasites, which are then consumed by macrophages.

Sand Fly Stages

Human Stages

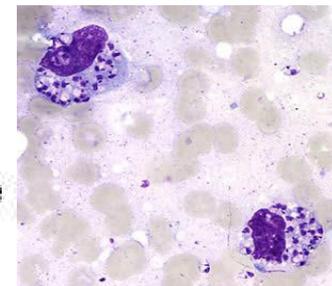
Amastigotes transform into promastigotes in midgut.

Promastigotes transform into amastigotes inside macrophages. ***diagnostic stage**

Ingestion of parasitized cell.

Sand fly ingests infected macrophages when it takes a blood meal.

Amastigotes multiply in cells (including macrophages) of various tissues. ***diagnostic stage**



Disease

- Three clinical syndromes:
 - Cutaneous (skin)
 - Localized, diffuse, *Leishmania recidivans*, post kala-azar dermal leish.
 - Mucocutaneous (mouth, nose, also called “espundia”)
 - Visceral (internal organs, also called “kala-azar”)
- Each syndrome can be caused by multiple different *Leishmania* species, and many species can cause multiple different syndromes
 - Determined by species of parasite, location of infected macrophages, and individual immune response.

Highly Endemic Areas

- 90% of cutaneous leishmaniasis occur in Afghanistan, Brazil, Iran, Peru, Saudi Arabia, and Syria.
- 90% mucocutaneous leishmaniasis occur in Bolivia, Brazil, and Peru
- 90% of all visceral leishmaniasis cases occur in Bangladesh, Brazil, India, Nepal, and Sudan

WHO Leishmaniasis: Burden of Disease

Cutaneous Leishmaniasis (CL)

- Overwhelming majority of Leishmaniasis
 - 1 to 1.5 million cases/year
- Endemic in widely scattered regions throughout the world
- Generally not life-threatening, but potentially permanently disfiguring
- Wide spectrum of clinical presentations that differs somewhat between New and Old World due to regional *Leishmania* species

Old World Cutaneous Leishmaniasis

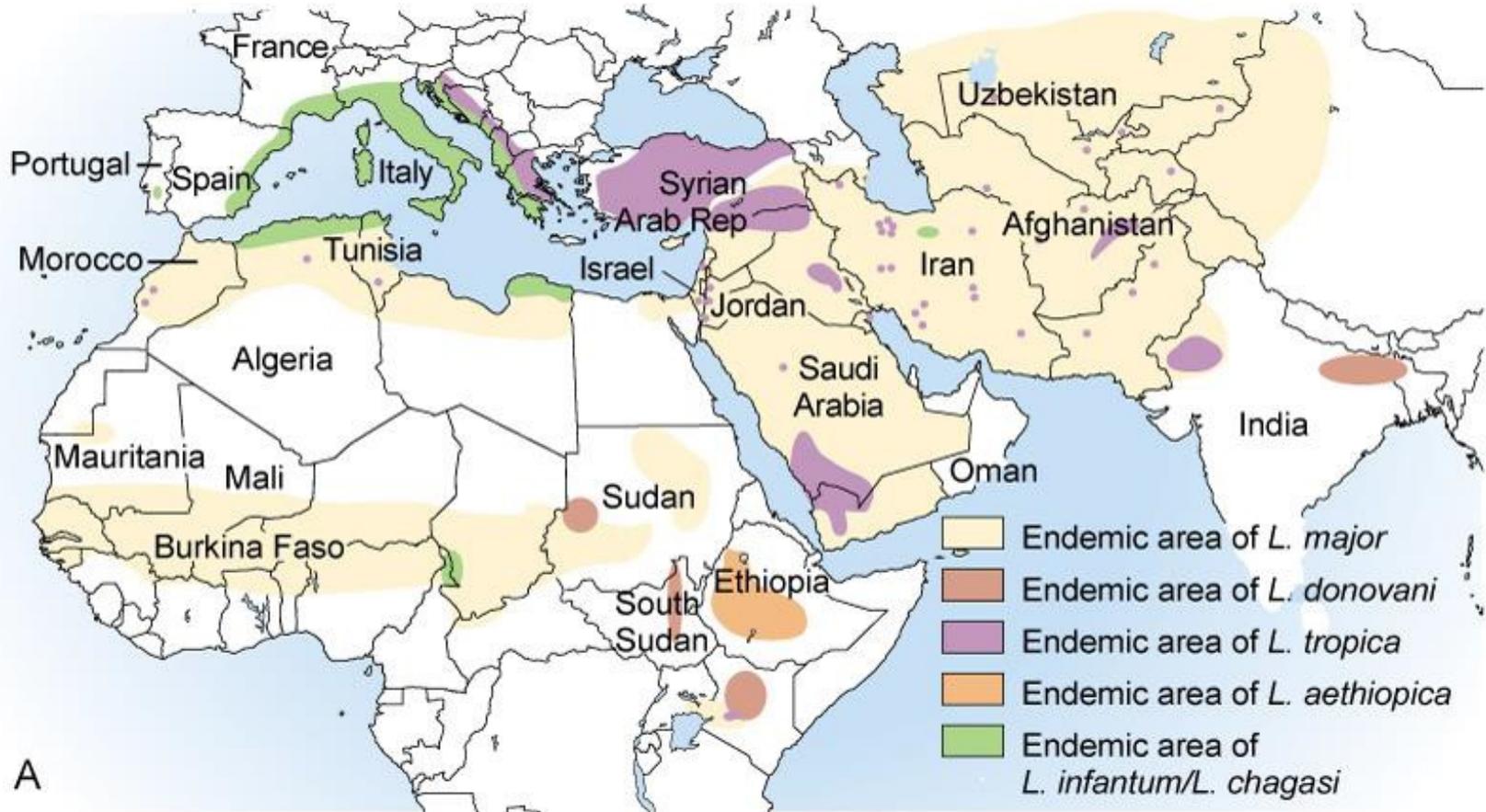


Fig. 277-2A. **Distribution of cutaneous leishmaniasis (CL).** **A**, Old World (Eastern Hemisphere) CL. **B**, New World (Western Hemisphere) CL. Other species causing CL in the New World are not shown but can be found in Table 277-1.

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PPID, 8th ed., pg. 3093

New World Cutaneous Leishmaniasis

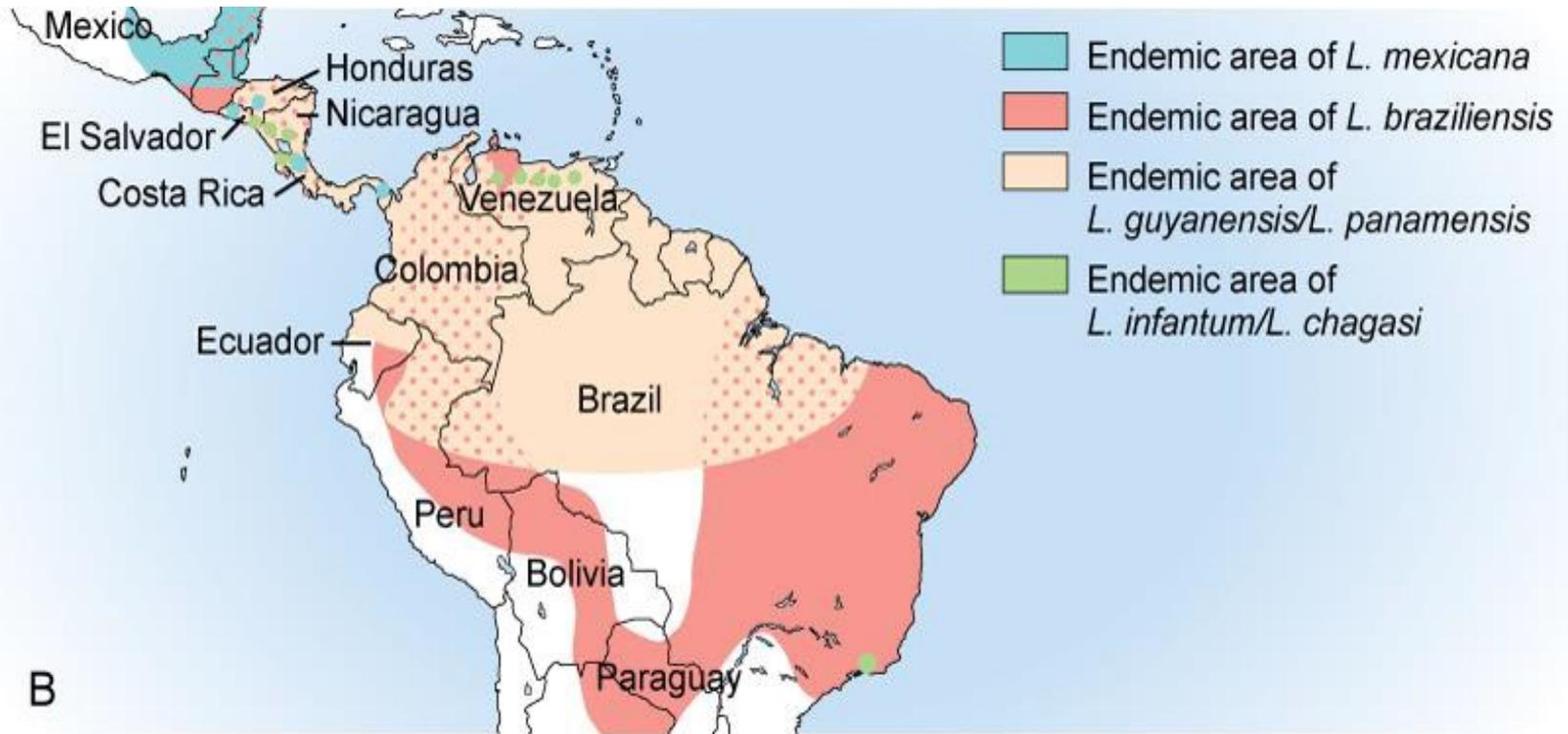


Fig. 277-2B. **Distribution of cutaneous leishmaniasis (CL).** A, Old World (Eastern Hemisphere) CL. B, New World (Western Hemisphere) CL. Other species causing CL in the New World are not shown but can be found in Table 277-1.

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Common CL Presentations

- New World CL

- Localized disease
- Diffuse disease
- Disseminated disease
- Mucosal disease*



Courtesy of Dr. Glenn Wortman, Washington, DC
Fig. 277-10. New World cutaneous leishmaniasis caused by *Leishmania guyanensis*.

- Old World CL

- Localized disease
- Diffuse disease
- Post-kala-azar dermal leishmaniasis
- Leishmaniasis recidivans

*Mucocutaneous Leishmaniasis (espundia) is considered distinct from CL

PPID, 8th ed., pg. 3099

"In some cities infection is so common and so inevitable that normal children are expected to have the disease soon after they begin playing outdoors, and visitors seldom escape a sore as a souvenir. Since one attack gives immunity, Oriental sores appearing on an adult person in Baghdad brands him as a new arrival .."

- Chandler A., in "Introduction to Parasitology" 1944



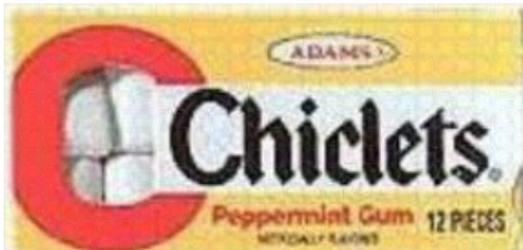
Coleman, et al. J Med Entomol 2006



Photos from Dr. Glenn Wortmann

Chiclero's Ulcer

- Localized cutaneous leishmaniasis (ear)
- Majority of cases caused by *L. mexicana*
- Chicleros – men who collect the chicle latex from which chiclets chewing gum is made



Can Med Assoc J 1986; 134: 216

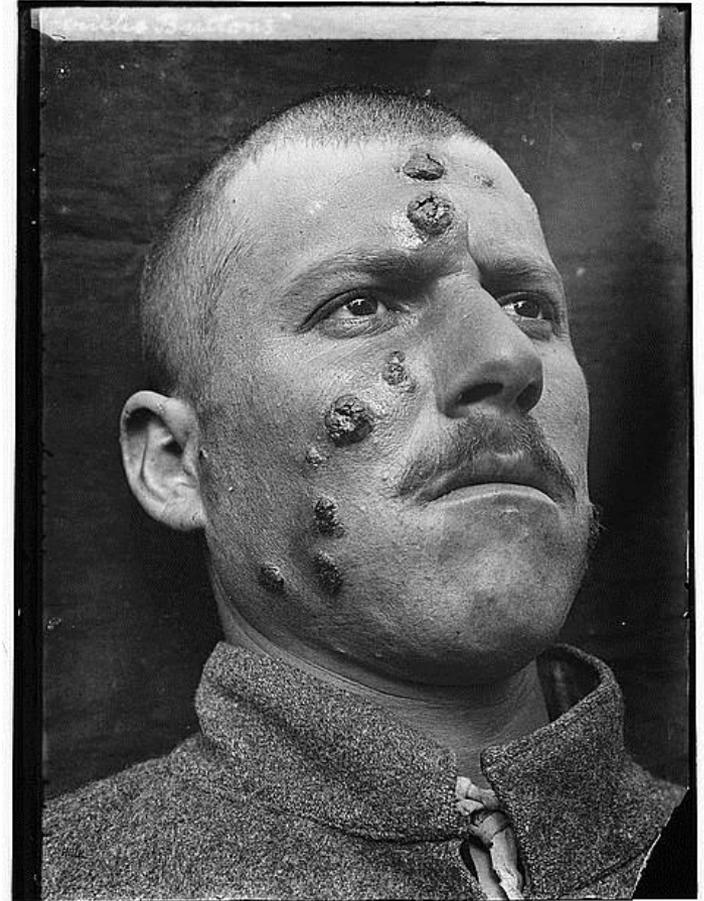


Photo: Dr. Jason Blaylock

Diffuse Cutaneous Leishmaniasis

- Multiple diffuse spreading nodules
 - **Do not ulcerate**
 - Generally face and extremities
- Protracted course-**May be lifelong!**

Jericho Buttons



www.loc.gov

Disseminated Cutaneous Leishmaniasis



- Characterized by **hundreds of lesions**
 - Papules, nodules, ulcers, acne-like
- Seen in Brazilian agricultural workers and immunocompromised
- Low parasite burden
- May involve mucosa

www.ajtmh.org

Post-kala-azar Dermal Leishmaniasis (PKDL)

- Follows treatment of visceral leishmaniasis
 - up to 4 years later
- Macules progressing to papules, nodules and verrucous (wart-like) forms
 - May resolve or remain chronic (up to 20 years)
 - Can be confused with leprosy

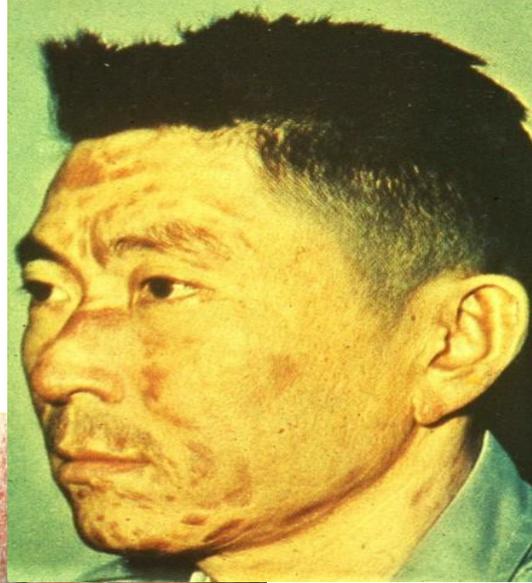


Courtesy Dr. Tom Simpson, Baltimore, MD.

Fig. 277-7. **Post-kala-azar dermal leishmaniasis.** Papular lesions after the treatment of visceral leishmaniasis in Kenya.

PPID, 8th ed., pg. 3097

PKDL



USUHS teaching slides

Leishmaniasis recidivans



PPID, 8th ed., pg. 3100

- Small papules that spread outward leaving a central scar
 - frequently on face
- Chronic
 - waxes and wanes
 - difficult to treat
 - may recur

Leishmaniasis Recidivans

Recurrence after 43 Years:

A Clinical and Immunologic Report
after Successful Treatment

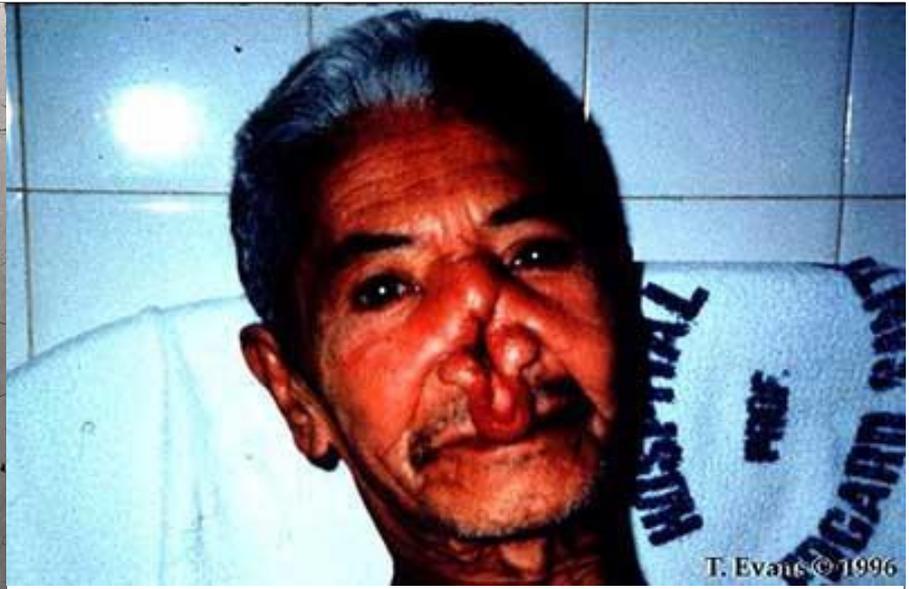
**Mary A. Marovich,^{1*} Rosalia Lira,¹ Marc Shepard,² Glenn H. Fuchs,³
Richard Kruezer,⁴ Thomas B. Nutman,¹ and Franklin A. Neva¹**

¹Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and Departments of ²Medicine and ³Dermatology, George Washington University, and ⁴Walter Reed Army Institute of Research, Washington, DC

Mucocutaneous Leishmaniasis (ML)

- 2-5% of persons with New World CL develop mucous membrane involvement
 - Nose, oral cavity, pharynx, larynx
 - Concurrent or months to **decades** after CL resolves (**can also be primary presentation**)
 - Can be severely mutilating and **life-threatening**





Long-standing cases

PPID, 8th ed., pg. 3099



Visceral Leishmaniasis (VL)

- Leishmanial infection of the internal organs
- Unlike CL, generally similar in all regions
- Incubation: 2-8 months (10 days to >1 year)
- Wide spectrum of presentations
 - majority asymptomatic (6.5-18:1 ratio)
 - asymptomatic to subacute to severe multi-organ disease
 - can spontaneously resolve over weeks to months, or progress to **fatality** if not treated

Visceral Leishmaniasis in the Old World

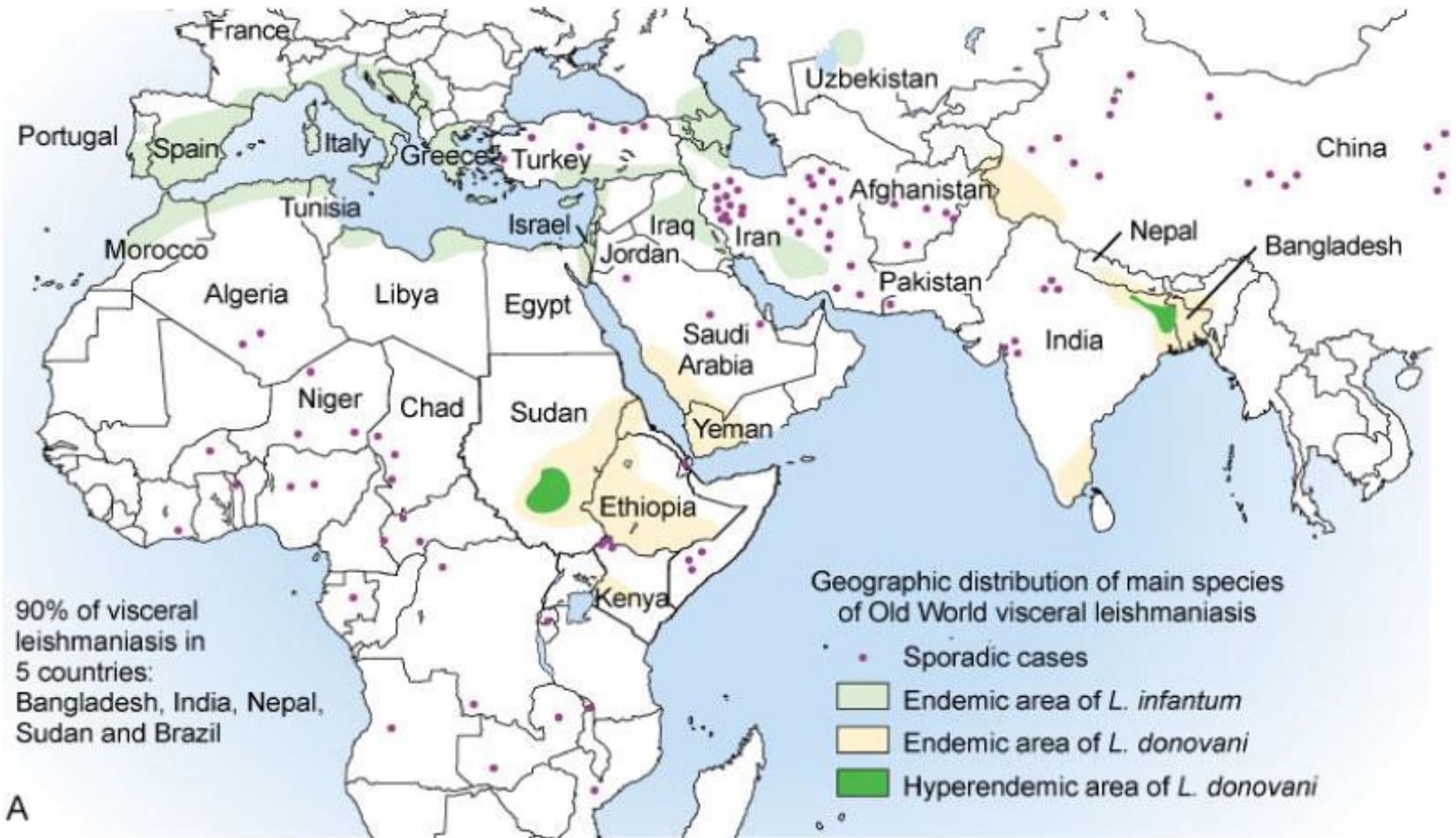


Fig. 277-3A. **Distribution of visceral leishmaniasis (VL).** A, Old World (Eastern Hemisphere) VL. B, New World (Western Hemisphere) VL.

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Visceral Leishmaniasis in the New World

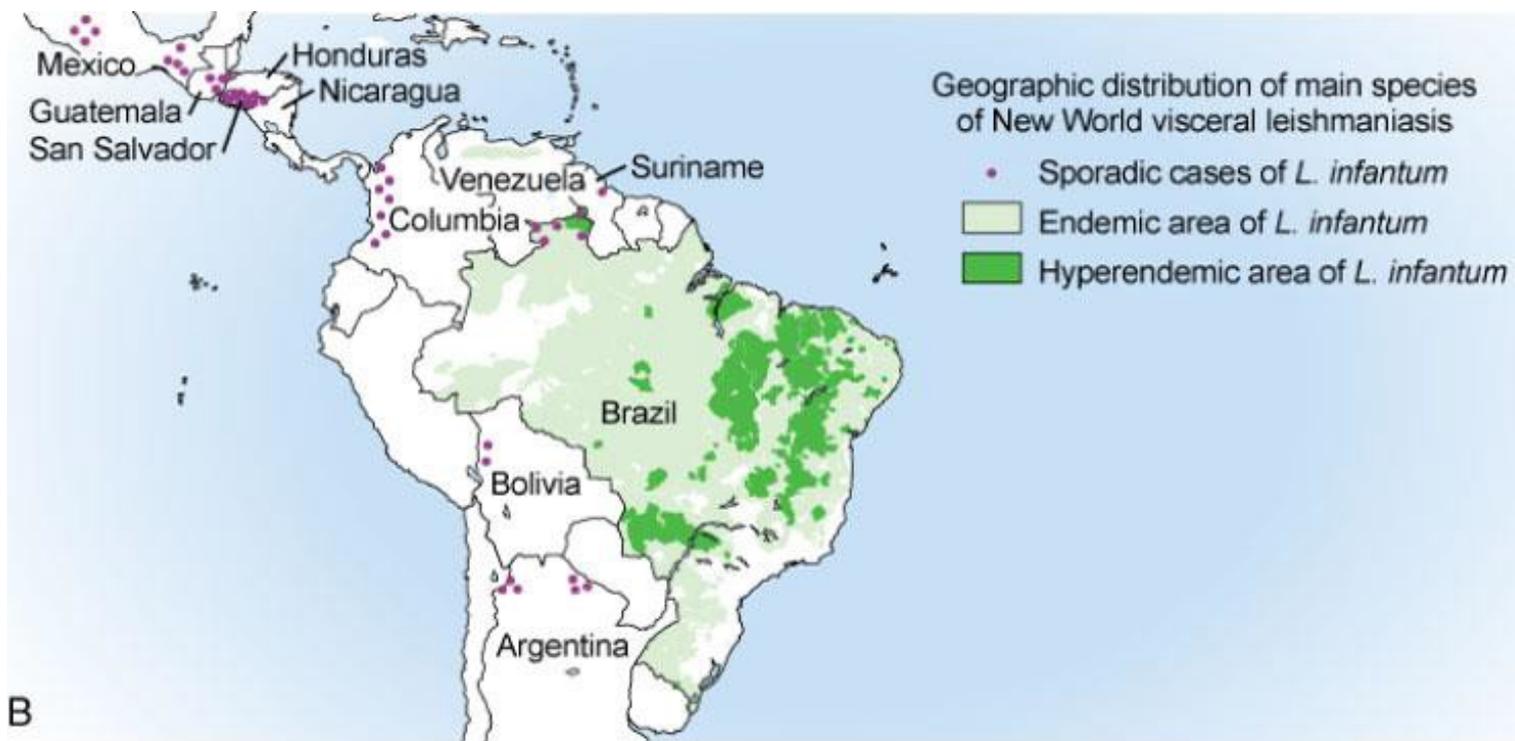


Fig. 277-3B. **Distribution of visceral leishmaniasis (VL).** A, Old World (Eastern Hemisphere) VL. B, New World (Western Hemisphere) VL.

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kala-azar (black or fatal sickness)

- Severe VL
 - Classic pentad: prolonged fever, weight loss, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia
- Progressive (variable rates)
- > 90% mortality within first two years
- Can be opportunistic infection in immunocompromised state



Courtesy Dr. Charles Oster, Washington, DC.

Fig. 277-6. Children with visceral leishmaniasis in Kenya. Note signs of malnourishment and protruding abdomen with massive hepatomegaly.

PPID, 8th ed., pg. 3095

Viscerotropic Leishmaniasis from Desert Storm (*L. tropica*)

- Rare, low-grade, syndrome first identified in 8 patients returning from Operation Desert Storm
 - Fevers: 6 of 8
 - Weight loss: 2 of 8
 - Nausea, vomiting, low-grade watery diarrhea: 2 of 8
 - Lymphadenopathy: 2 of 8
 - Hepatosplenomegaly: 2 of 8
 - Anemia: 3 of 8
 - Leukopenia or thrombocytopenia: 0 of 8
 - Elevated liver enzymes: 6 of 8
 - No symptoms: 1 of 8
- Similar syndromes since found in Brazil and Italy

Magill et al, NEJM 1993;328(19)

Diagnosis

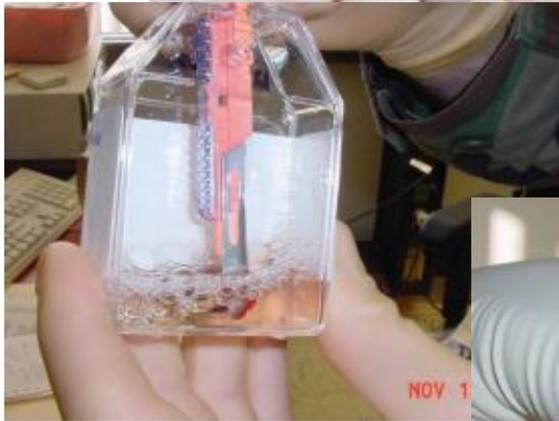
- Clinical Diagnosis
- Cutaneous Leishmaniasis
 - Biopsy/Aspiration/Scraping
 - Amastigotes in a smear
 - Promastigotes in culture
 - PCR of sample (DNA/RNA)
- Visceral Leishmaniasis
 - Biopsy of Bone Marrow or Spleen
 - Touch Prep, PCR, Culture
 - Immunologic
 - rK39 leish. antigen direct agglutination test



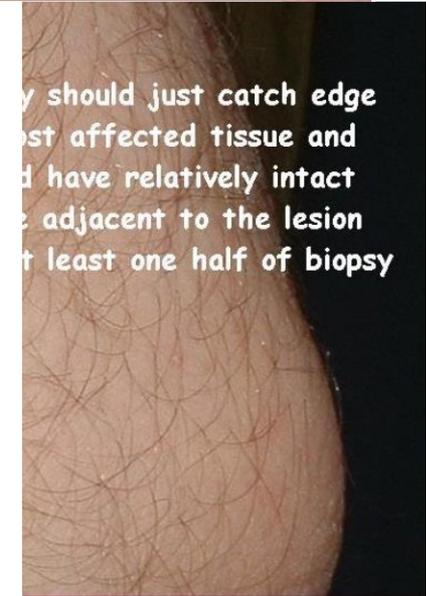
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NOV 13 2003



NOV 13 2003

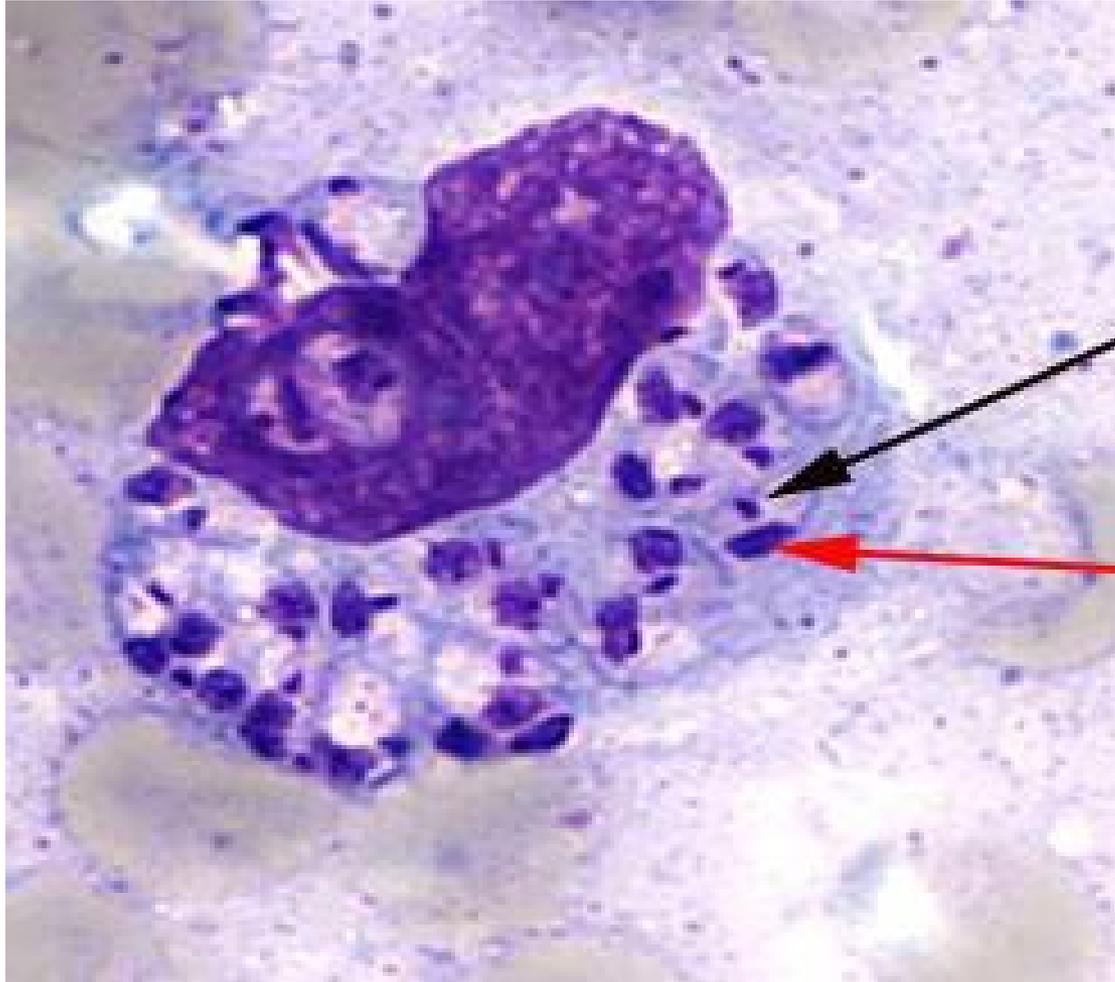


...y should just catch edge
...ost affected tissue and
...d have relatively intact
...e adjacent to the lesion
...t least one half of biopsy



NOV 13 2003

Tissue Diagnosis –skin, spleen, bone marrow



- Infected Macrophage with amastigotes
 - a nucleus (red arrow)
 - a rod-shaped kinetoplast (black arrow).

Diagnosis - culture

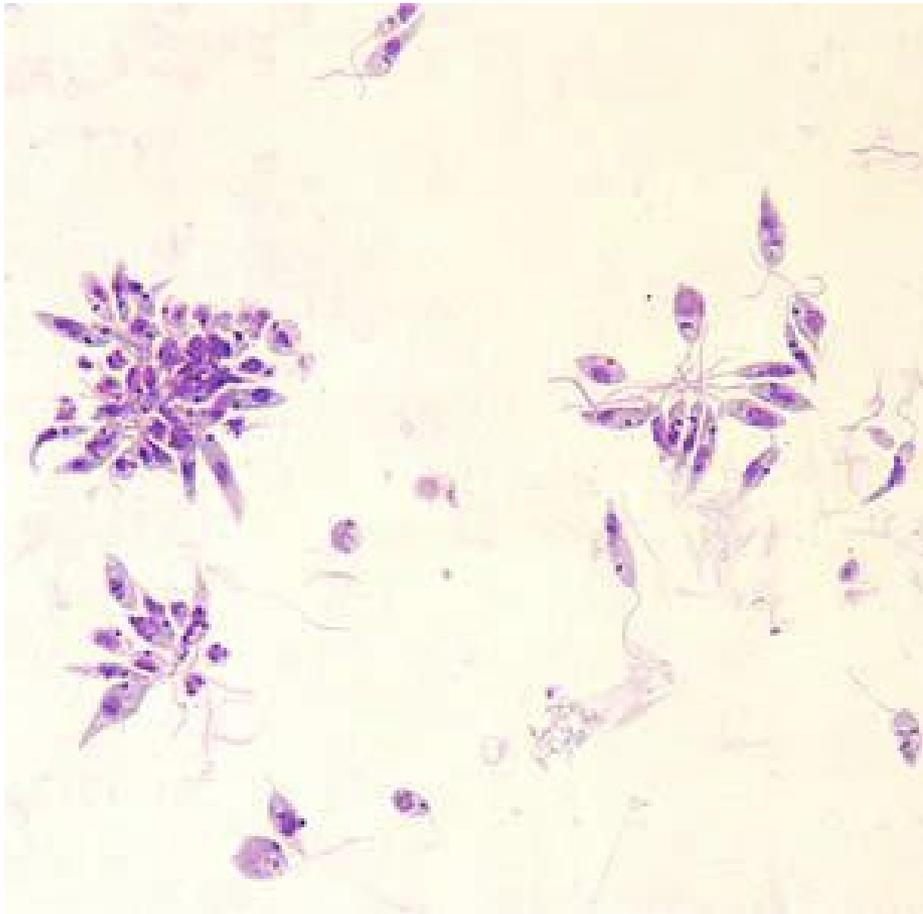


Photo: CDC

Promastigotes

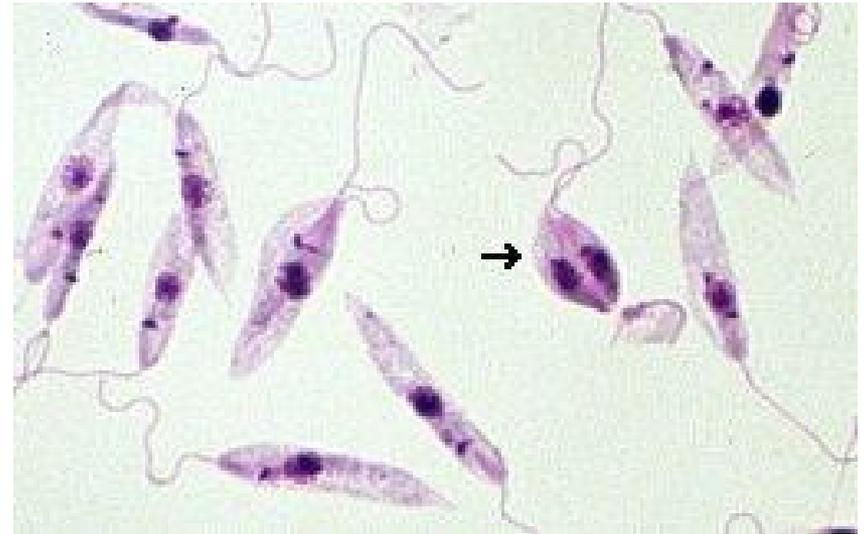


Photo: www.msu.edu

Diagnosis

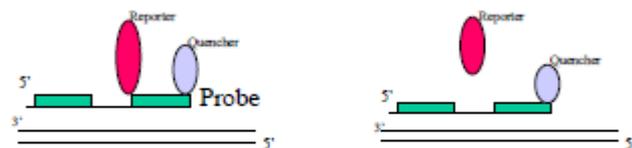
Montenegro Skin Test

- AKA Leishmanin Test
- Injection of dead promastigotes into skin
 - DTH Reaction (wheal) suggests infection
- Not licensed in U.S

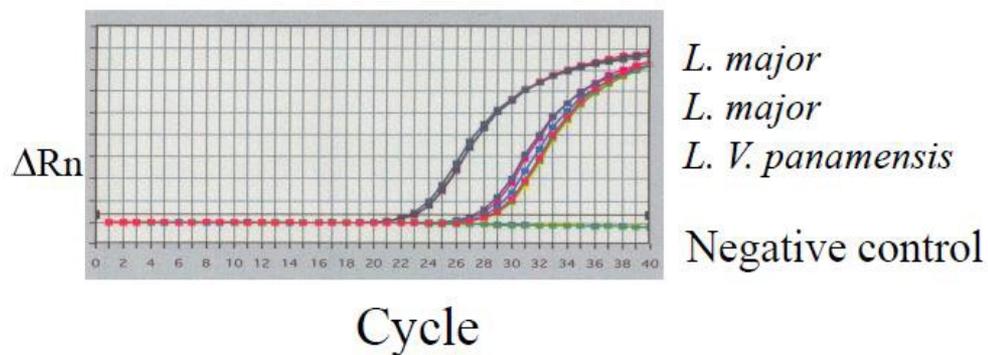


PCR

Real-Time PCR



During each extension cycle, the Taq DNA polymerase cleaves the reporter dye from the probe





InBios

Kalazar Detect

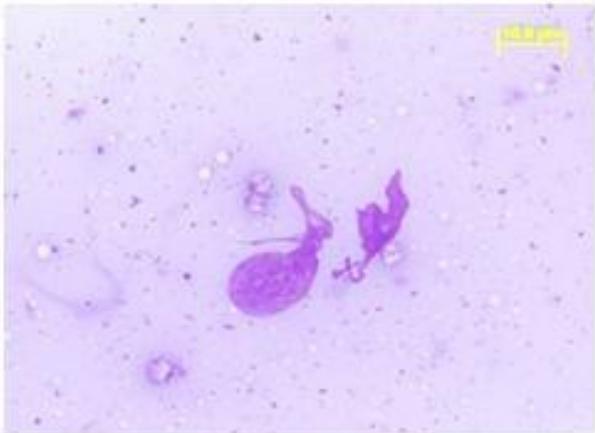
Lot #: DC1015 Exp: 08/2004

Store at Room Temperature

For Research Use Only

Manufactured in the USA by *InBios* International, Inc.
Seattle, Washington 98104

- **Leishmania Diagnostics Laboratory**
- http://wrair-www.army.mil/OtherServices_LD.L.aspx
- usarmy.detrick.medcom-wrair.mbx.leishmania-diagnostic@mail.mil
- **Juan Mendez - 240-595-7353**
- **ID or Dermatology Electronic Consult Service**



Treatment

- Treatment is not standardized
 - What works on one species and clinical presentation may fail in another
 - Must adapt to regional experience
 - Much is anecdotal and off-label
- In general, treatments result in **clinical cure, but not parasitological cure**
 - Lifelong potential for reactivation in immunocompromised

Treatment Options

- CL

- Watchful waiting
- Local destructive therapies
 - Liquid NO₂
 - Thermo-Med device
- Topical creams
 - Paromomycin
- Systemic treatment
 - Amphotericins (Ambisome)
 - Pentavalent Antimonials
 - Sodium stibogluconate (Pentostam)*
 - Meglumine Antimoniate
- (Glucantime)
 - Azoles (Fluconazole, Ketoconazole, Itraconazole)
 - Pentamidine
 - Miltefosine (Impavido)**

- ML, VL

- Systemic treatment

- Pentavalent Antimonials
 - Sodium stibogluconate (Pentostam)*
 - Meglumine Antimoniate (Glucantime)
- Azoles (Fluconazole, Ketoconazole, Itraconazole)
- Amphotericins (Ambisome)***
- Miltefosine (Impavido)**
- Paromomycin

- Alone or in combination

Available in US on IND

** Only Drug FDA approved for CL in US

*** Only drug FDA approved for VL in US

CL-When to consider doing nothing

CRITERIA	FAVORS NO TREATMENT	TREATMENT USUALLY INDICATED
Age and direction of healing	Clearly improving compared to prior month	Worsening lesions
Number of lesions	One or a few	>5 and in different locations
Complexity	Uncomplicated	Restricts movement or wearing of clothes, cosmetic concerns
Size of lesion(s)	Small (<1 cm)	Very large (>5cm)
Immune status	Immunocompetent	Immunocompromised
Mucosal involvement	None	Yes
Location	Nonexposed skin	Exposed skin, especially facial
<i>L. braziliensis</i>?	No or unlikely	Yes or likely*
How bothersome to patient and family?	No or little concern	Very concerned or preoccupied

*If Bolivia, Brazil, Peru, should be treated with systemic therapy due to risk of mucosal involvement

Adapted from PPID, 8th ed., pg. 3104

Watchful Waiting

- CL due to *L. major* (MON-26) in Saudi Arabia
 - Healing time (after study enrollment)
 - 6 weeks – 6%
 - 3 months – 34%
 - Alrajhi, *et al.*, NEJM 2002; 346
- CL in Guatemala
 - *L. mexicana* healing/cure – 68% (avg. 14 wks)
 - *L. braziliensis* healing/cure – 6% (avg. 13 wks)
 - Herwaldt, *et al.*, J Infect Dis 1992; 165

No Treatment

- CL acquired in Afghanistan
- Evaluated in Nov 2008 with 3 cm ulcer
- No treatment
- Follow-up in Jun 2009



Photo courtesy of Dr. Julie Ake

Locally Destructive Therapies

LNO₂

- Freezes lesions to kill parasites
- May cause hypopigmentation
- Not standardized
 - Cryoprobe suggested
- Painful / blister formation

ThermoMed

- Heats lesions to kill parasites
- ~ 70 % efficacy in CL caused by *L. major* in Iraq and *L. tropica* in Afghanistan



Reithinger, et al CID 2005
Aronson, et al PloS Negl Trop Dis 2010
Photo: Dr. Glenn Wortmann



Topical Cream: Paromomycin

- Aminoglycoside
- Compounded
 - 15% paromomycin
 - +/- 0.5% gentamicin
- Apply to affected area twice a day x 28 days
- 81% cure -*L. major*

[N Engl J Med.](#) 2013 Feb
7;368(6):524-32



Systemic Treatment: Miltefosine

- Phosphocholine analogue
- **Oral**
- 28 day regimen
 - 50mg po bid x 28 days
- Used worldwide for all forms of Leishmaniasis
- FDA approved for CL only (2014)
- Side effects:
 - **nausea, vomiting, abdominal pain**
 - LFT abnormalities
 - Increased creatinine
- **Teratogenic –Do not Use in Pregnancy!**



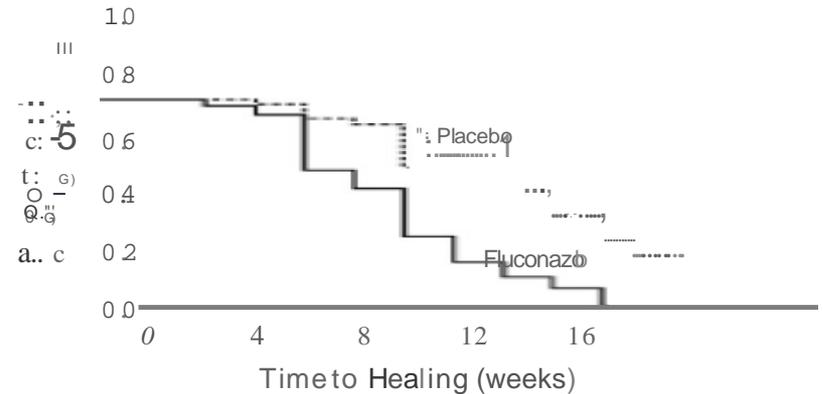
Systemic Treatment: Azoles

- Fluconazole
- Ketoconazole, Itraconazole
- Limited data
- Variable regimens
 - Oral
 - 4-6 weeks or longer
 - Weight based
- Variable efficacy



Fluconazole

- Prospective study
 - 200mg daily for 42 days
 - 6 weeks: 29% vs 6% placebo
 - 3 months: 79% vs 34% placebo



Alrajhi. et al. NEJM 2002;346:891

Interventions for Old World cutaneous leishmaniasis (Review)

Authors conclusions

Most trials have been designed and reported poorly resulting in a lack of evidence for potentially beneficial treatments. There is a desperate need for large well conducted studies that evaluate long-term effects of current therapies. We suggest the creation of an international platform to improve quality and standardization of future trials in order to inform clinical practice.

In *Leishmania major* infections, there was good RCT evidence of benefit of cure around 3 months after treatment when compared to placebo for 200 mg oral fluconazole (1 RCT n = 200, RR 2.78; 95% CI 1.86, 4.16), topical 15% paromomycin + 12% methylbenzothiazolone chloride (PR-MBCL) (1 RCT n = 60, RR 3.09; 95% CI 1.14, 8.37) and photodynamic therapy (1 RCT n = 60, RR 7.02; 95% CI 3.80, 17.55). Topical PR-MBCL was less efficacious than photodynamic therapy (1 RCT n = 65, RR 0.44; 95% CI 0.29, 0.66). Oral pentoxifylline was a good adjuvant therapy to intramuscular meglumine antimoniate (IMMA) when compared to IMMA plus placebo (1 RCT n = 64, RR 1.63; 95% CI 1.11, 2.39).

In *Leishmania tropica* infections, there was good evidence of benefit for the use of 200 mg oral itraconazole for 6 weeks compared with placebo (1 RCT n = 20, RR 7.00; 95% CI 1.04, 46.95), for intralesional sodium stibogluconate (1 RCT n = 292, RR 2.62; 95% CI 1.78, 3.86), and for thermotherapy compared with intramuscular sodium stibogluconate (1 RCT n = 283, RR 2.99; 95% CI 2.04, 4.37).

This record should be cited as: Gonzalez U, Pinart M, Reveiz L, Alvar J. Intervencions for Old World cutaneous leishmaniasis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Arr. No.: CD005067. DOI: 10.1002/14651858.CD005067.pub3.

Systemic Treatment: Antimonials

- Sodium stibogluconate (Pentostam)
 - Investigational New Drug
 - Available from the CDC for civilians
 - Available from Walter Reed for military
 - Regimen
 - CL: intravenous 20mg/kg/day for 10-20 days
 - Outside US is often given intra-lesionally
 - VL: intravenous 20mg/kg/day for 28 days



0302 pre (4/21/03)



0302 post therapy 5/10/03



41 X 43 mm



Photos: Dr. Glenn Wortmann



Pentostam®

- Toxicities
 - Elevated amylase/lipase ~95%
 - Elevated liver enzymes ~50%
 - Arthralgias/myalgias ~65%
 - Rare significant EKG changes/cytopenias
 - Dermatological ~10%
 - Wide range of presentations
 - Herpes zoster virus (shingles)

DO NOT USE IN PREGNANCY

Aronson, et al. Clin Infect Dis 1998;27:1457-64
Wortmann, et al. Clin Infect Dis 1998;27:509-12
Wortmann, et al. Clin Infect Dis 2002;35:261-7

Systemic Treatment: Amphotericins

- Liposomal Amphotericin B (Ambisome)
 - Drug of choice for VL
 - Regimen (IV)
 - Immunocompetent
 - 3 mg/kg/day on days 1-5, 14, and 21
 - Immunocompromised
 - 4 mg/kg/day on days 1-5, 10, 17, 24, 31, 38
 - No established regimen for CL
 - Extensive side-effect profile



L. guyanensis- Fr Guiana
Ambisome for 7 doses

Systemic Treatment: Pentamidine

- No longer recommended for VL due to high toxicity
- One indication only
 - Short course (2 IM injections of 4mg/kg) has been found to be effective for CL caused by *L. guyananensis* in French Guyana and Surinam only

Systemic Dosing Summary

- **CUTANEOUS LEISHMANIASIS**

- Pentostam – 20 mg/kg IV x 10 -20 days
- Ambisome (liposomal amphotericin B)
 - **3 MG/KG ON DAYS 1-5, 14, & 21**
- Fluconazole – 8 mg/kg/day (4 – 12 weeks)
- Miltefosine –50mg po twice a day x 28 days

- **VISCERAL LEISHMANIASIS**

- Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
- Pentostam – 20 mg/kg IV x 28 days
- **MILTEFOSINE –50MG PO TWICE A DAY X 28 DAYS**

Systemic Dosing Summary

- CUTANEOUS LEISHMANIASIS

- Pentostam – 20 mg/kg IV x 10 -20 days
- Ambisome (liposomal amphotericin B)
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- Fluconazole – 8 mg/kg/day (4 – 12 weeks)
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- VISCERAL LEISHMANIASIS

- Ambisome (liposomal amphotericin B) 3 mg/kg on days 1-5, 14, & 21
- Pentostam – 20 mg/kg IV x 28 days
- **MILTEFOSINE –50MG PO TWICE A DAY X 28 DAYS**

Prevention

- Sandflies bite and are active at night (warmer months)
- Stay **indoors** between dusk and dawn
- Keep dogs and susceptible animals indoors at night
- Use fans - sandflies are **poor fliers** deterred by wind
- Sandflies are **small and can get through mesh** netting if not extremely fine
- House **construction** and modification; sandflies breed in cracks of houses
- Insecticides on people and animals
- Help from entomologists
- Dog vaccine available in Brazil

<http://www.cfsph.iastate.edu/Factsheets/pdfs/leishmaniasis.pdf>

Sandfly Habitat



TRENDS in Parasitology

[Volume 28, Issue 12](#), December 2012, Pages 531–538

Summary – Leishmaniasis

- Worldwide distribution
- Many species with different disease presentations
- Cutaneous form may be self-limited
- Think about mucocutaneous disease, especially in South America
- Resources available for diagnosis (WRAIR)
- Treatment response varies with species and host

Classification

- *Old World, Cutaneous Disease:*
 - *L. tropica*; *L. major*; *L. aethiopica*
 - *L. tropica* can cause visceral disease
- *Old World, Visceral Disease:*
 - *L. donovani* complex with 3 species (*L. donovani*, *L. infantum*, and *L. chagasi*)
- *New World, Cutaneous disease:*
 - *L. mexicana* complex with 3 main species (*L. mexicana*, *L. amazonensis*, and *L. venezuelensis*)
- *New World, Cutaneous and Mucocutaneous disease*
 - Subgenus *Viannia* with 4 main species (*L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana*)
- *New World, Visceral Disease*
 - *L. chagasi*

Leishmaniasis is endemic in Texas

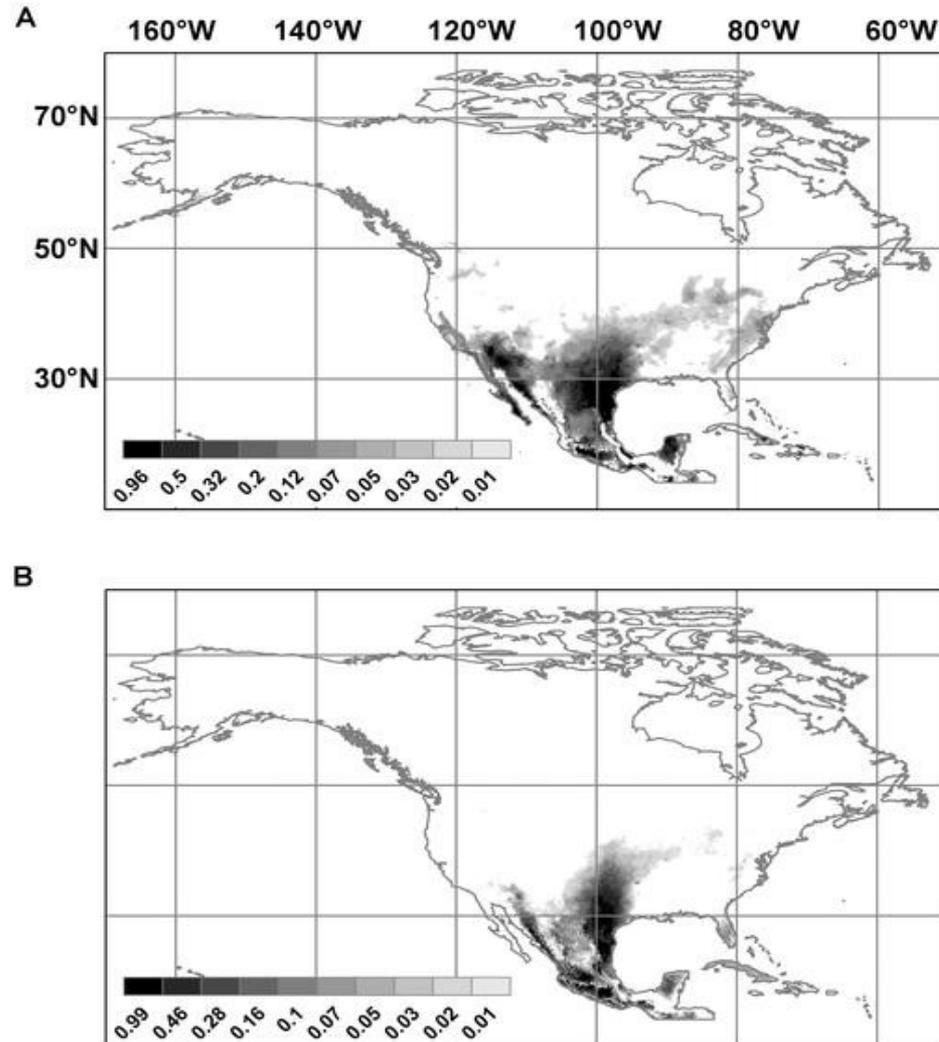


Figure 2. Predicted current distributions for leishmaniasis vector species.

González C, Wang O, Strutz SE, González-Salazar C, et al. (2010) Climate Change and Risk of Leishmaniasis in North America: Predictions from Ecological Niche Models of Vector and Reservoir Species. *PLoS Negl Trop Dis* 4(1): e585.

doi:10.1371/journal.pntd.0000585

<http://www.plosntd.org/article/info:doi/10.1371/journal.pntd.0000585>

What Other South American tropical disease is transmitted by sandflies ?

- Bartonellosis (Carrión's disease)
 - Also called Oroya Fever or Peruvian warts
 - Peru, Andes mountains
 - *Bartonella bacilliformis*
- Traveler infection is not common
- Fever, myalgia, headache, and anemia
- High mortality – 40%
- Chronic infection
- Rifampin, chloramphenicol
TMP/SMX, Streptomycin

