Leishmaniasis

'The study of the cause of things must be preceded by the study of things caused.'

Hughlings Jackson (1835-1911)

Definition & History

- **Infection by the protozoans of the genus Leishmania.**
- **Leishmaniasis may involve skin, mucus membranes, mouth, oropharynx and viscera.**
- **Early descriptions of the parasite in cutaneous lesions were by Cunningham, Borovsky, and Wright between 1885-1903.**

Definition & History

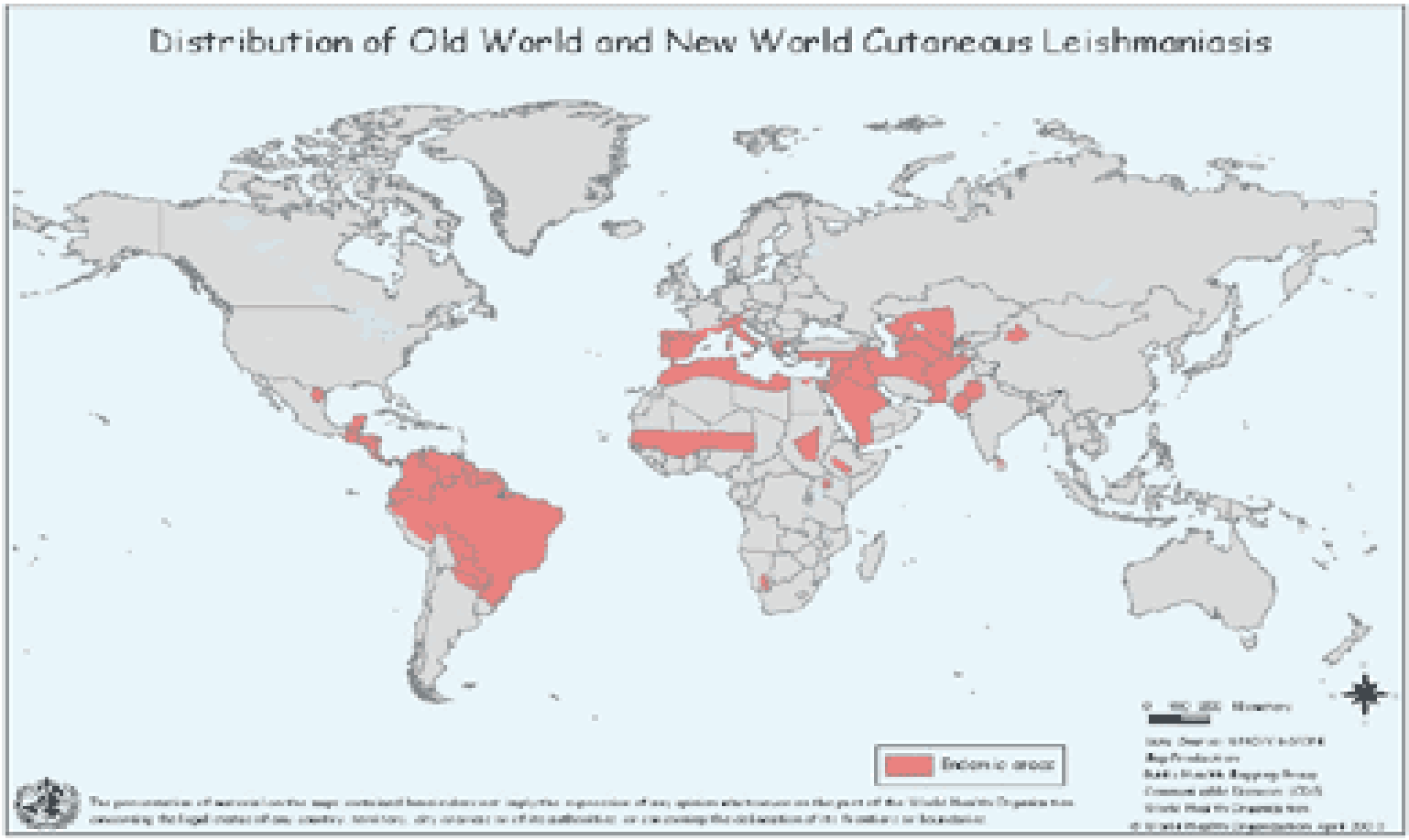
- In 1903 Leishman (top) and Donovan (bottom) separately described a visceral form.
- Identified organisms in the spleen.
- 1911--lesions of cutaneous leishmaniasis followed the sandfly bite.
- 1942--identified *L. donovani* in volunteers experimentally subjected to the bite of the sandfly.

Leishmaniasis-synonyms

- Mucocutaneous
  - "espundia"
- Visceral
  - "Kala-azar"
  - "dum-dum fever"
  - "espundia"
- Cutaneous
  - Delhi boil
  - Baghdad boil
  - Chiclero's ulcer
  - Oriental sore,
  - Reta,
  - Year-long sore
  - Aleppo's boil,
  - Biskara button,
  - Buton de Crete
  - Forest yaws
  - Pian bois

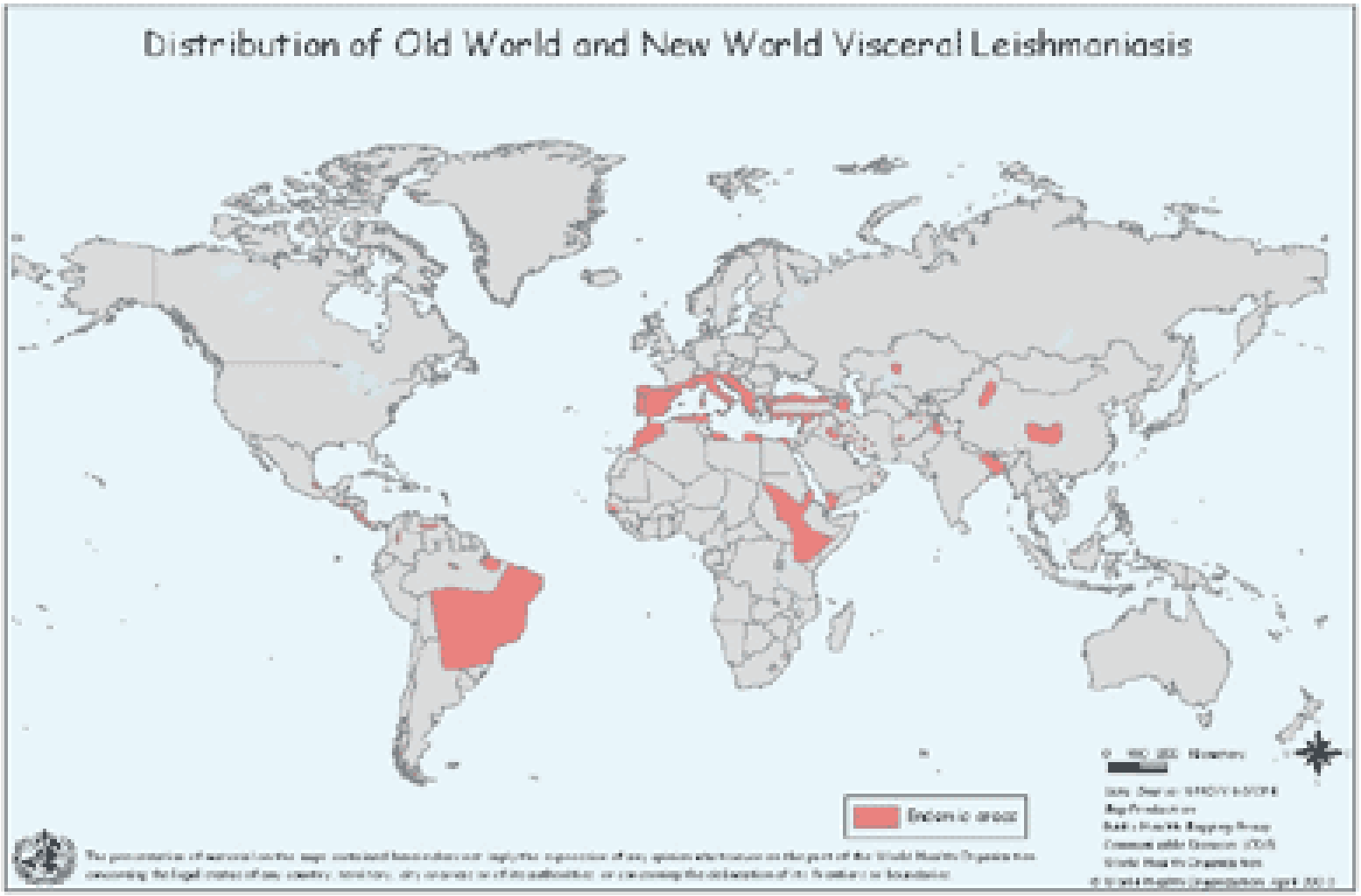
- No vaccine
- However, infection with many of the species of Leishmania results in permanent immunity to reinfection with the same species.

Geographic Distribution

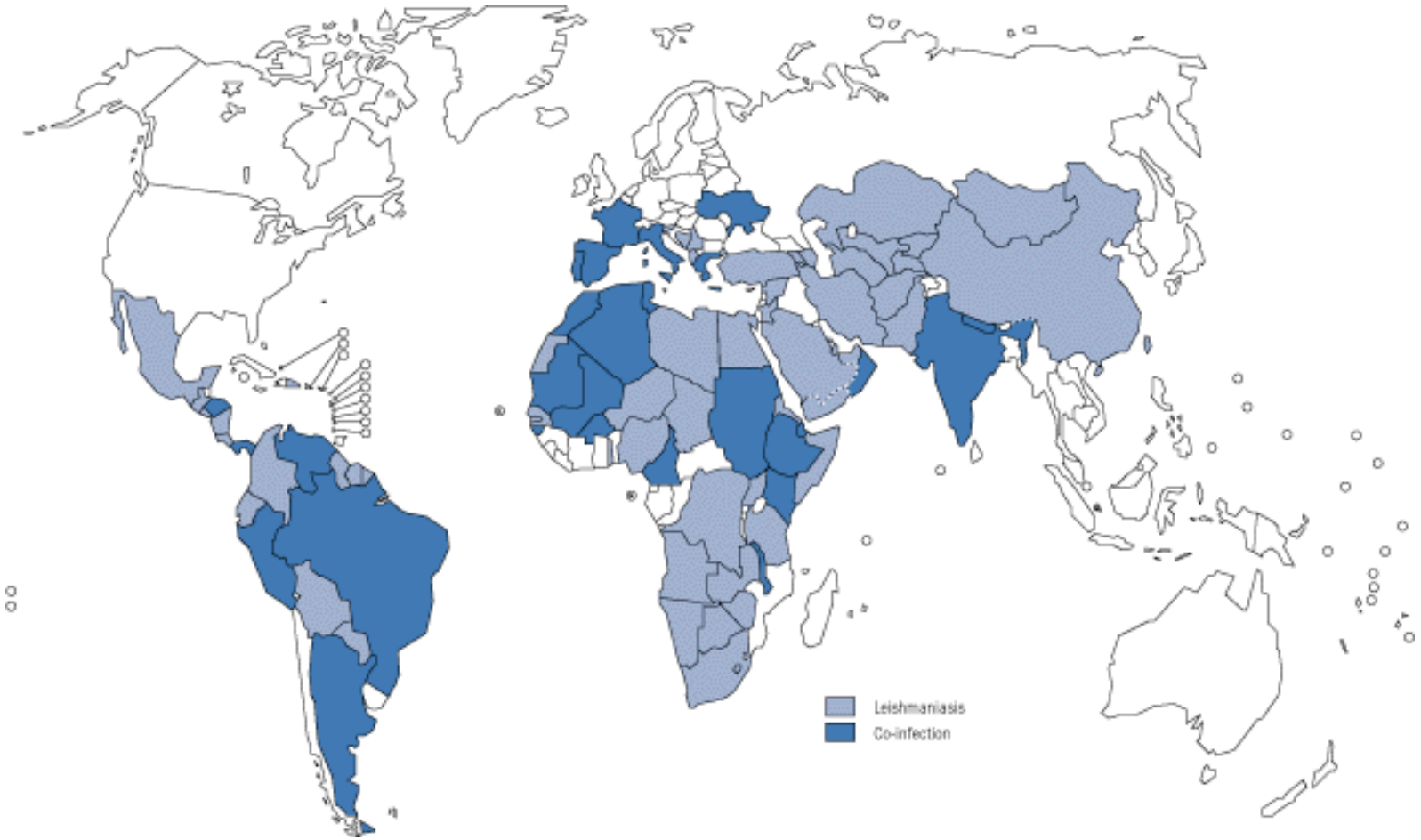


***A few indigenous North American infections have been identified In Texas. Bray, R.S. Leishmaniasis in the Old World. *Br. Med. Bull.* 1972:28:39-43**

Geographic Distribution



Geographic Distribution



With increased travel to endemic regions, diagnosis of leishmaniasis continues to challenge the clinician and pathologist.

Leishmania--Epidemiology

- The number of humans infected difficult to determine.
- Conservative estimates suggest that several million are infected.
- More than 350 million live in within an area of transmission.
- Present in at least 88 countries.

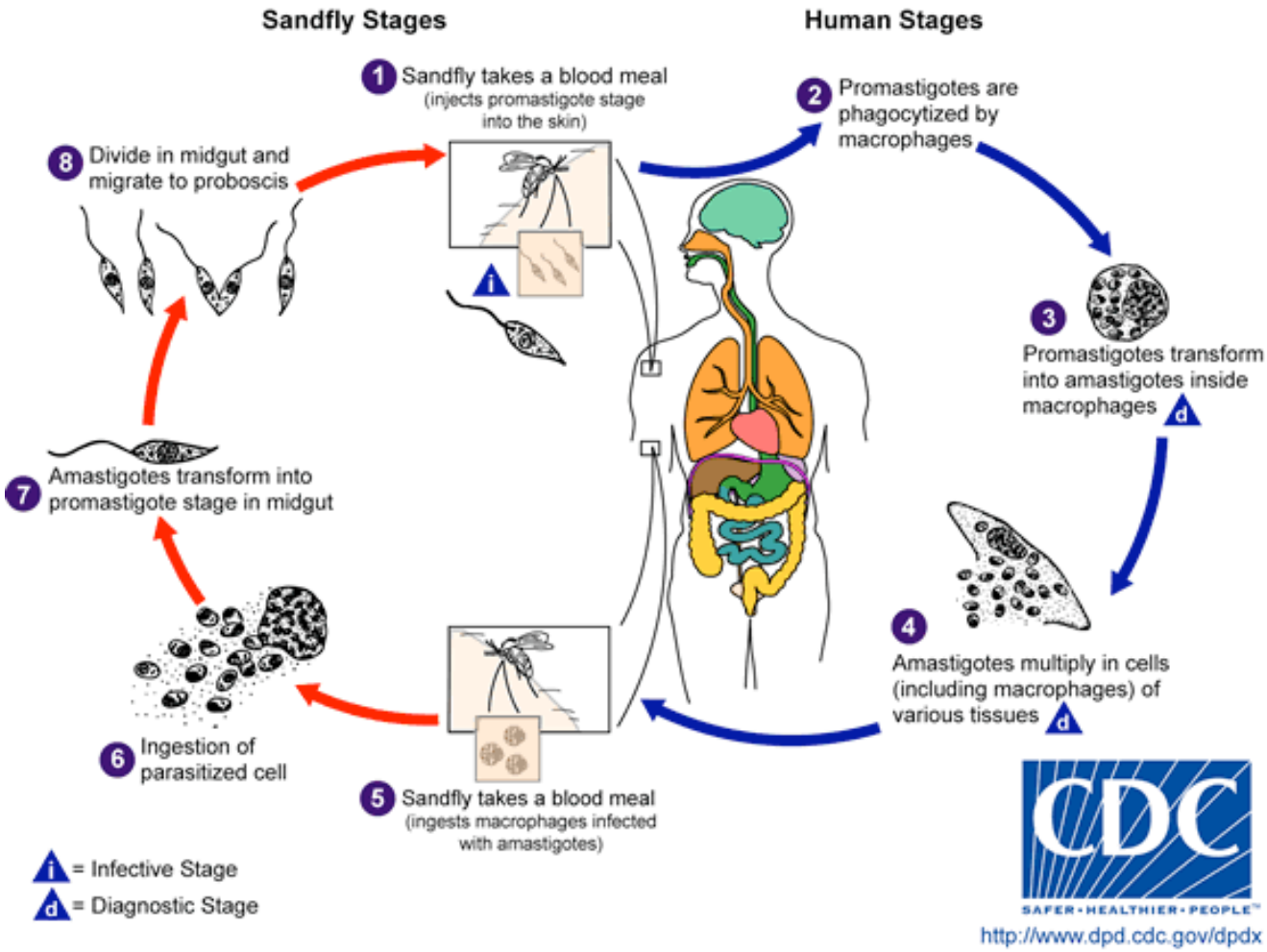
Leishmania--Epidemiology

- **In the Eastern hemisphere, no less than fifteen species regularly infect people:**
  - ***L. leishmania amazonensis***
  - ***L. viannia braziliensis***
  - ***L. v. colombiensis***
  - ***L. l. donovani***
  - ***L. l. garnhami***
  - ***L. v. guyanensis***
  - ***L. l. infantum chagasi***
- *L. v. lainsoni*
- *L. v. lindenbergi*
- *L. l. mexicana*
- *L. v. naiffi*
- *L. v. panamensis*
- *L. l. pifanoi*
- *L. v. shawi*
- *L. l. venezualensis*

Leishmania--Epidemiology

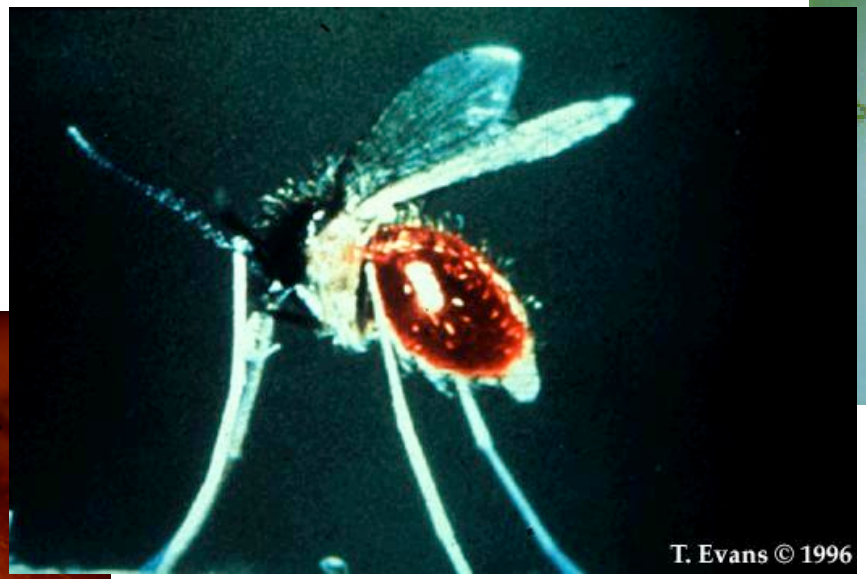
- **In the Western hemisphere, no less than fifteen species regularly infect people:**
  - ***L. l. donovani***
  - ***L. l. infantum***
  - ***L. l. aethiopica***
  - ***L. l. major***
  - ***L. l. tropica***
- **As may be expected, clinical conditions caused by *Leishmania spp.* vary greatly, depending upon the species of Leishmania and the immune status (genetic make up) of the host.**

Life Cycle



Like the Trypanosomes, *Leishmania spp*. are heteroxenous hemoflagellates.

Leishmaniasis – Vector



In Texas, the reservoir is the wood rat and the vector is *Lutzomyia anthophora*.

Female Sand fly

- ***Phlebotomus spp.*** **(Old World)**
- ***Lutzomyia spp.*** **(New World)**

Some canines also have leishmaniasis.

Sandflies

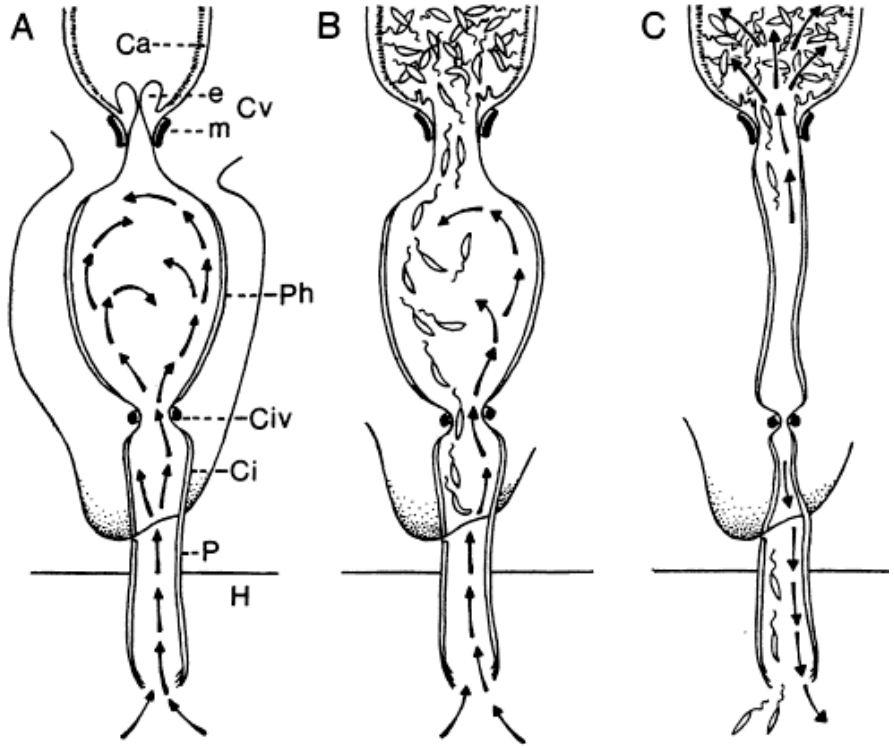
- 1.5-5.5 mm long
- Transmission of human leishmaniasis is accomplished by less than 10% of the 600 known sandfly species.
- Nocturnal.

Sandflies

- Infection begins with the fly bite.
- Injects saliva containing numerous well-characterized bioactive components, *e.g.*, maxadilan (a potent vasodilator).
- Leishmania inhibit fly regurgitation.
  - Increases chance of infection.

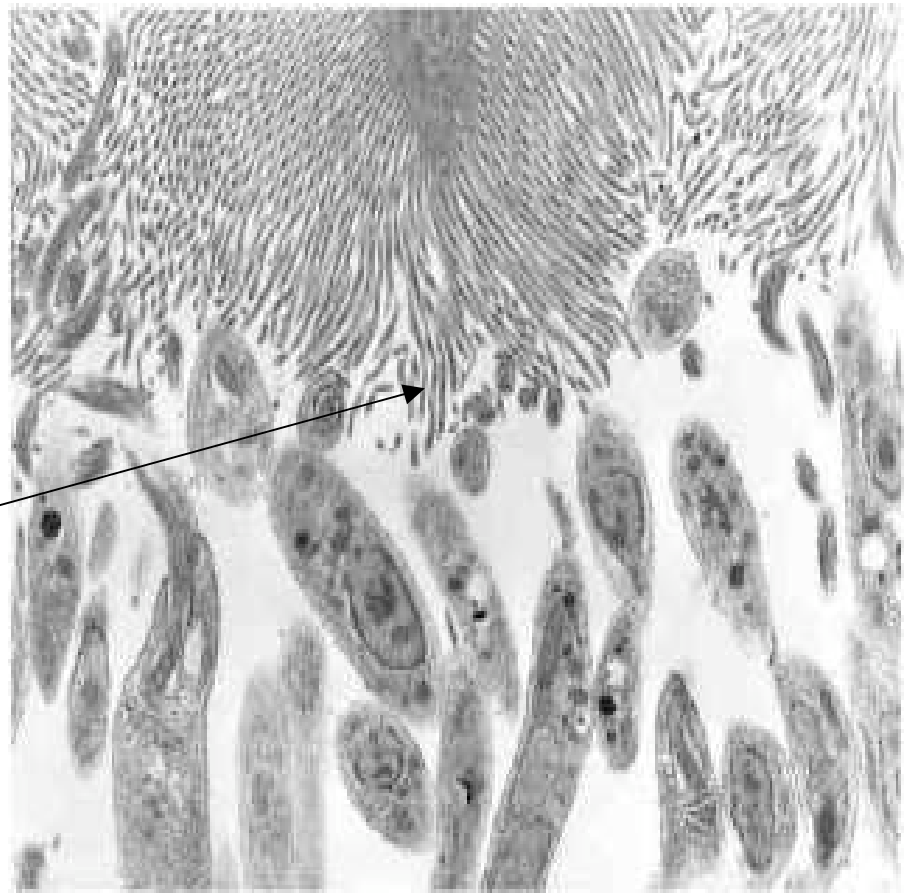
Leishmania spp. affect fly feeding mechanism

- **Food ingested by action of 2 pumps—pharyngeal (ph) and cibarial (Ci).**
  - **Ca-Cardia**
  - **e-epithelial cells**
  - **m-sphincter muscle**
  - **Civ-cibarial valve**
  - **Cv-cardiac valve**
  - **H-host skin**



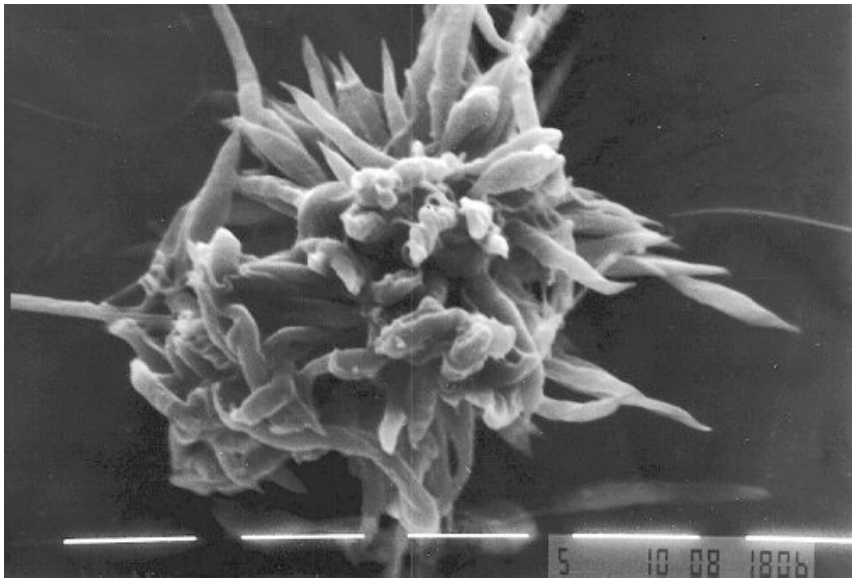
There are 4 critical phases of development of the parasite in the insect vector:

- 1) Transformation of amastigotes to promastigote forms and rapid growth of the parasite occurs during blood meal digestion.
- 2) Migration out from the digested blood meal encased in the peritrophic matrix.
- 3) Binding of the parasite to the midgut epithelium and subsequent anterior migration of the parasites.
- 4) Transformation to the mammalian-infective form of the parasite (metacyclic promastigotes) and transfer during a subsequent feed.



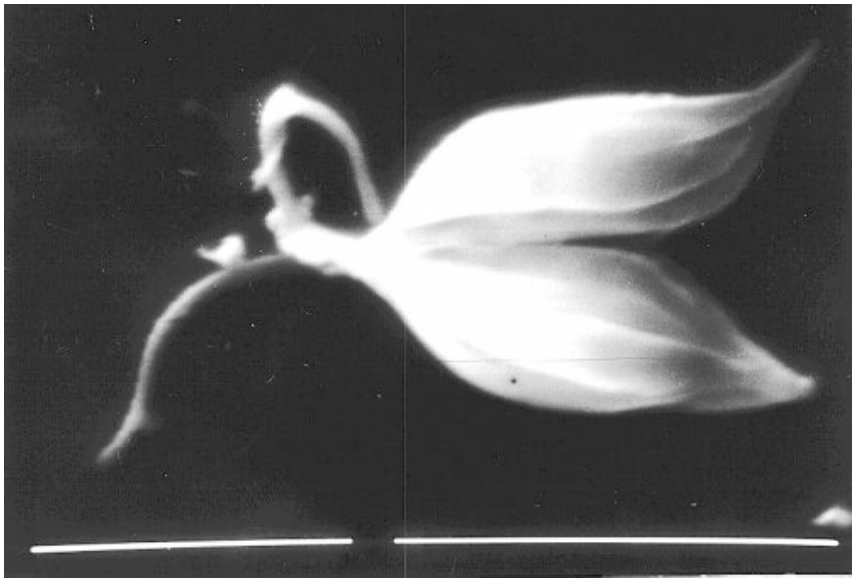
Rosette Formation

- **Occurs during the development of the metacyclic promastigote stage in the fly.**
- **Promastigotes bind to the gut tract via their flagella.**



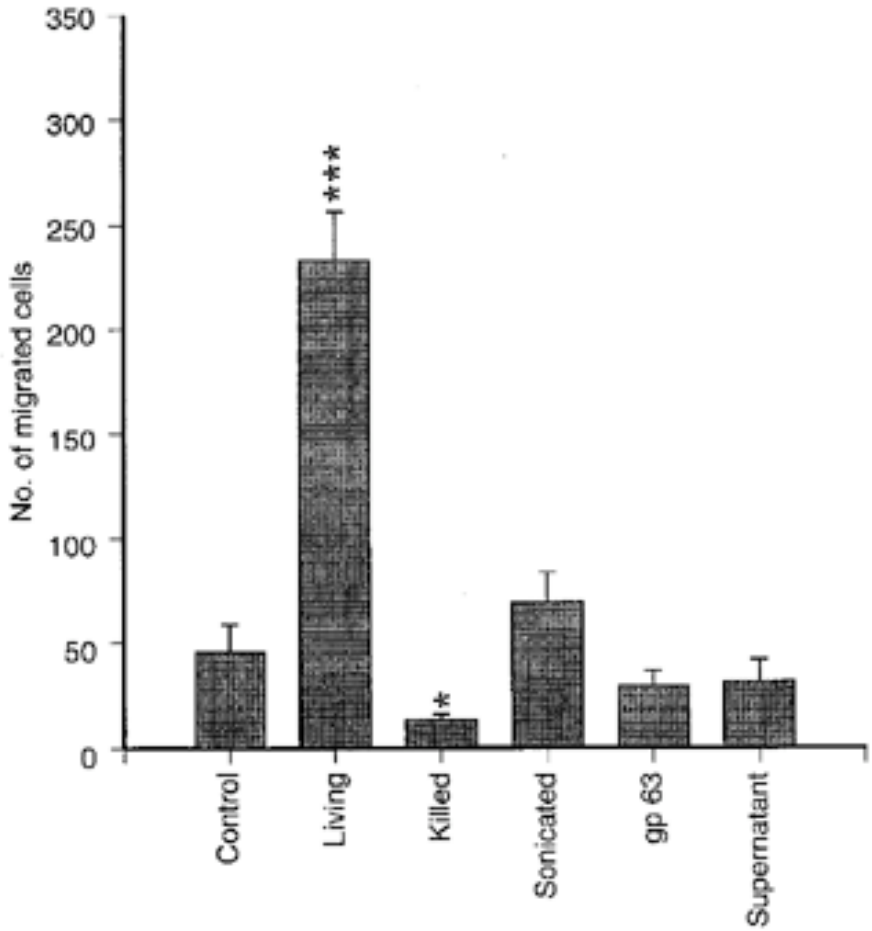
Promastigote—Binary fission

- **Flagellated metacyclic promastigote resides in the anterior midgut and thorax.**
- **Injected with fly saliva.**
  - **Maxadilan induced negative effects on host immune cell functions.**
    - **Interferes with IL-10 & TNF-α production.**
    - **Upregulates IL-6 production in macrophages.**
    - **Upreulates PGE2**



MØ Migration in the Skin

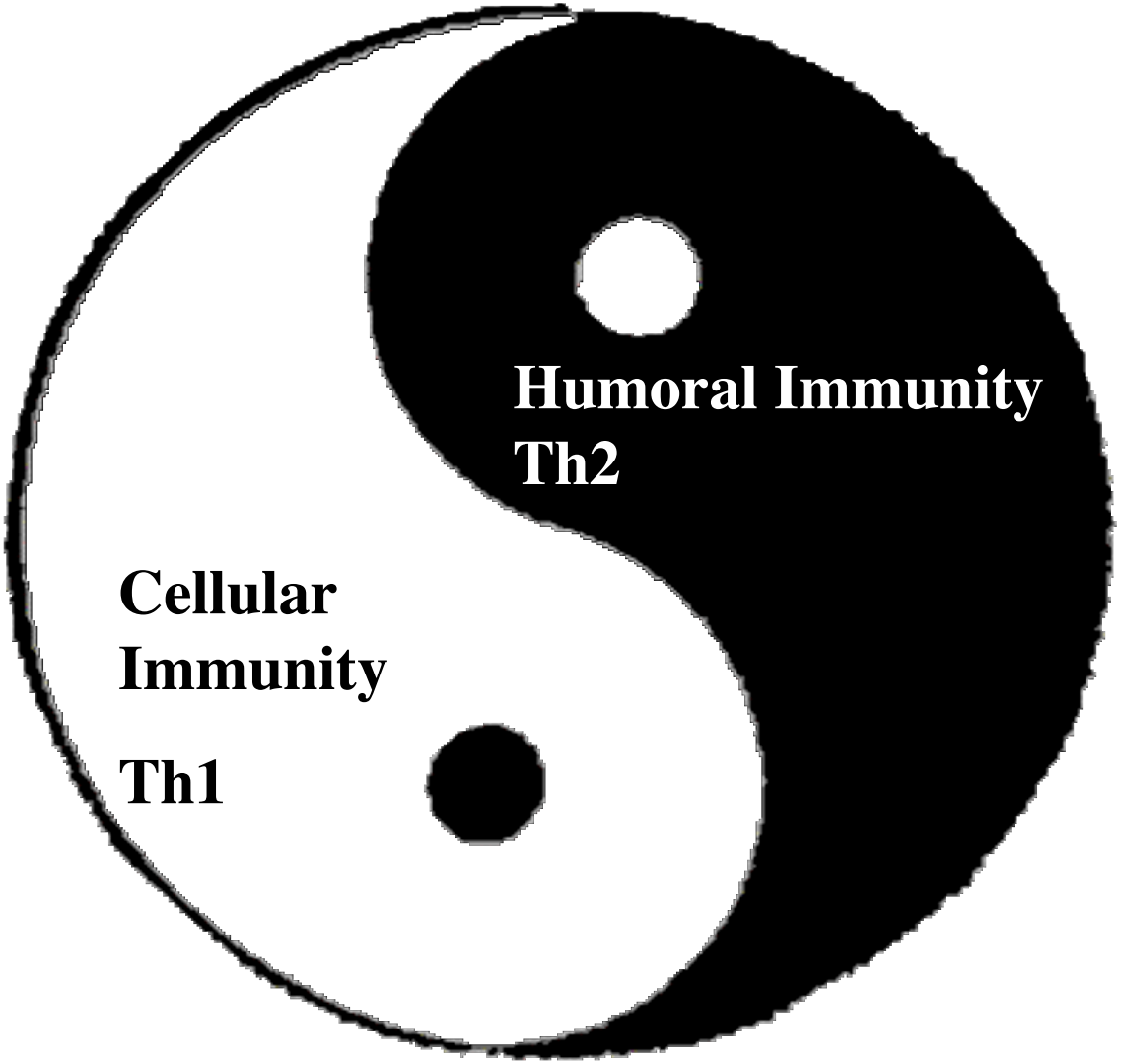
- **Living promastigotes simulate MØ migration to the infection site.**
- **Antibody coated promastigotes utilize C3 to become phagocytised.**

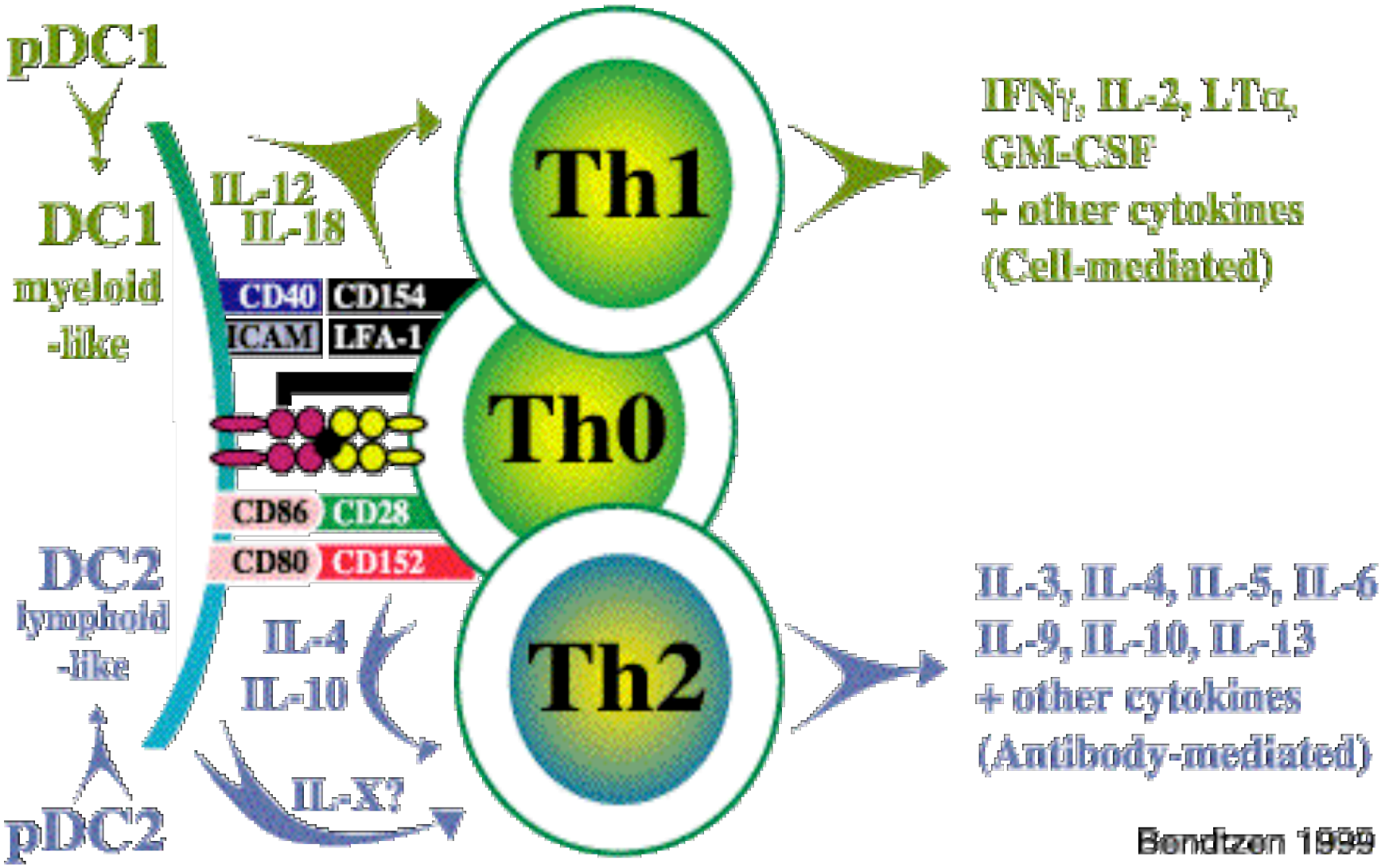


Leishmania--MØ

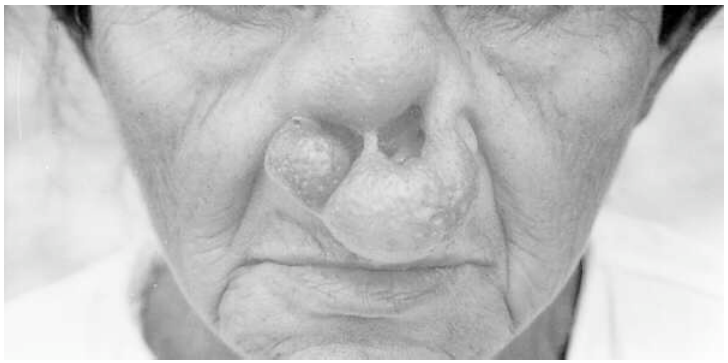
- **At the skin, differences between species of Leishmania become obvious.**
- **Those that cause only cutaneous lesions remain at the site throughout the infection.**
  - **Histiocytes**

Immune System Dynamics

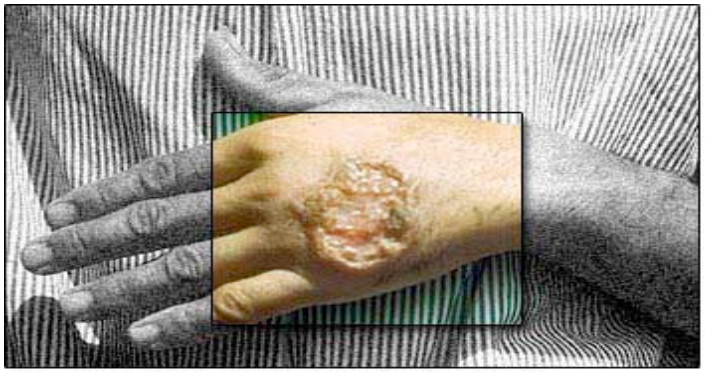



pDC1
DC1
myeloid
-like
IL-12
IL-18
CD40
CD154
ICAM
LFA-1
CD86
CD28
CD80
CD152
DC2
lymphoid
-like
IL-4
IL-10
IL-X?
pDC2
Th1
Th0
Th2
IFNγ, IL-2, LTα,
GM-CSF
+ other cytokines
(Cell-mediated)
IL-3, IL-4, IL-5, IL-6
IL-9, IL-10, IL-13
+ other cytokines
(Antibody-mediated)
Bendtzen 1999

Leishmaniasis and Th Responses

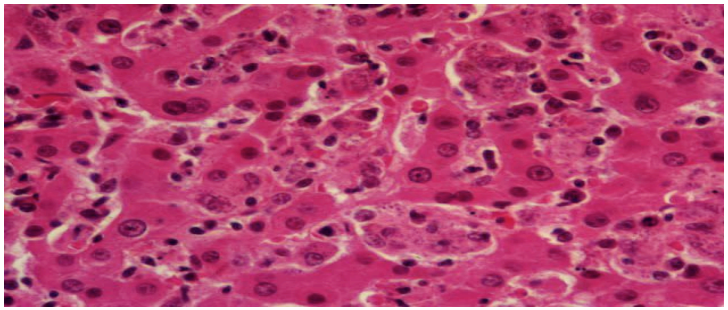


Mucocutaneous-Th2-humoral



Skin lesion from a person with cutaneous leishmaniasis
(CDC/Dr. D.S. Martin).

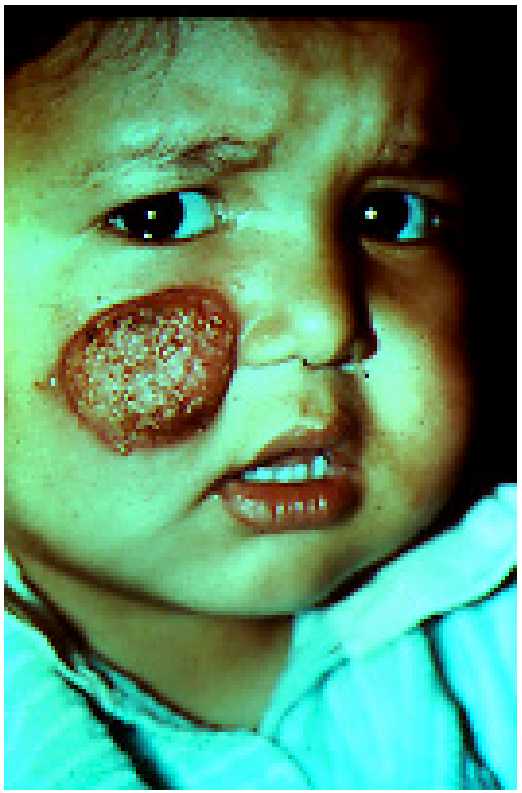
Cutaneous-Th1-cellular



Visceral-Th1/Th2-Splenomegaly (Amastigotes)

Cutaneous Leishmaniasis

- Caused by 4 Old World and at least 15 New World species of Leishmania.
- Oriental sore—common in endemic areas of the Middle East, India, and Africa.
- A rudimentary form of vaccination referred to as “leishmanization” was practiced in the Middle East.
  - Controlled the region of the body where the scar developed.

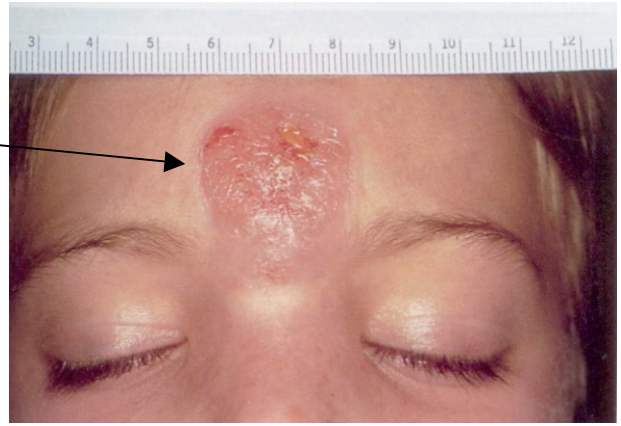


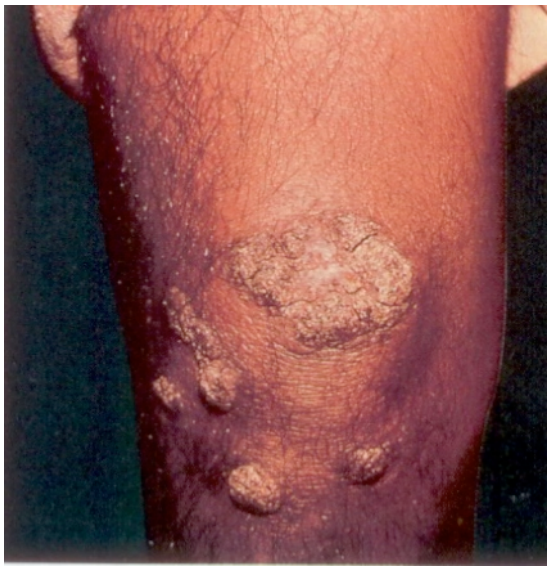
Cutaneous Leishmaniasis

- 4 Types
  - Acute
  - Chronic
  - Diffuse cutaneous
  - Post kala-azar dermal leishmaniasis

Cutaneous Leishmaniasis--Acute

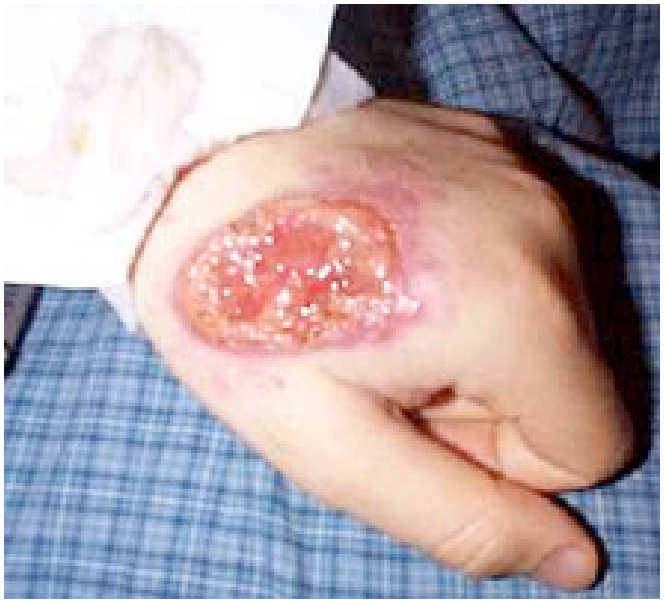
- Pruritic papule develops at the site of inoculation.
- Well developed 2-8 weeks.
- Ulceration is followed by spontaneous healing in 3-12 months.
- Some lesions are papular or verrucous.





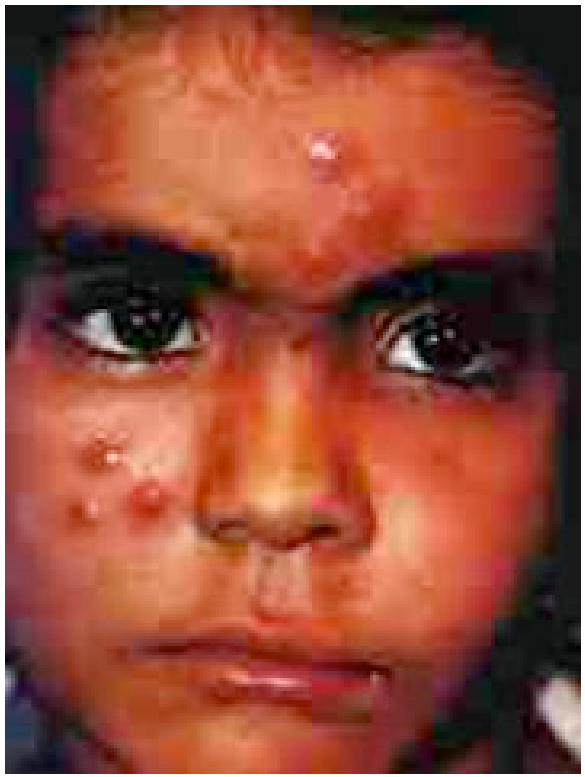
Cutaneous Leishmaniasis--
Chronic

- **Rare.**
- **May present as an acute lesion but then persist (linger for years), resolve, or recur.**



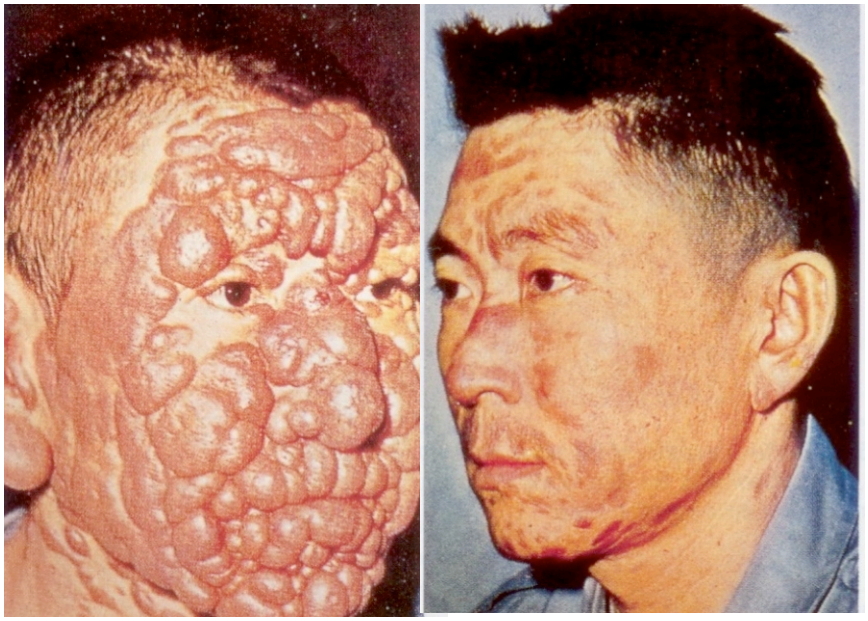
Cutaneous Leishmaniasis--
Diffuse

- Early lesion is shiny, erythematous nodule.
- Multiple nodules aggregate and coalesce, forming plaques.
- Dissemination occurs from these primary sites.
- Face, limbs, and buttocks may be involved.

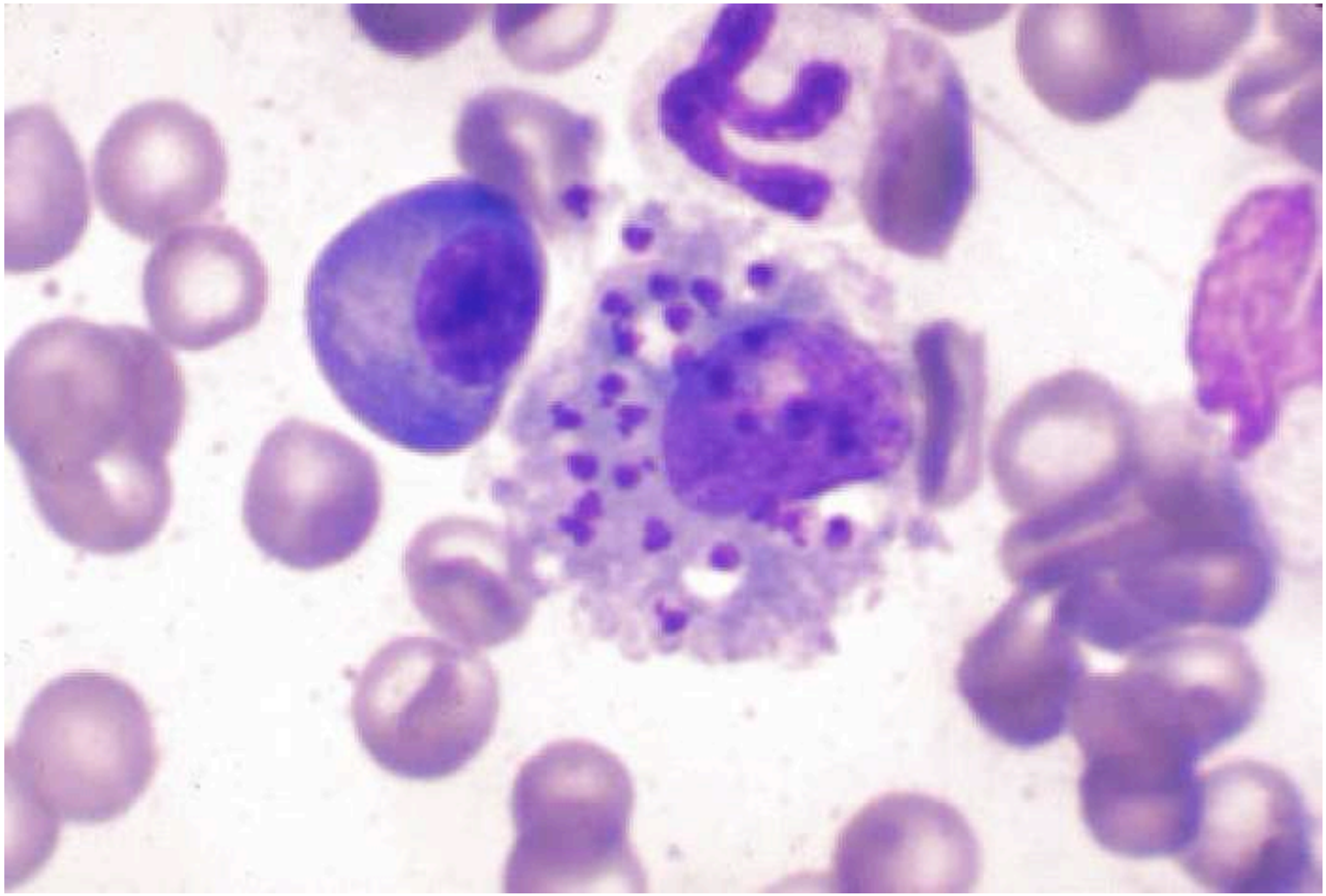


Cutaneous Leishmaniasis—Post kala-azar dermal leishmaniasis

- PKDL
- 6% of treated patients develop skin lesions without history of re-exposure.
- 1-5 years after 1st exposure
- Hyperpigmented macules turn into firm nodules.
- Typically around mouth and nose (trunk and limbs too).
- Nodules composed of histiocytes.



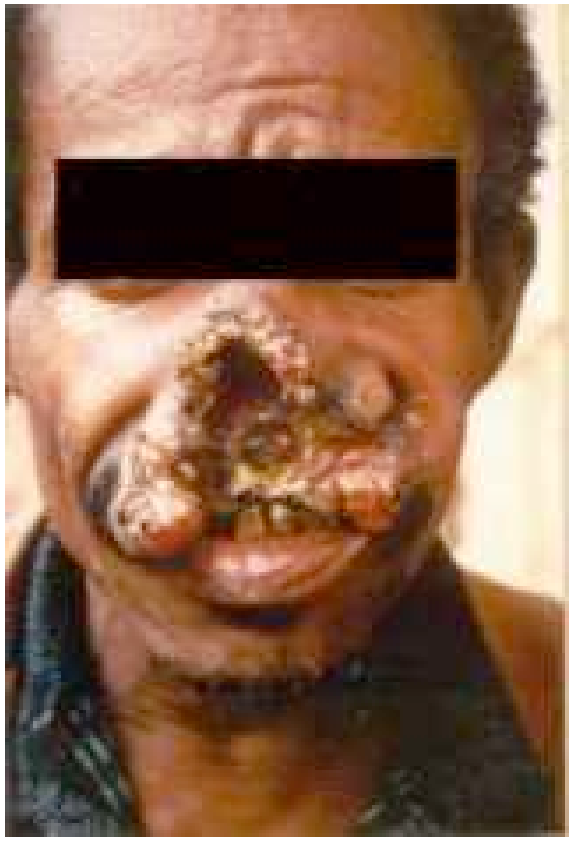
2 years later—following therapy

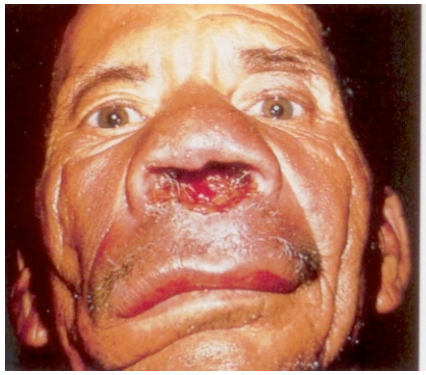


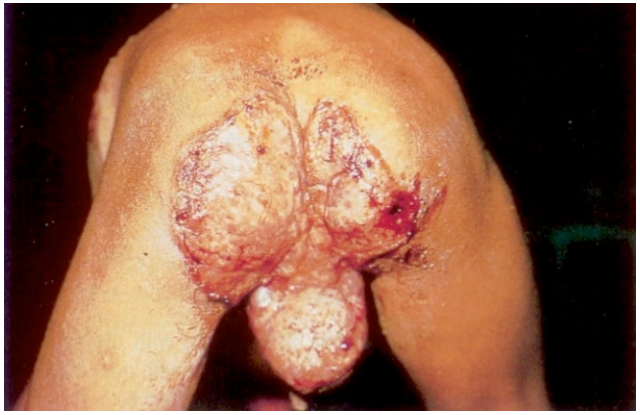
Mucocutaneous Leishmaniasis

- **2-3% of *L. v. braziliensis* infections 'metastasize' to mucocutaneous junctions.**
  - **Oral cavity**
  - **Urogenital**
  - **Anal areas**
- **Infrequently L. v. *guyanensis* and *L. v. panamensis* cause similar disease.**

Mucocutaneous Leishmaniasis

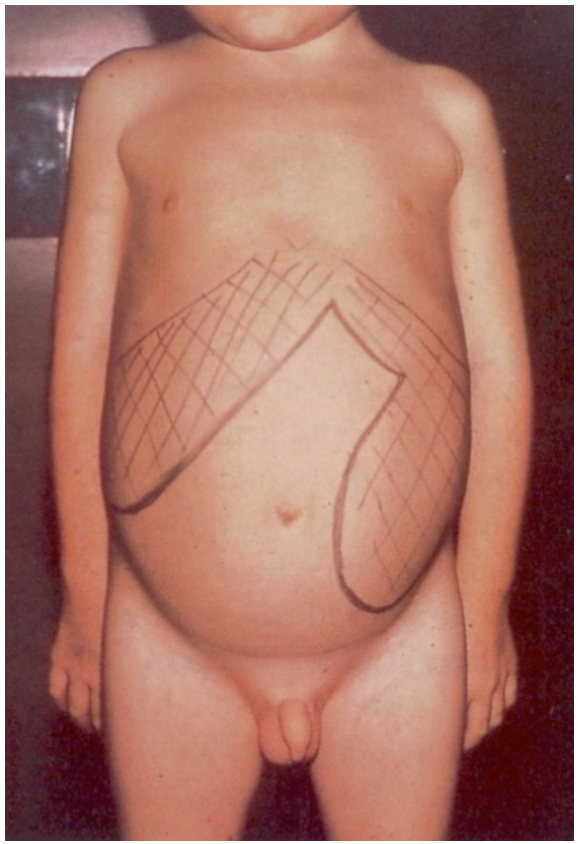






Visceral Leishmaniasis ('Kala-azar')

- Characterized by hepatosplenomegaly and high fever.
  - Progressive wasting
  - Death if untreated
- Primarily affects children.
- Latent period of 4-6 months (up to 10 years).
- More difficult to diagnose.
- Children with absent response to INF-γ had a 67% chance of developing visceral leishmaniasis.
- Called black fever because this describes the patients skin at the height of the infection.
- 3-6 month incubation.



Differential Diagnosis

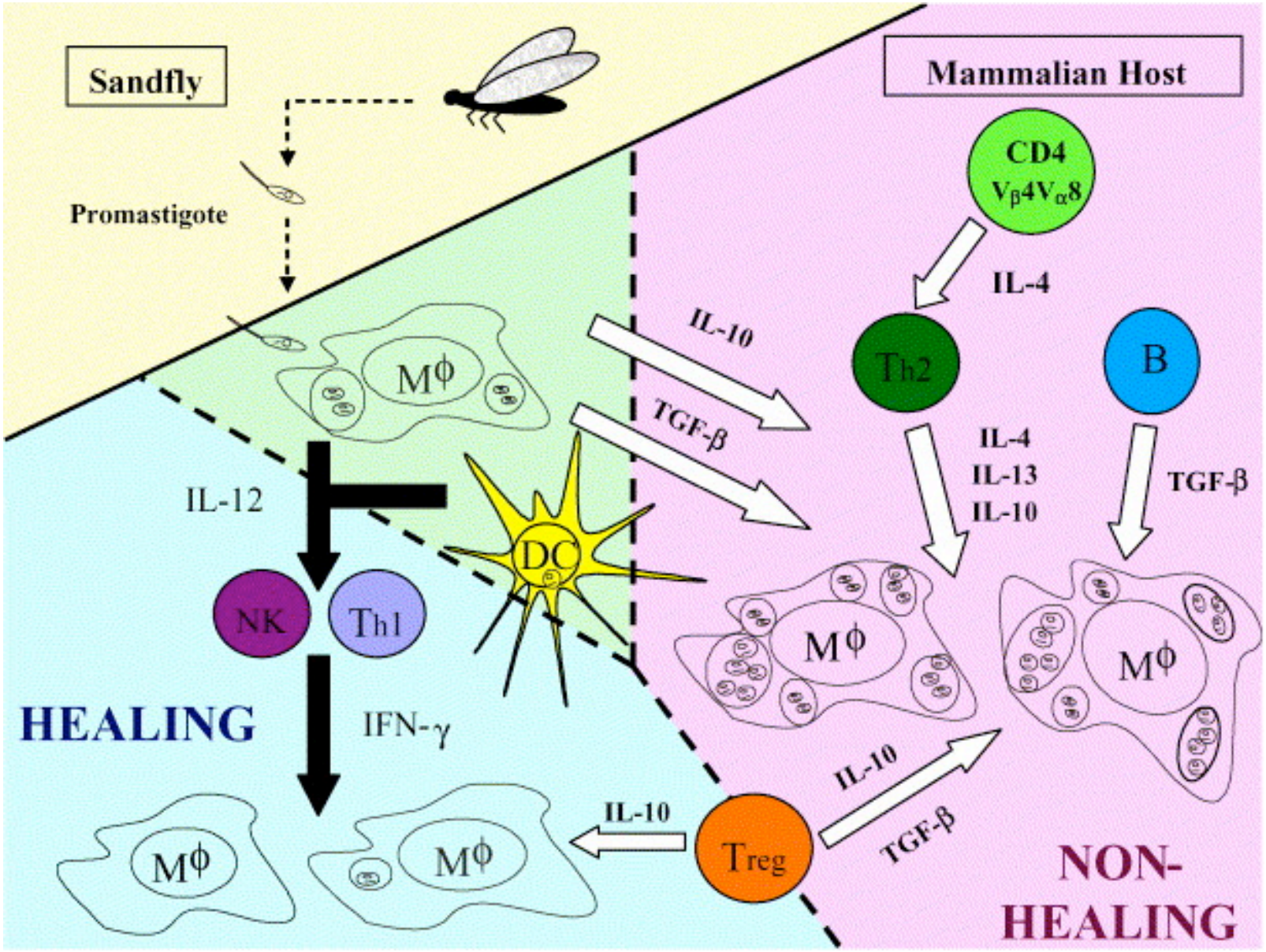
- **Leishmania is identified microscopically within macrophages. It may resemble:**
  - ***T. gondii***
  - ***Histoplasma capsulatum*** **(same size and shape—distinguished using fungal stains).**

Leishmaniasis – Diagnosis

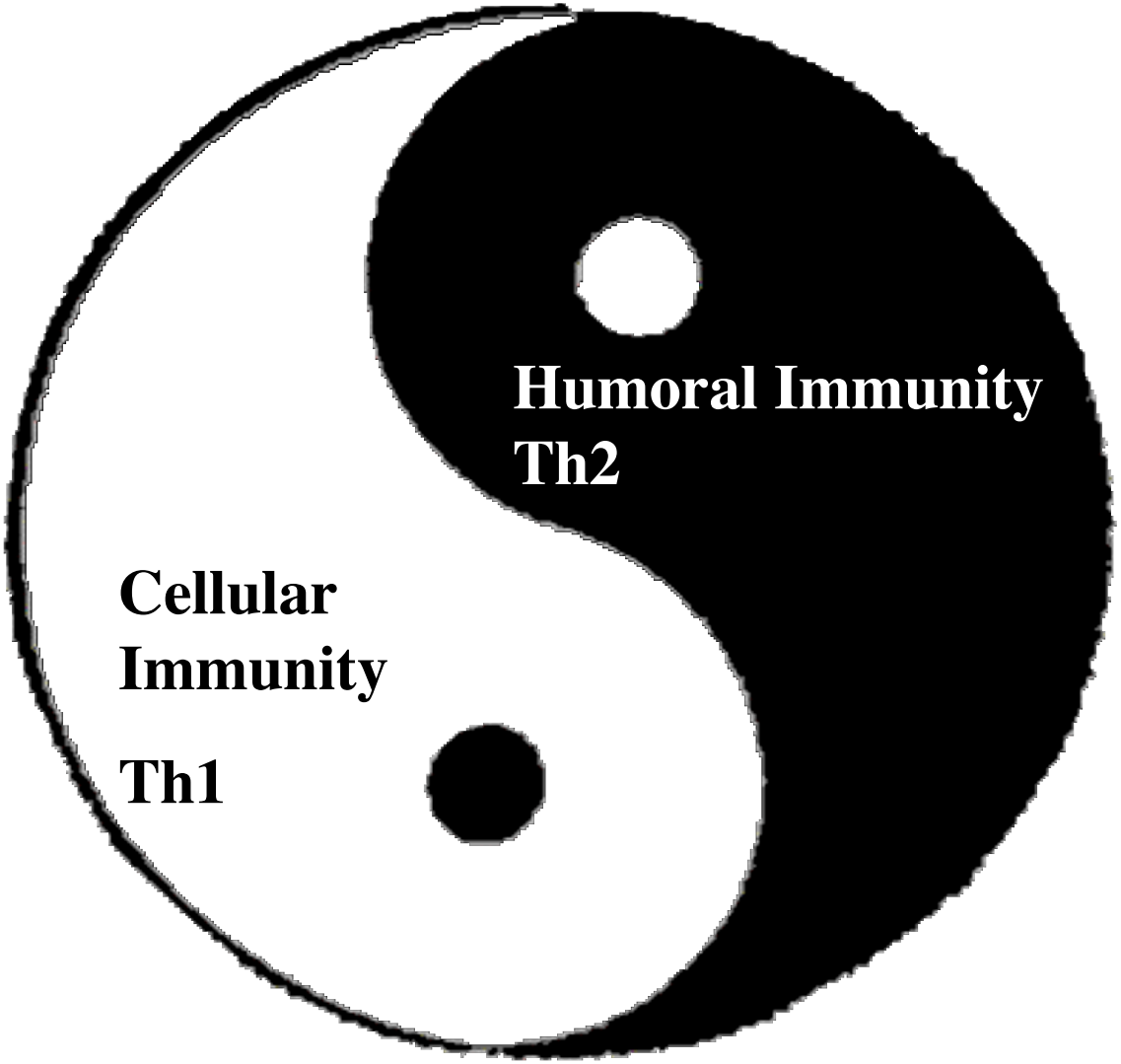
- Microscopy
- Biopsy
  - Lesion, liver, spleen, bone marrow
- PCR
- Serologic testing
  - ELISA
  - Direct agglutination test

Leishmaniasis–Treatment

- Pentavalent antimonial drugs
  - Pentostam (sodium stibogluconate)
  - Glucantime
  - Aminosidine (Gabbromicina)
    - effective for cutaneous leishmaniasis, better tolerated
  - Humatin (paramomycin)
  - Severe toxic side effects with most antimonials
- Antifungals (ketoconizole, amphotericin B)
- Allopurinol
- Anticancer – Miltefosine (hexadecylphosphocholine)
  - 90% effective for visceral form


Sandfly
Promastigote
Mammalian Host
CD4
Vβ4Vα8
IL-4
Th2
B
IL-10
TGF-β
IL-4
IL-13
IL-10
TGF-β
Mϕ
IL-12
DC
NK
Th1
HEALING
IFN-γ
Mϕ
Mϕ
Mϕ
IL-10
Treg
IL-10
TGF-β
NON-
HEALING

Immune System Dynamics



How can infection with one pathogen exacerbate or diminish the symptoms caused by a second pathogen?

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Cellular Immunology

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Cellular Immunology xxx (2006) xxx–xxx

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Acute cysticercosis favours rapid and more severe lesions caused by *Leishmania major* and *Leishmania mexicana* infection, a role for alternatively activated macrophages

Miriam Rodríguez-Sosa [a], Irma Rivera-Montoya [a], Arlett Espinoza [a], Miriam Romero-Grijalva [a], Roberto López-Flores [b], Jorge González [b], Luis I. Terrazas [a,*]

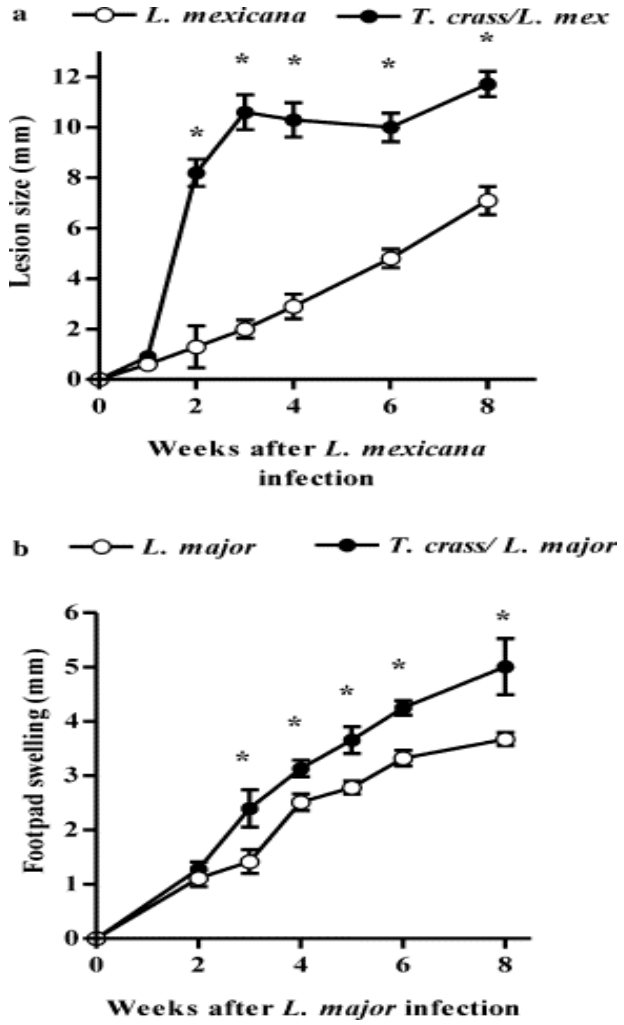
[a] *Laboratory of Immunoparasitology, Unidad de Biomedicina, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Mexico*

[b] *Carrera de Medicina, Facultad de Estudios Superiores Iztacala, Mexico*

Received 5 July 2006; accepted 18 September 2006

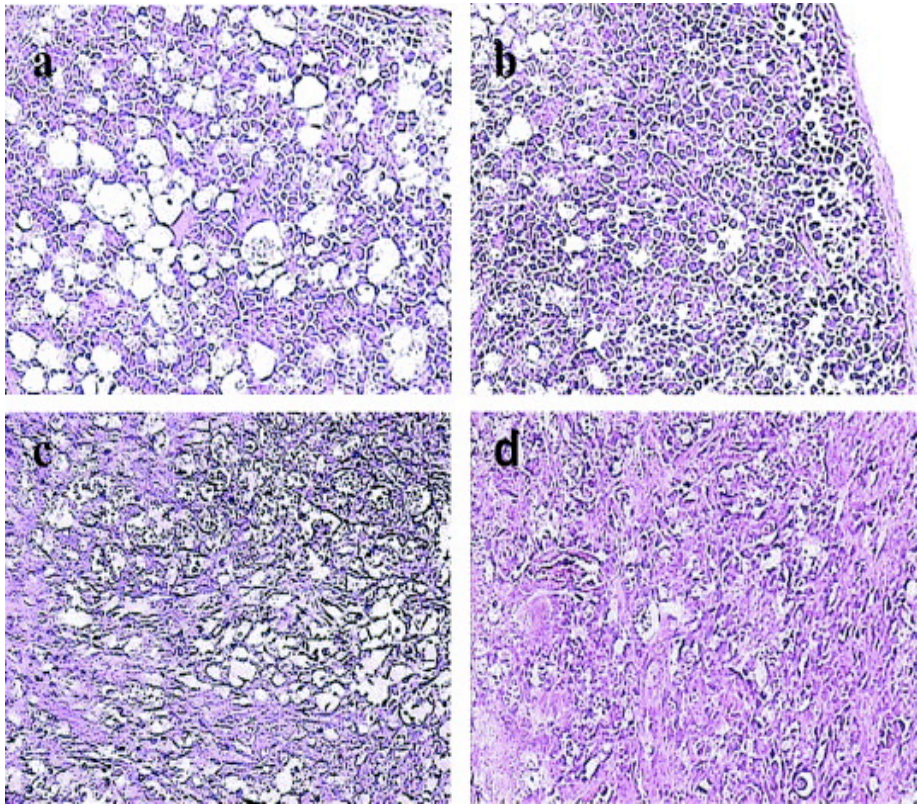
Lesion size following co-infection

- **Lesions caused by both *L. major* and *L. mexicana* were exacerbated when co-infected with *Taenia crassiceps*.**



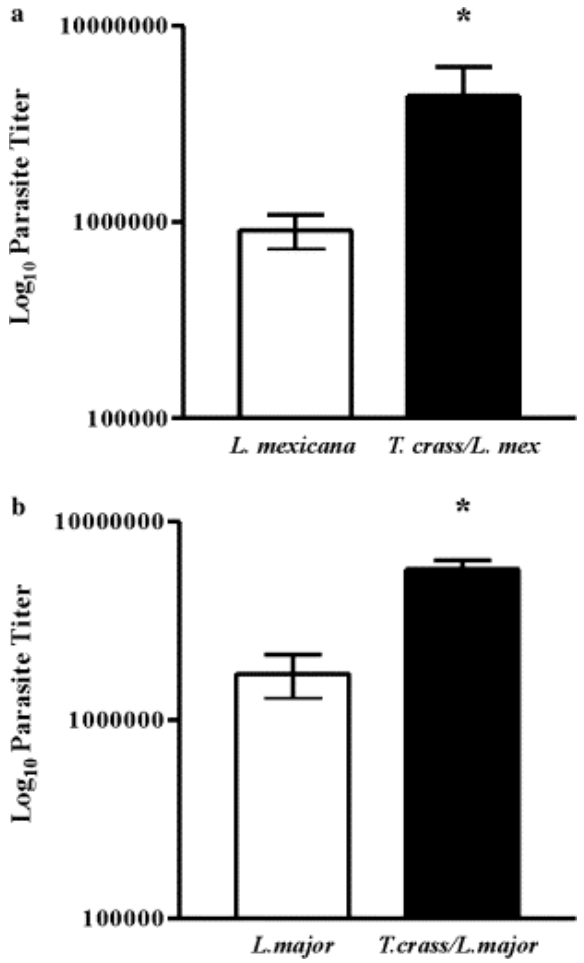
Histologic exam of lesion in co-infected mice (skin)

- **A. *T. crassiceps/L. mexicana*.**
- **B. *L. mexicana* only.**
- **C. T. crassiceps/L. major**
- **D. *L. major* only**
- **E. ???**

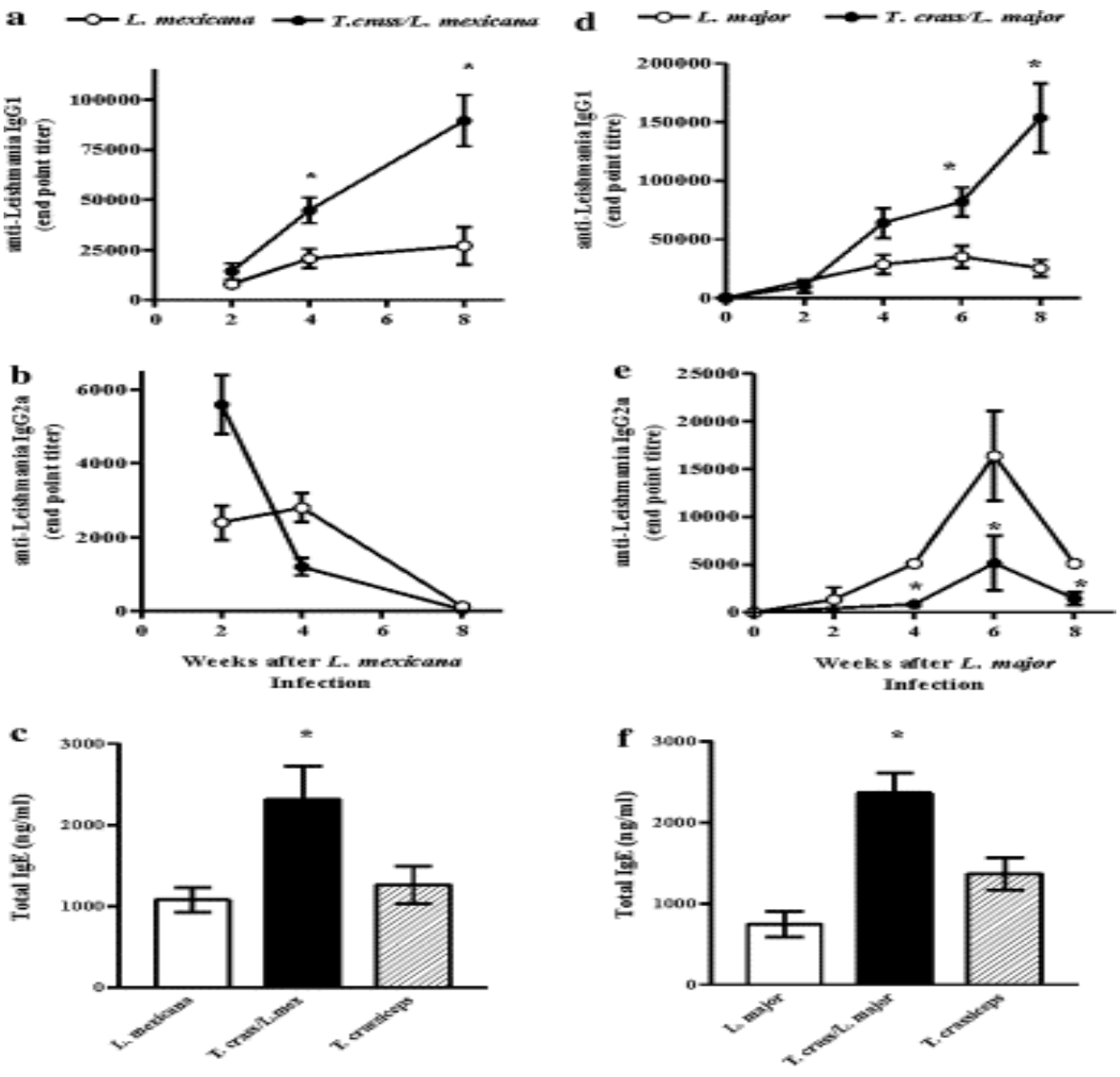


Parasite burdens in co-infected mice

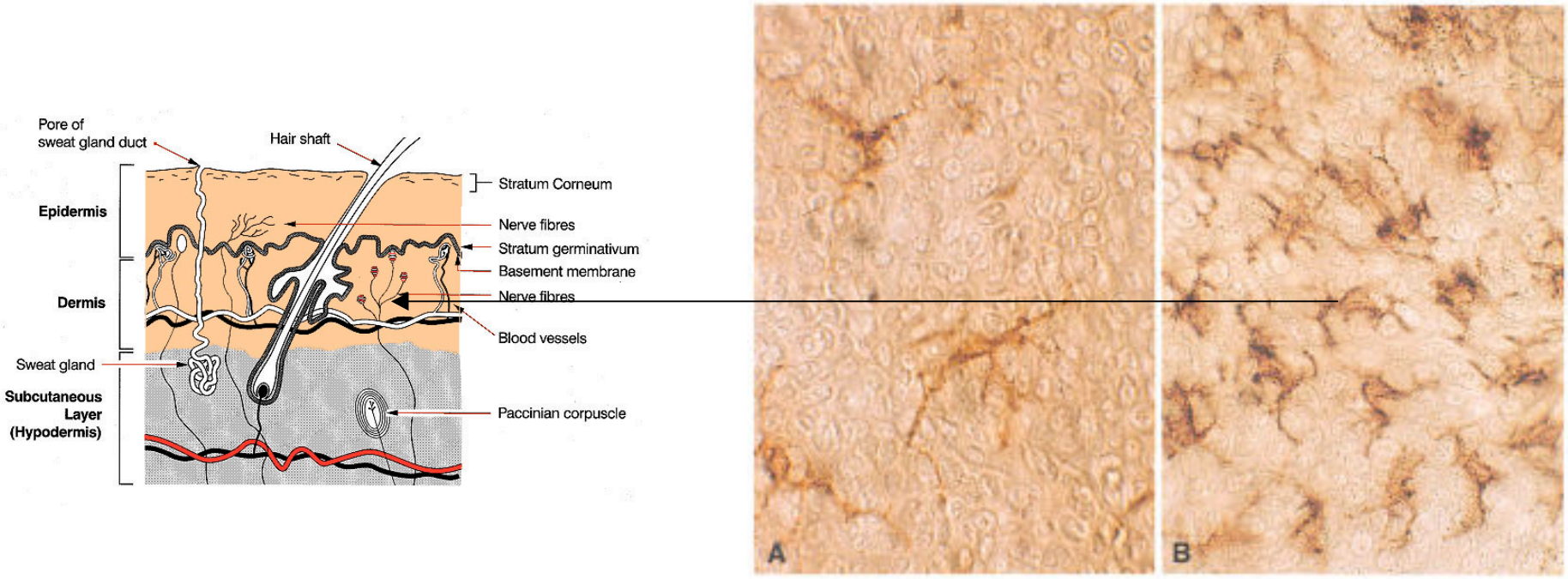
- **Parasite burdens from lymph nodes draining the site of infection.**



Antibody response in singly and co-infected mice

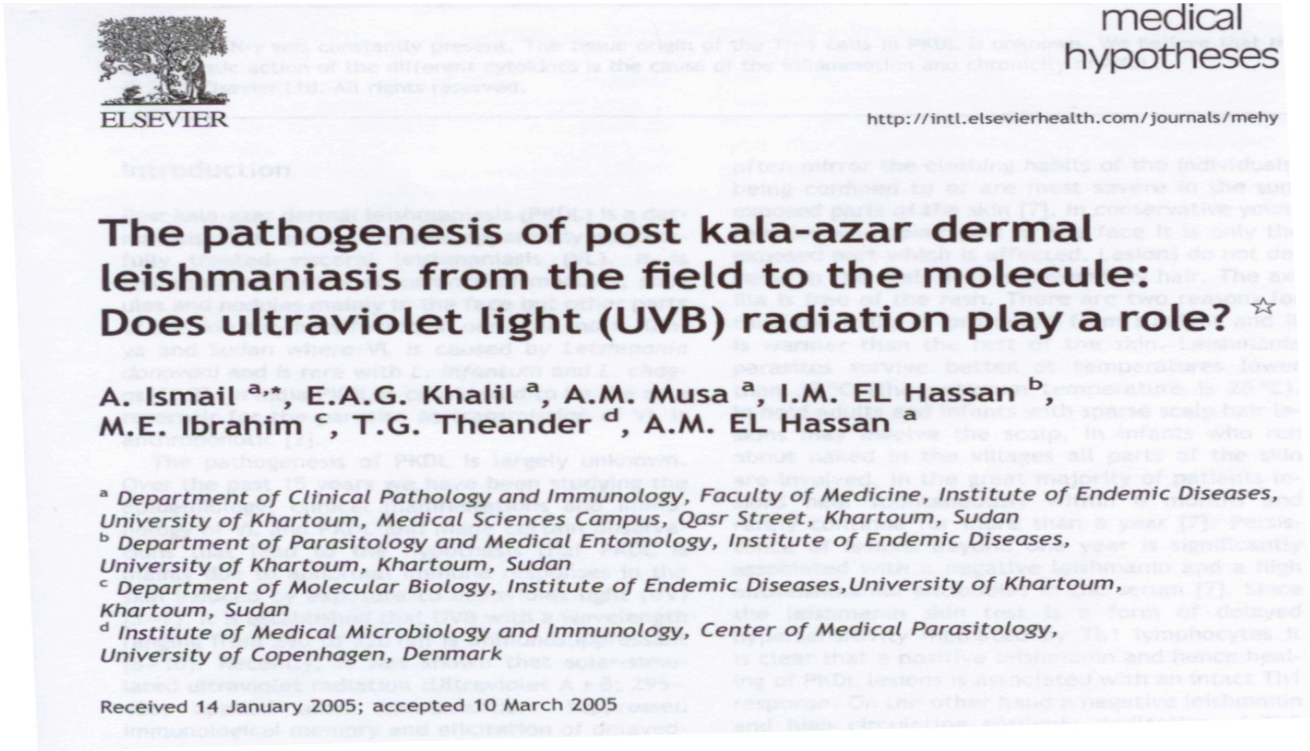


Mounting a Response



Ultraviolet Light

- **UVA/UVB**
- **Immune suppression**
  - **Local**
  - **systemic**
- **Shifts IR from Th1 to Th2**
- **Upregulation of Th2 cytokines (keratinocytes).**



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The pathogenesis of post kala-azar dermal leishmaniasis from the field to the molecule: Does ultraviolet light (UVB) radiation play a role? ☆

A. Ismail [a,*], E.A.G. Khalil [a], A.M. Musa [a], I.M. EL Hassan [b], M.E. Ibrahim [c], T.G. Theander [d], A.M. EL Hassan [a]

[a] *Department of Clinical Pathology and Immunology, Faculty of Medicine, Institute of Endemic Diseases, University of Khartoum, Medical Sciences Campus, Qasr Street, Khartoum, Sudan*
[b] *Department of Parasitology and Medical Entomology, Institute of Endemic Diseases, University of Khartoum, Khartoum, Sudan*
[c] *Department of Molecular Biology, Institute of Endemic Diseases,University of Khartoum, Khartoum, Sudan*
[d] *Institute of Medical Microbiology and Immunology, Center of Medical Parasitology, University of Copenhagen, Denmark*

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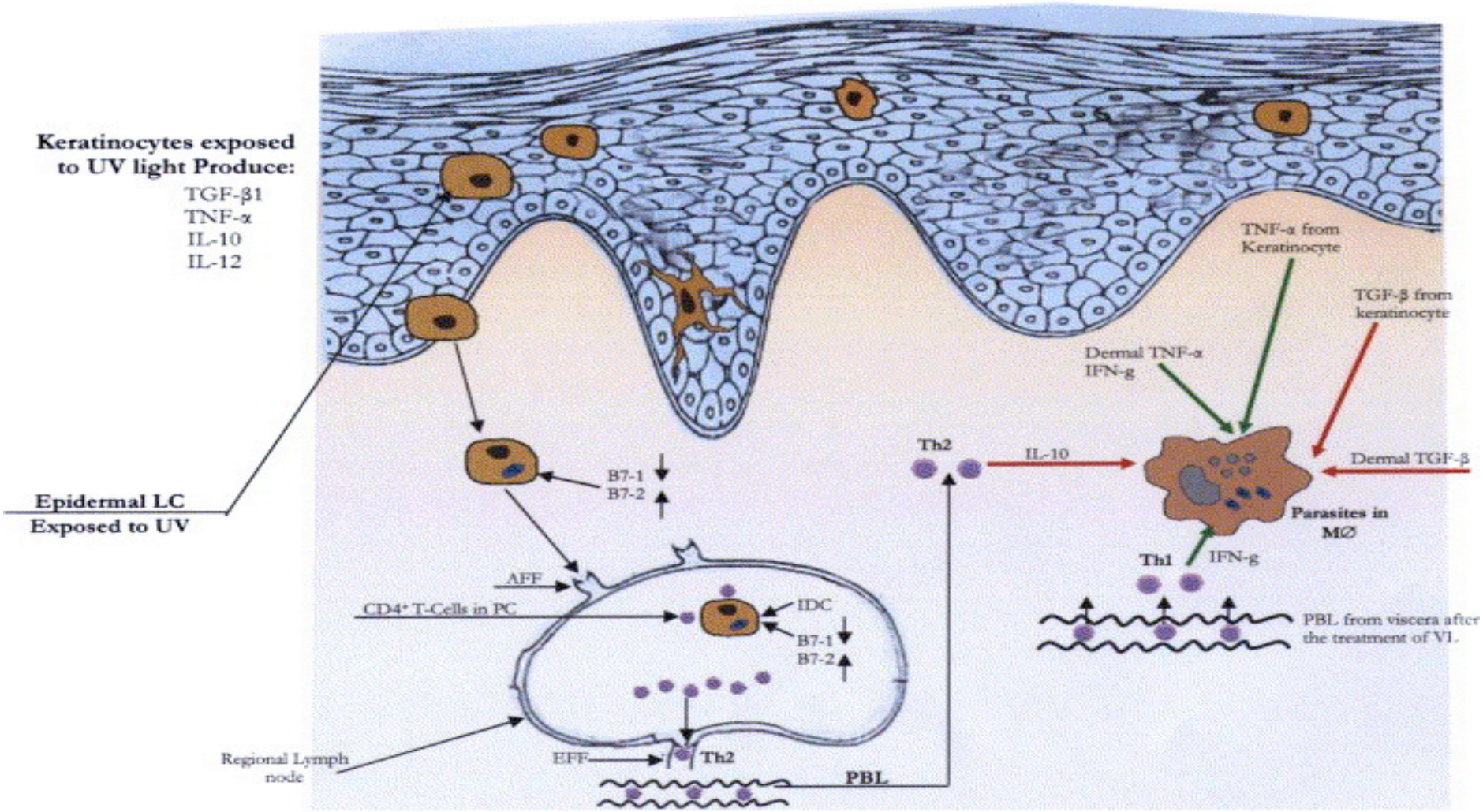
- **PKDL lesions mirror the clothing habits of patients.**
- **Lesions are confined to or are most severe in sun-exposed parts of the skin.**
- **Morphological and functional changes in Langerhans' cells that are found in PKDL lesions are compatible with the effects of UVB light.**

Pathogenesis of PKDL



VL: Visceral Leishmaniasis
LC: Langerhanse Cells
UV: Ultraviolet Light
MØ: Macrophage
PC: Paracortex
PBL: Peripheral Blood Lymphocytes
PKDL: Post Kala-azar Dermal Leishmaniasis
AFF: Afferent
EFF: Efferent
NK: Natural Killer Cells

IDC: Interdigitating Cells
TNF-α: Tumour Necrosis Factor Alpha
TGF-β: Transforming Growth Factor Beta
IFN-g: Interferon Gamma
Th1: T-helper -1
Th2: T-helper-2
IL-4: Interleukin-4
IL-10: Interleukin-10
IL-12: Interleukin-12