Leishmaniasis

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Disclaimers

Including:

The views expressed do not necessarily represent those of the Centers for Disease Control and Prevention

principles
&
perspective

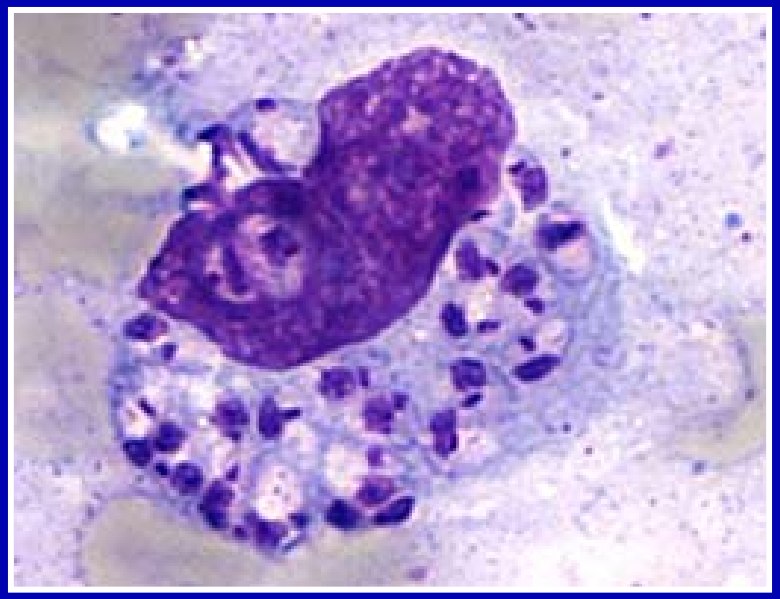
Leishmaniasis

- Leishmaniasis is a parasitic disease with multiple forms, most notably, visceral (VL), cutaneous (CL), & mucosal (ML)
- *Leishmania* parasites are:
  - Unicellular (protozoan parasites)
  - Intracellular (obligate intracellular pathogens)
  - Spread by phlebotomine sand flies

PATHOGENS:

"tiny" (~2-5 µm), intracellular

PARASITES



VECTORS:

"tiny" (~2-3 mm), inaudible

SANDFLIES

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Leishmaniasis: Multiple . . .

- **Syndromes (forms)**
- ***Leishmania* species *(>20 infect humans)***
- **Sandfly species *(~30 are vectors)***
- **Ecologies & transmission cycles *(~88 countries)***
  - **Tropics & subtropics to southern Europe**
  - **Jungles to deserts**
  - **Rural to urban**
  - **Zoonotic to anthroponotic**
- **Host factors *(eg, immunogenetics)***

Specificity amidst diversity

(and vice versa)

Simplicity amidst complexity

(and vice versa)

Don't generalize or oversimplify

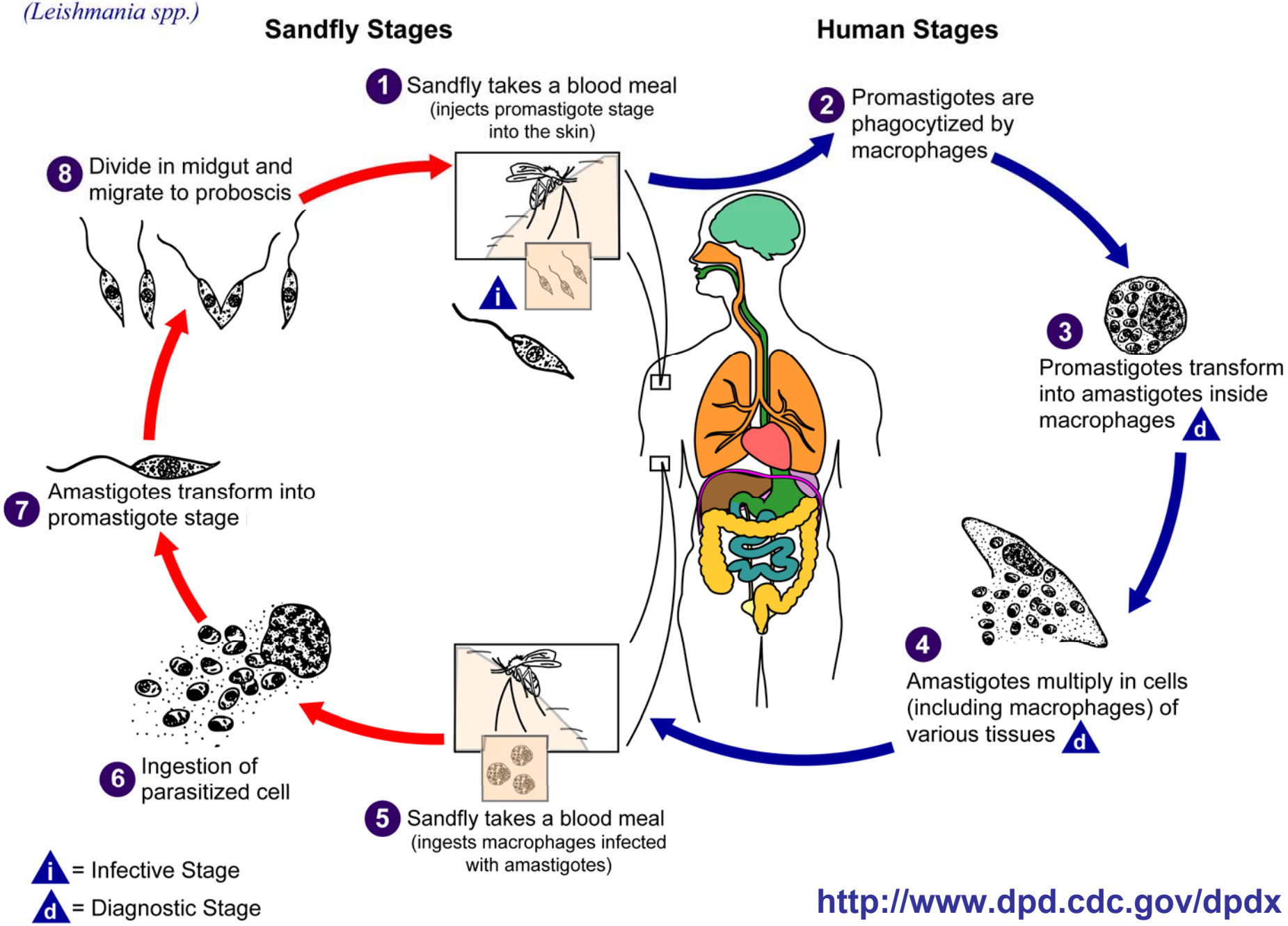
The multitudinous combinations of:

- heterogeneous *Leishmania* species/strains, syndromes, & geographic areas
  - further modified by host factors & immunoinflammatory "responses"
- may be associated with diverse manifestations of infection & diverse responses to particular therapies

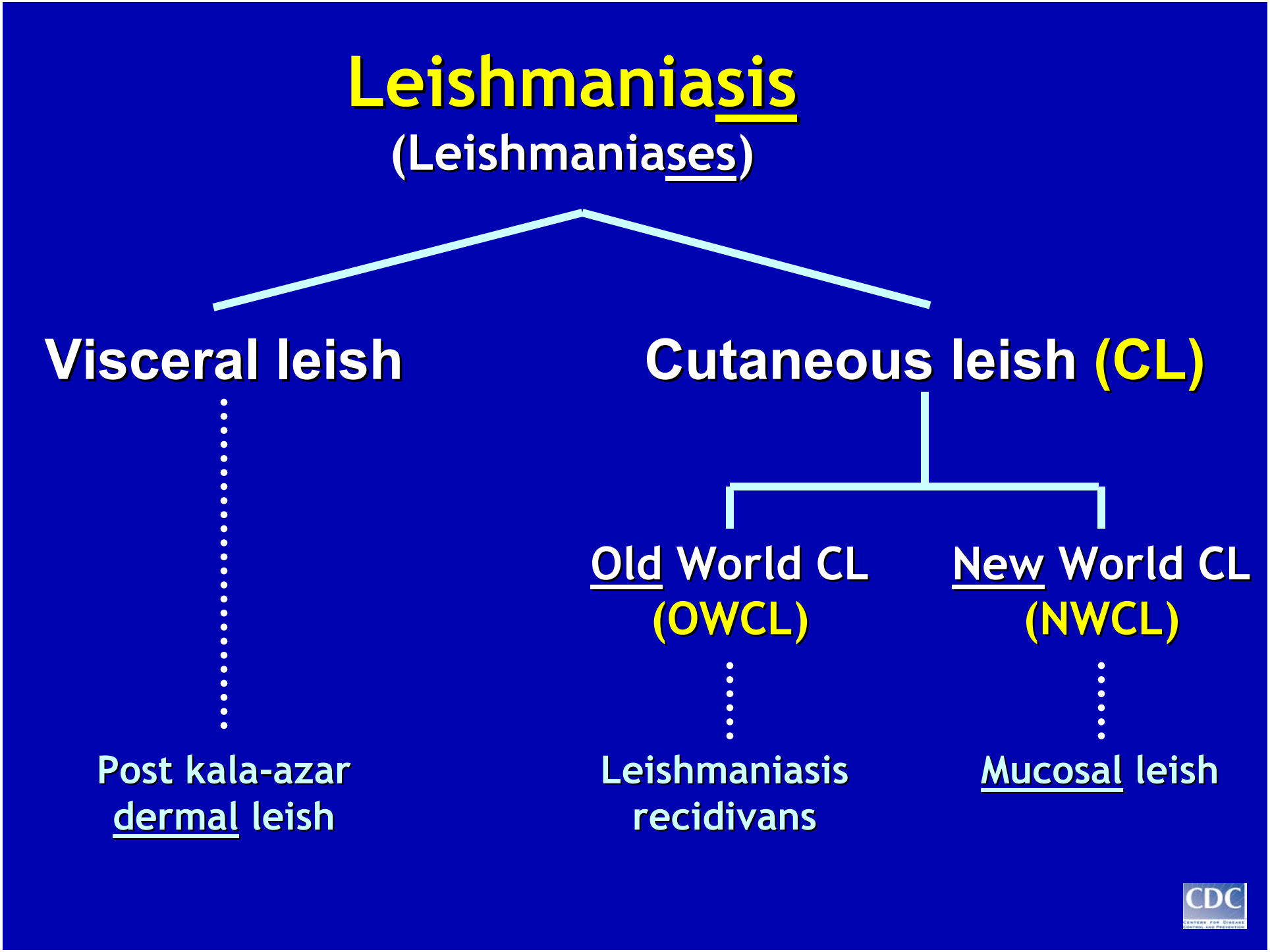
Public Health Image Library (PHIL); image 10277 (F Collins)

Leishmaniasis

(Leishmania spp.)



http://www.dpd.cdc.gov/dpdx


Leishmaniasis
(Leishmaniases)
Visceral leish
Cutaneous leish (CL)
Old World CL
(OWCL)
New World CL
(NWCL)
Post kala-azar
dermal leish
Leishmaniasis
recidivans
Mucosal leish
CDC

Leishmaniasis

(~2M cases/yr)

Visceral leish

(~0.5 million cases/yr)

Cutaneous leish (CL)

(~1.5 million cases/yr)

- Old World CL (~75% of CL cases)
- New World CL (~25% of CL cases)

Where is leishmaniasis found?

- Overall, VL is found in focal areas of ~65 countries:
  - But most (>90%) of the world's cases occur in the Indian subcontinent (India, Bangladesh, and Nepal), Sudan, & Brazil
- Overall, CL is found in focal areas of ~88 countries:
  - But most (>90%) of the world's cases occur in 8 countries: Afghanistan, Algeria, Iran, Iraq, Saudi Arabia, and Syria *(Old World)*; & Brazil and Peru *(New World)*

Caveat

Cases evaluated in the U.S. reflect

travel & immigration patterns

— & —

foreign affairs / policies

Visceral leishmaniasis

- **Species**: typically, ***L. donovani* & *L. infantum (chagasi)***
- **Spectrum:** asymptomatic to life threatening
- **Incubation period:** typically, weeks to months (can be years in persons who become immunocompromised)
- **Onset:** abrupt or gradual
- **Stereotypical manifestations:** fever, weight loss, hepatosplenomegaly (especially, splenomegaly), & pancytopenia (low blood counts)
- **Severe (advanced) cases** typically are fatal, if untreated

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Visceral leishmaniasis

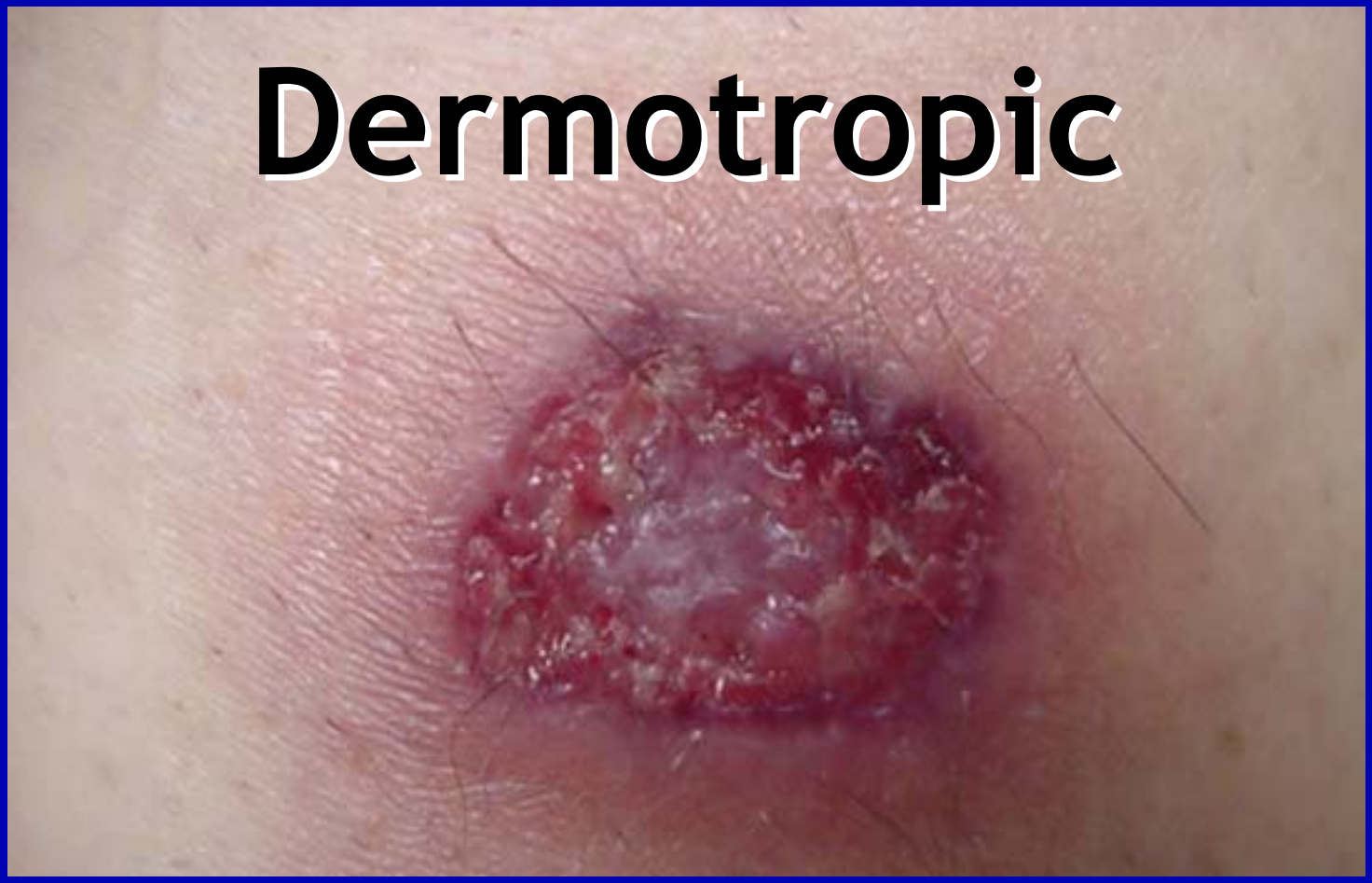
— classic "kala-azar" —

— caused by *Leishmania donovani* —

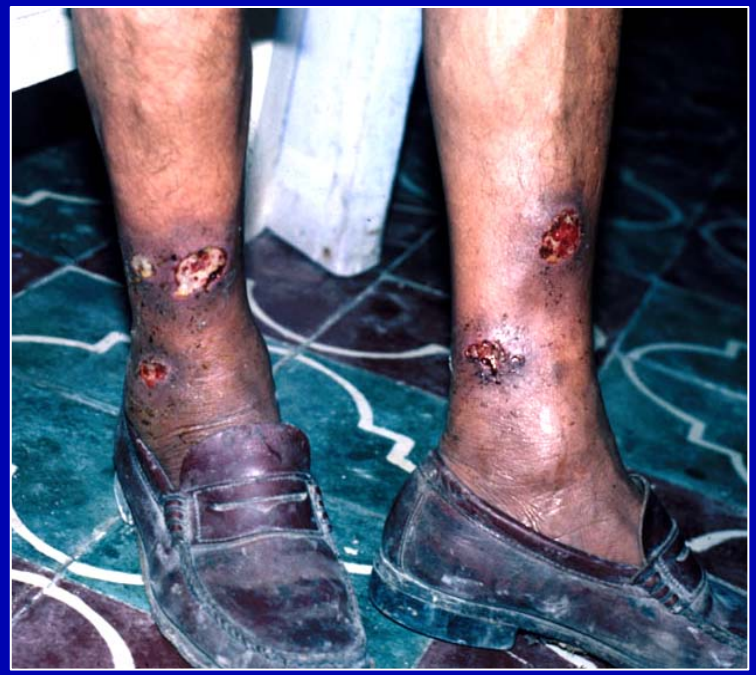
WHO/TDR/Crump; Image 9706884

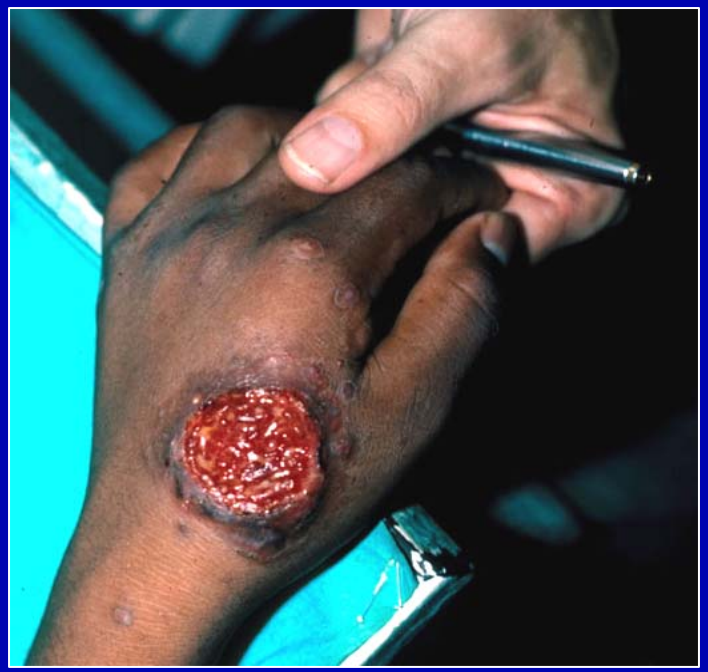
CDC

Dermotropic



Cutaneous leishmaniasis





CDC

How
is the diagnosis
parasitologically confirmed?

&

How often
is the diagnosis
parasitologically confirmed?

Leish: Diagnostic approaches

- **Clinical & epidemiologic**
- **Parasitologic**
  - **Amastigotes (on a "slide")**
  - **Promastigotes (in culture)**
  - **Parasite DNA**
- **Immunologic**
  - **Serology *(helpful primarily for classic VL)***
  - **Delayed type hypersensitivity *(skin test not licensed in the U.S.)***
  - **Other *(investigational)***

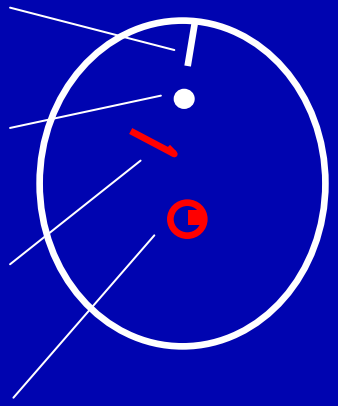
A-mastigote

Axoneme

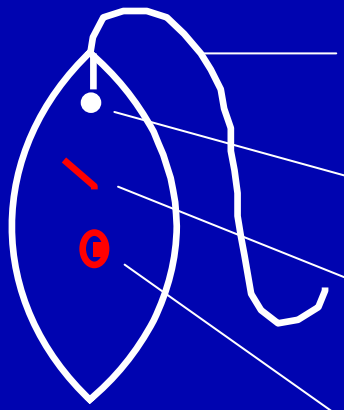
Basal body

Kinetoplast

Nucleus



PRO-mastigote

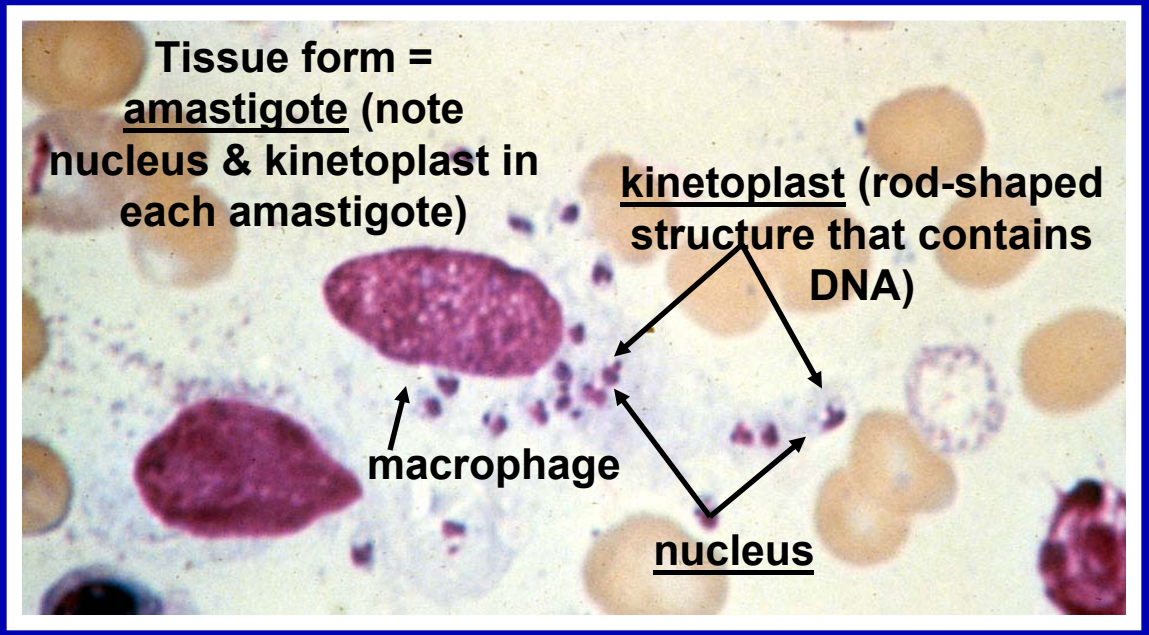


Flagellum

Basal body

Kinetoplast

Nucleus


Tissue form = amastigote (note nucleus & kinetoplast in each amastigote)
kinetoplast (rod-shaped structure that contains DNA)
macrophage
nucleus

In association with

Operations Desert Storm/Shield,

DoD identified:

- ~20 cases of CL ("dermotropic leish"); *L. major*
- ~12 cases of "viscerotropic leish"; *L. tropica*

"Viscerotropic leishmaniasis" from Desert Storm: the first 8 (of 12) cases documented by DoD

Table 1. Clinical Presentation of Eight Male Patients with Visceral Leishmaniasis, at the Time of Confirmatory Culture.

Patient No.	Incubation Period (Mo)	Signs and Symptoms at Presentation	Fever	Abdominal Pain*	Malaise*	Fatigue*	Physical Examination
1	2	Adenopathy	Yes	++	+	++	Hepatomegaly, splenomegaly, adenopathy
2	1–4	Fever	Yes	+	++	+	Normal findings
3	2–8	Gastroenteritis	No	+++	+++	+	Splenomegaly
4	2–6	None	No	No	No	No	Normal findings
5	4–12	Chronic fatigue with hepato-splenomegaly	Yes	+	+	+++	Hepatomegaly, splenomegaly
6	7–14	Chronic fatigue with adenopathy	No	+	+	+++	Hepatomegaly, adenopathy
7	1–6	Mononucleosis	Yes	+/−	+++	+	Normal findings
8	3–12	Fever of unknown origin	Yes	+	++	++	Hepatomegaly, splenomegaly

*One plus sign indicates that the patient reported the symptom when questioned by the examiner; two plus signs, that the patient himself reported the symptom without questioning; and three plus signs, that the symptom was the primary one. Patient 7, represented by the plus–minus sign, reported abdominal pain of brief duration associated with diarrhea.

#7: also had illness a/w HIV seroconversion

#8: also had newly diagnosed renal cancer

(Magill et al., NEJM 1993)

CDC

Visceral leishmaniasis

VS

Viscerotropic leishmaniasis

VS

Dermotropic leishmaniasis

Operations Desert Storm / Shield

VS

Operations Iraqi & Enduring Freedom

Leish: Risk assessment

- **Place**
  - Area of X country
  - Microfoci of sand fly "activity"
  - "Force of infection" in a particular place & time
- **Personal factors & activities**
  - Type, timing (day vs night), duration *(but 1 infected bite is "enough")*; sleeping conditions; use of protective measures; . . .

Patient who has leishmaniasis

↓

What are the Rx goals?
(Individualize care of each patient)

↓

Ideally, want 100% effective & safe, 1-dose, oral Rx targeted to amastigotes (in phagolysosomes of macrophages), which it KILLS, causing complete & lasting sterile cure & immunity

Individualized care

- Is Rx indicated? What is the worst that could happen with no or suboptimal Rx (eg, death, substantial morbidity, mucosal leish)?
- Should a drug regimen that usually is highly & rapidly effective be used, or could a potentially less effective & less toxic but more easily administrable Rx be tried 1st?

Individualized care

- Does the patient have other medical disorders that could affect the course of the leish infection or increase risk for toxic effects of certain drugs?
- Which therapeutic agents are available?
  - What is known about their efficacy & toxicity profiles for treating the species of interest from the region of interest?

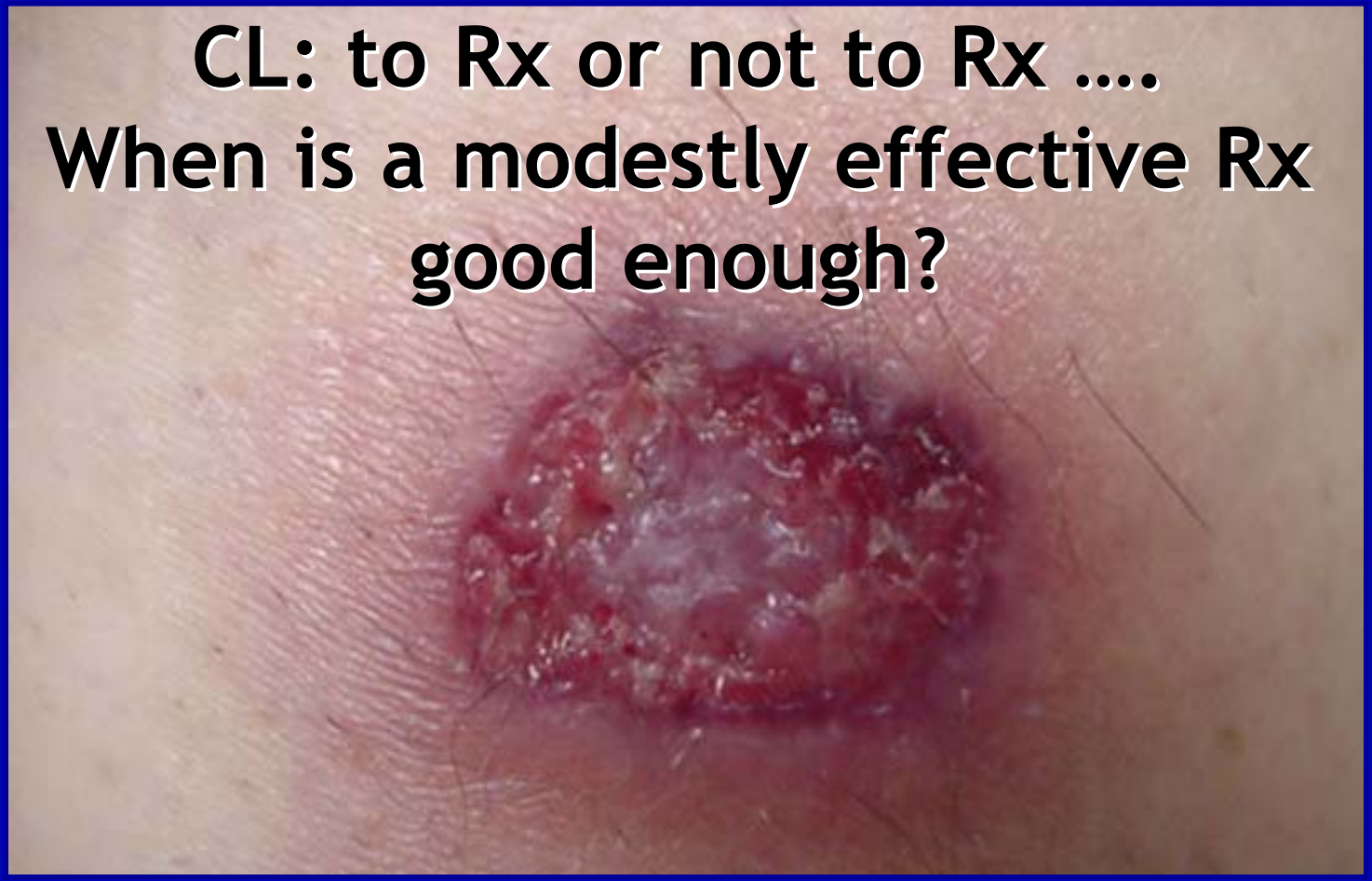
CL: motivations to treat

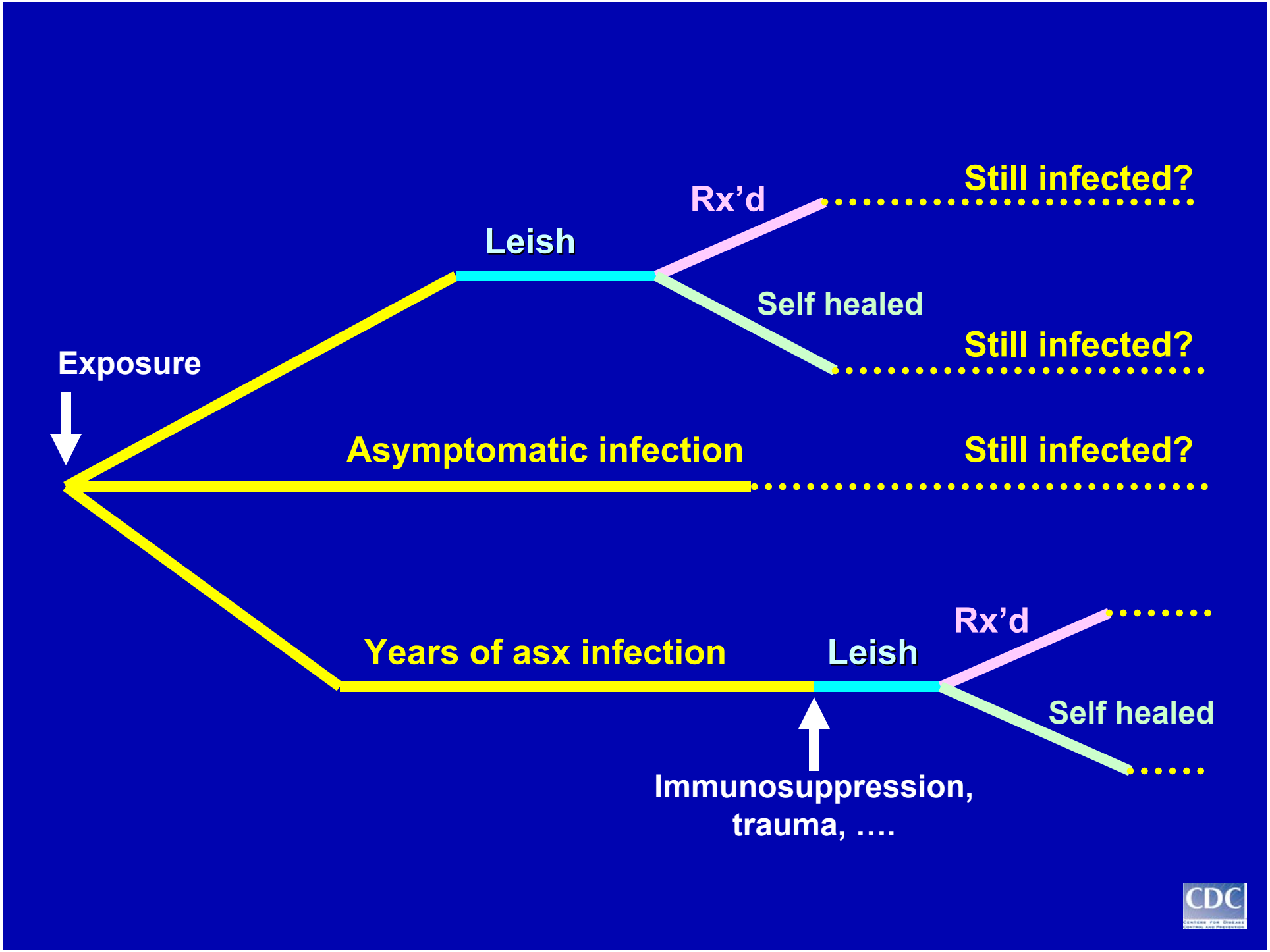
- Patient's goal: Heal lesions faster than they would spontaneously ... & ... w/o a scar
- Prevent relapse of local lesions
- Prevent / Rx local dissemination (eg, lymphadenopathy, sporotrichoid spread)
- Prevent / Rx mucosal leishmaniasis
- Prevent transmission of infection, if humans could be reservoir hosts

Leish: Parenteral therapies

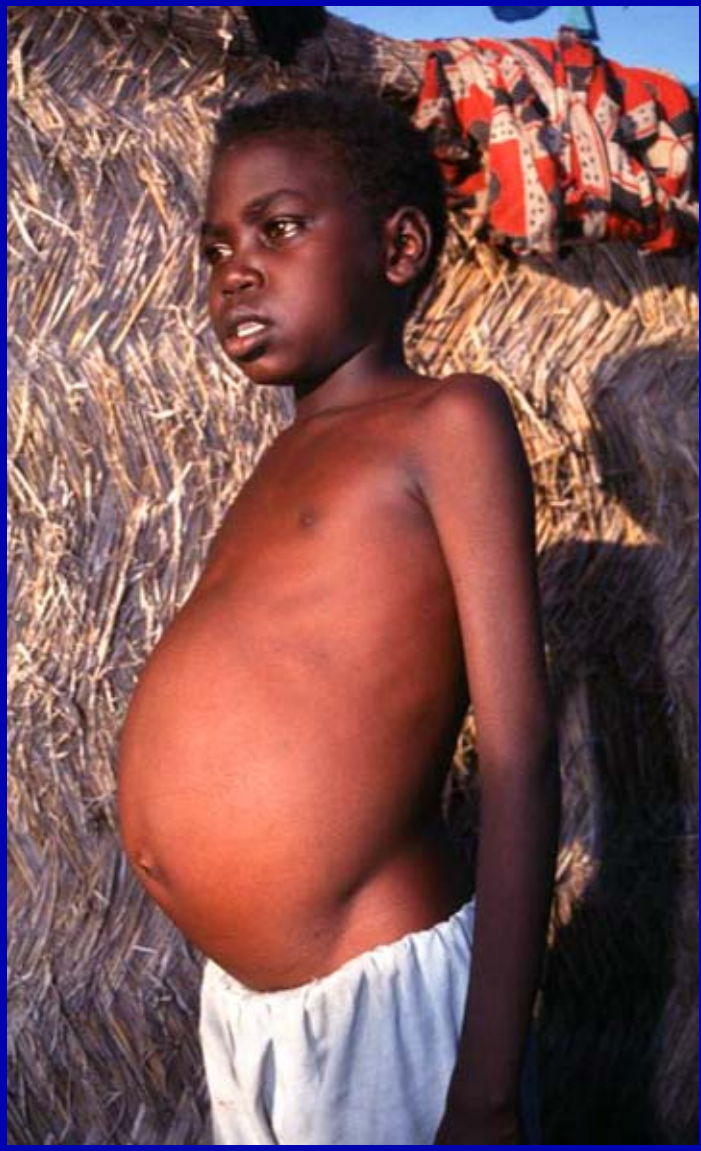
- Pentavalent antimonials *(CDC IND)*
- Conventional ampho B *(off label)*
- Lipid formulations of ampho B
  (AmBisome: FDA approved for Rx of VL)
- Pentamidine *(off label)*
- Paromomycin *(not available in US)*
- Immunotherapies *(investigational)*

CL: to Rx or not to Rx ….
When is a modestly effective Rx good enough?




Still infected?
Rx'd
Leish
Self healed
Still infected?
Exposure
Asymptomatic infection
Still infected?
Rx'd
Years of asx infection
Leish
Self healed
Immunosuppression,
trauma, ….

(WHO/TDR/Crump; image 9706828)



(WHO/TDR/Crump; image 9706920)