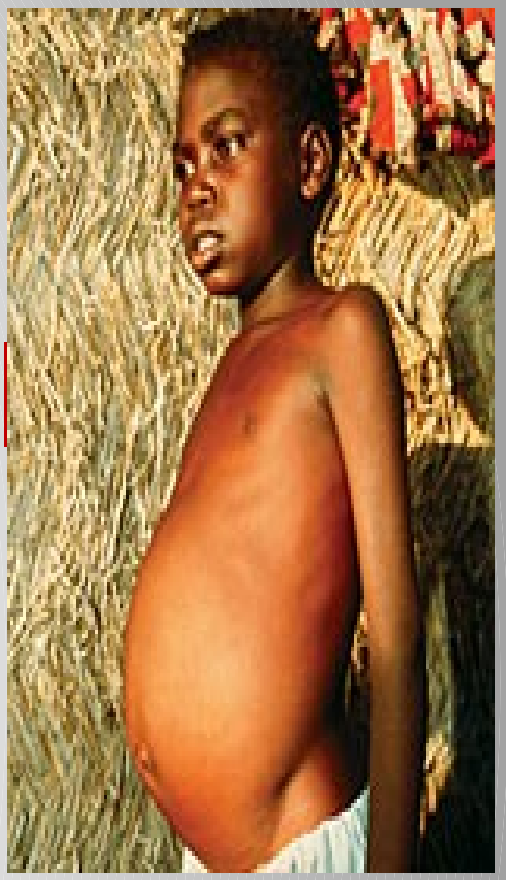
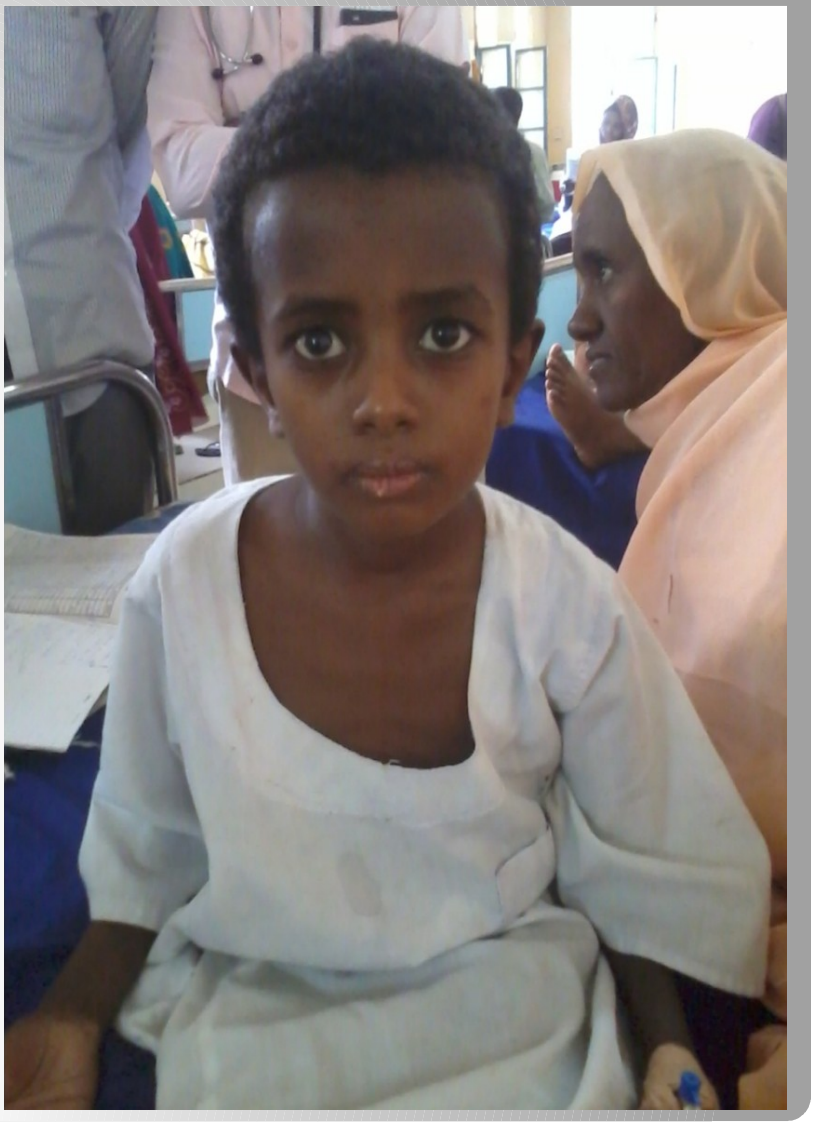
VISERAL LEISHMANIASIS (KALA-AZAR)



:OUTLINES

- DEFINITION.
- EPIDEMIOLOGY.
- PARASITE & VECTOR.
- PATHOLOGY & LIFE CYCLE.
- CLINICAL PICTURE.
- COMPLICATIONS.
- DIAGNOSIS.
- INVESTIGATIONS.
- MANAGEMENT
- TREATMENT'S UPDATES.
- CONTROL.



!!Charge your battery…let’s start

DEFINITION

LEISHMANIASIS

is a vector-borne systemic protozoan disease (caused by obligate intracellular parasite) and transmitted by phlebotomine sandflies.

4 main clinical syndromes:

- Cutaneous leishmaniasis.
- Muco-cutaneous leishmaniasis (Espundia).
- Visceral leishmaniasis (kala-azar).
- Post (Para)-kala-azar dermal leishmaniasis (PKDL).

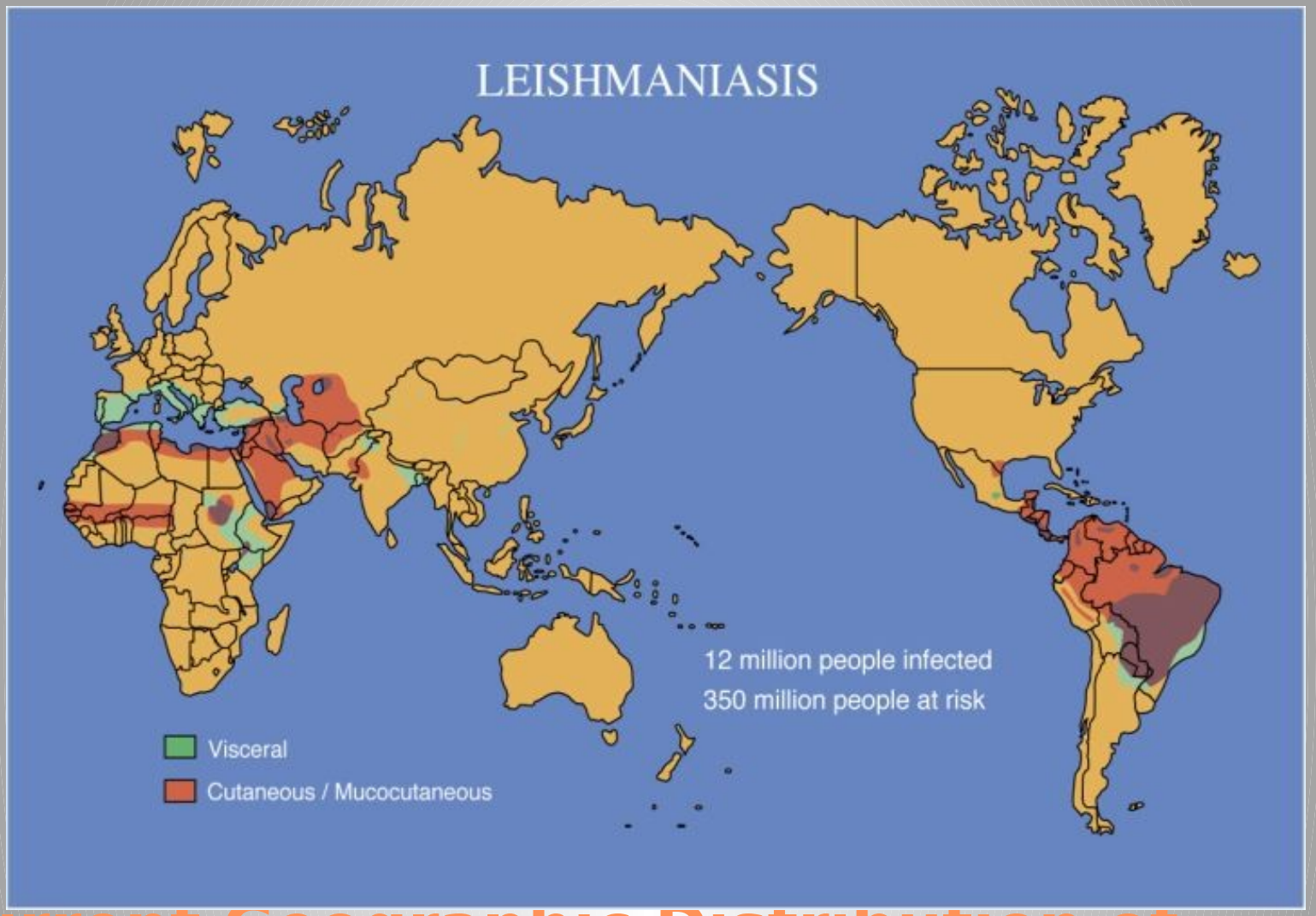
EPIDEMIOLOGY

Visceral leishmaniasis
Magnitude of the problem

- Most severe form of leishmaniasis.
- 2nd largest parasitic killer in the world.
- Responsible for 500,000 infection each year world wide.
- Of particular concern (according to WHO)is HIV/VL co-infection.

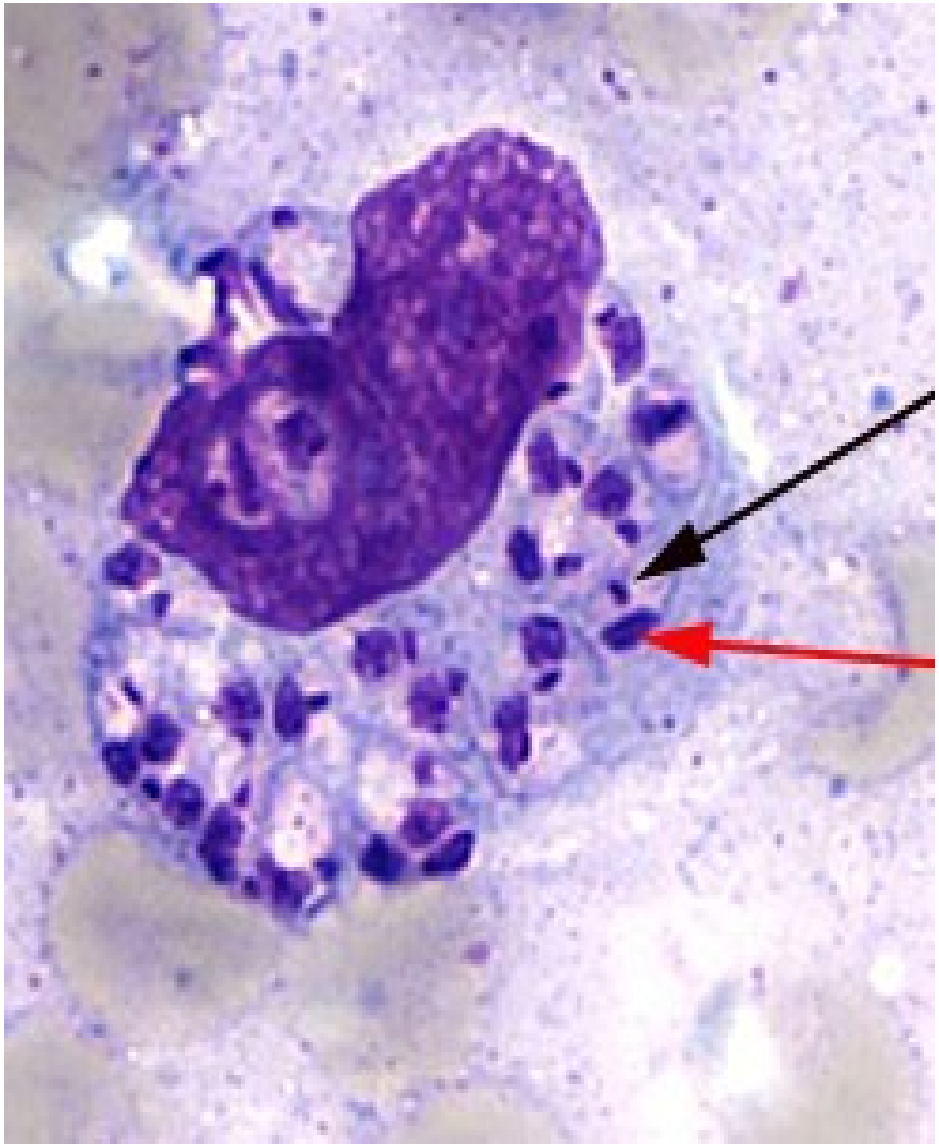
:EPIDEMIOLOGY

- Poverty related disease associated with ↓ immunity , lack of resources .
- 100% Fatal if left untreated.
- Threatened ~ 350 million people in 88 country around the world.
- Endemic in large areas of the tropics, subtropics and the Mediterranean basin.
- 90% of cases of leishmaniasis are found in; Bangladesh, Brazil, India, Nepal & sudan.
- In sudan it’s found in the east , south & west.



Current Geographic Distribution of Leishmaniasis

Parasite & Vector

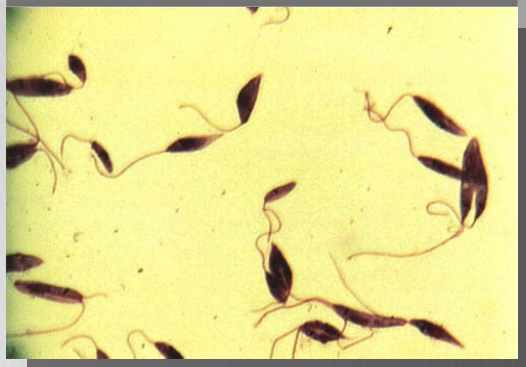


Light-microscopic examination of a stained bone marrow specimen from a patient with visceral leishmaniasis—showing a macrophage (a special type of white blood cell) containing multiple *Leishmania***amastigotes** (the tissue stage of the parasite). Note that each amastigote has a **nucleus** (red arrow) and a rod-shaped**kinetoplast** (black arrow). Visualization of the kinetoplast is important for diagnostic purposes, to be confident the patient has leishmaniasis. (Credit: CDC/DPDx)

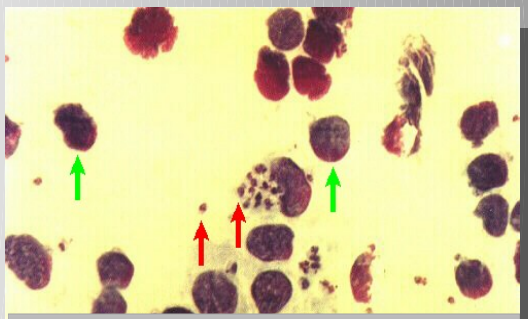
:PARASITE

- **Leishmania parasite has 2 Forms**:
  - **Flagellate** (**Promastigote**):
    - _ Extracellular form.
    - _ Found in Vector &Culture.
  - **Aflagellate** (**Amastigote**):
    - _ Intracellular form.
    - _ Found in Host.

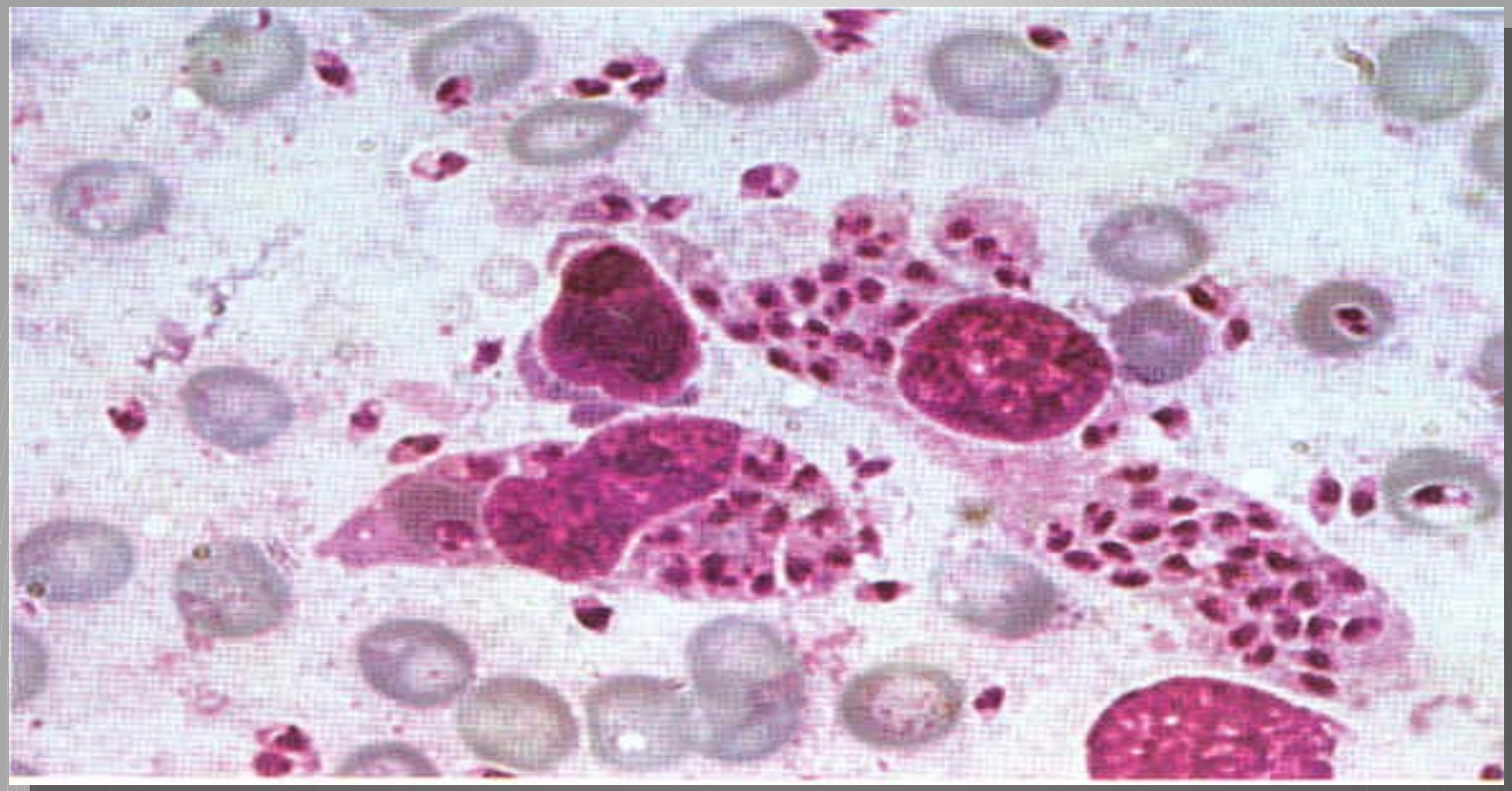
Promastigote



- **2 leishmania species causing VL ;**
  - ***L.donovani***; in East Africa and Indian subcontinent
  - ***L.infantum*;** in Europe, North Africa and Latin America (**Chagas disease**).



Amastigote



Leishmania (Leishman-Donovan or LD bodies).
Lying inside macrophage cells from liver (Giemsa stain)

VECTOR:

- Female sand fly of the genus
  - Phlebotomus → old world.
  - lutzomia → new world.
- 2-4 mm length with hairy body.
- Found in inter-tropical & temperate areas.
- Active at evening & night.
- Lay it's egg in the burrows' of rodents , bark of old trees, ruined buildings & cracks in the house.
- Can fly for several 100s meters around it's habitat.

VECTOR:

- Of 500 species of Phlebotomus sand fly leishmania is transmitted via ~30 species. e.g. ;
  - P. Orientalis → Sudan.
  - P. Argentipis → India.
  - P. Martini → Kenya.

Reservoir:

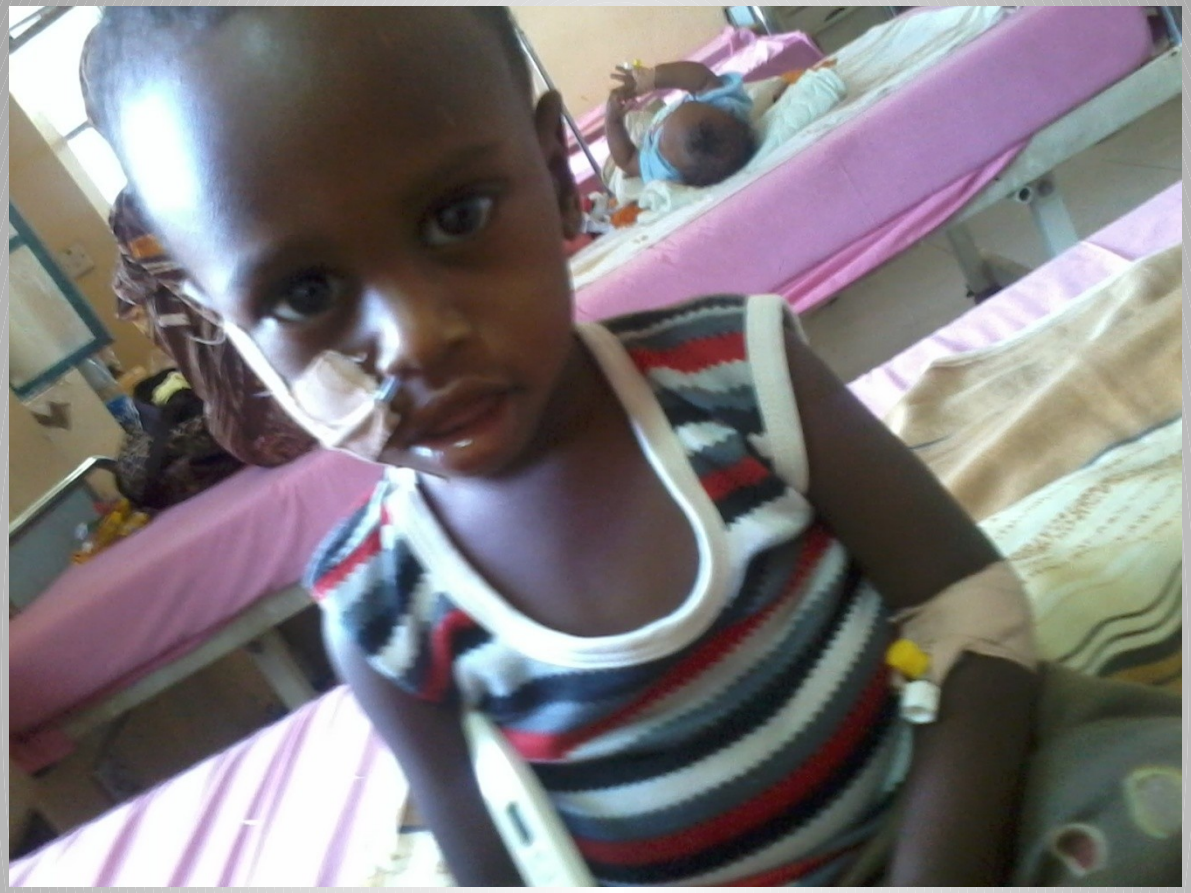
According to the reservoir ; 2 types of VL:

1) Zoonotic VL:

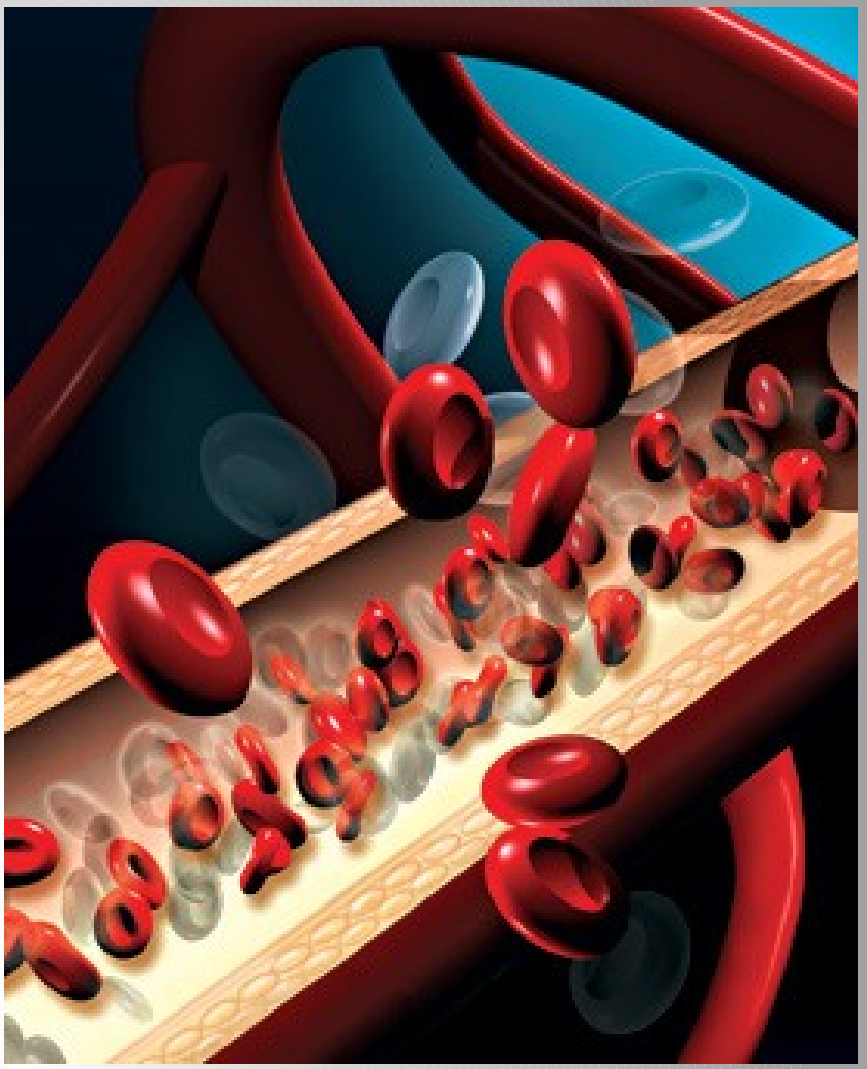
- Animal (Dogs) → vector → human.
- Found in areas of *L. infantum.*

2) Anthroponotic VL:

- Human → vector → human.
- Found in areas of *L. donovani* .



LIFE CYCLE & PATHOLOGY



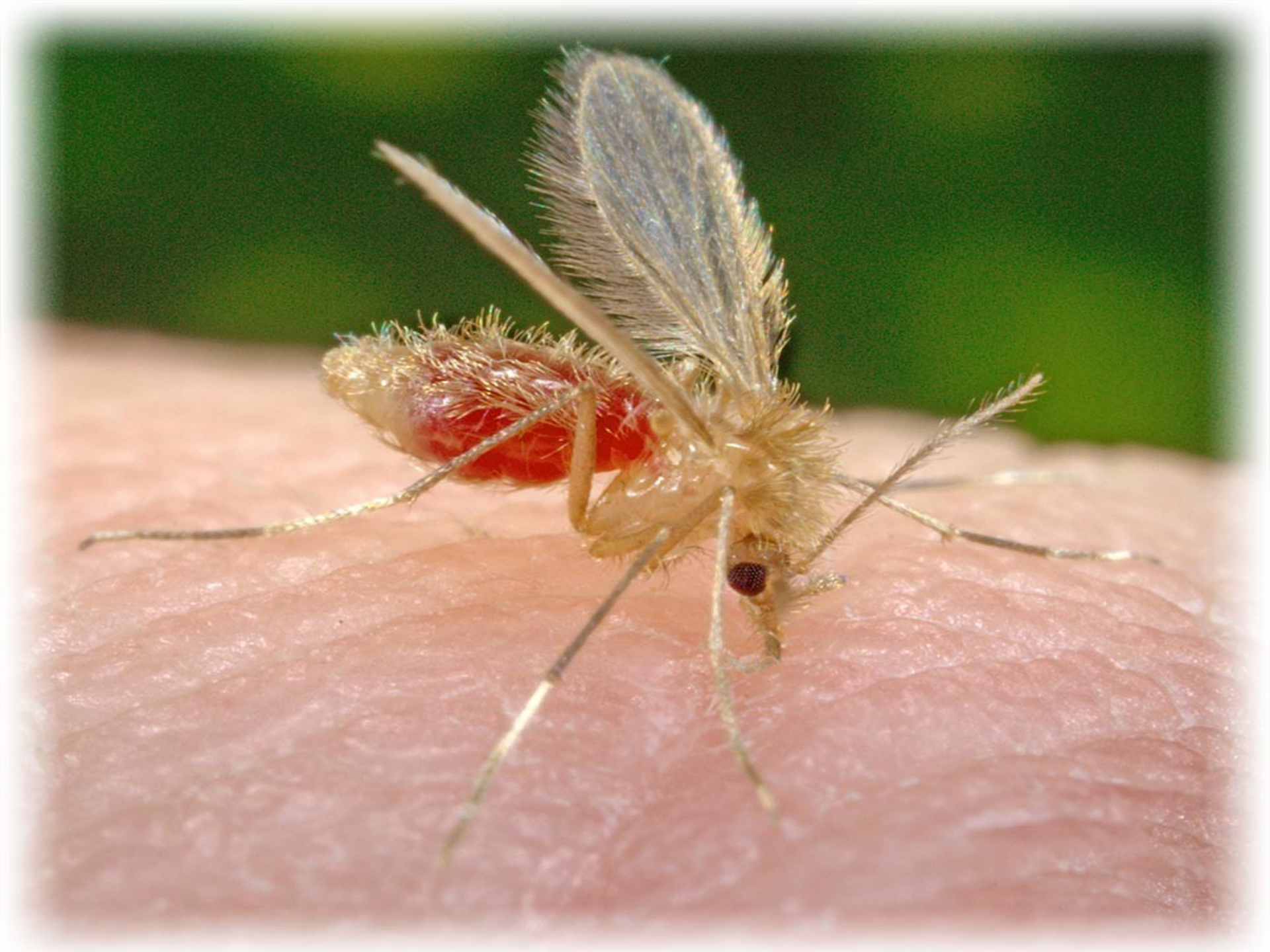
PATHOLOGY

***Disease transmission:**

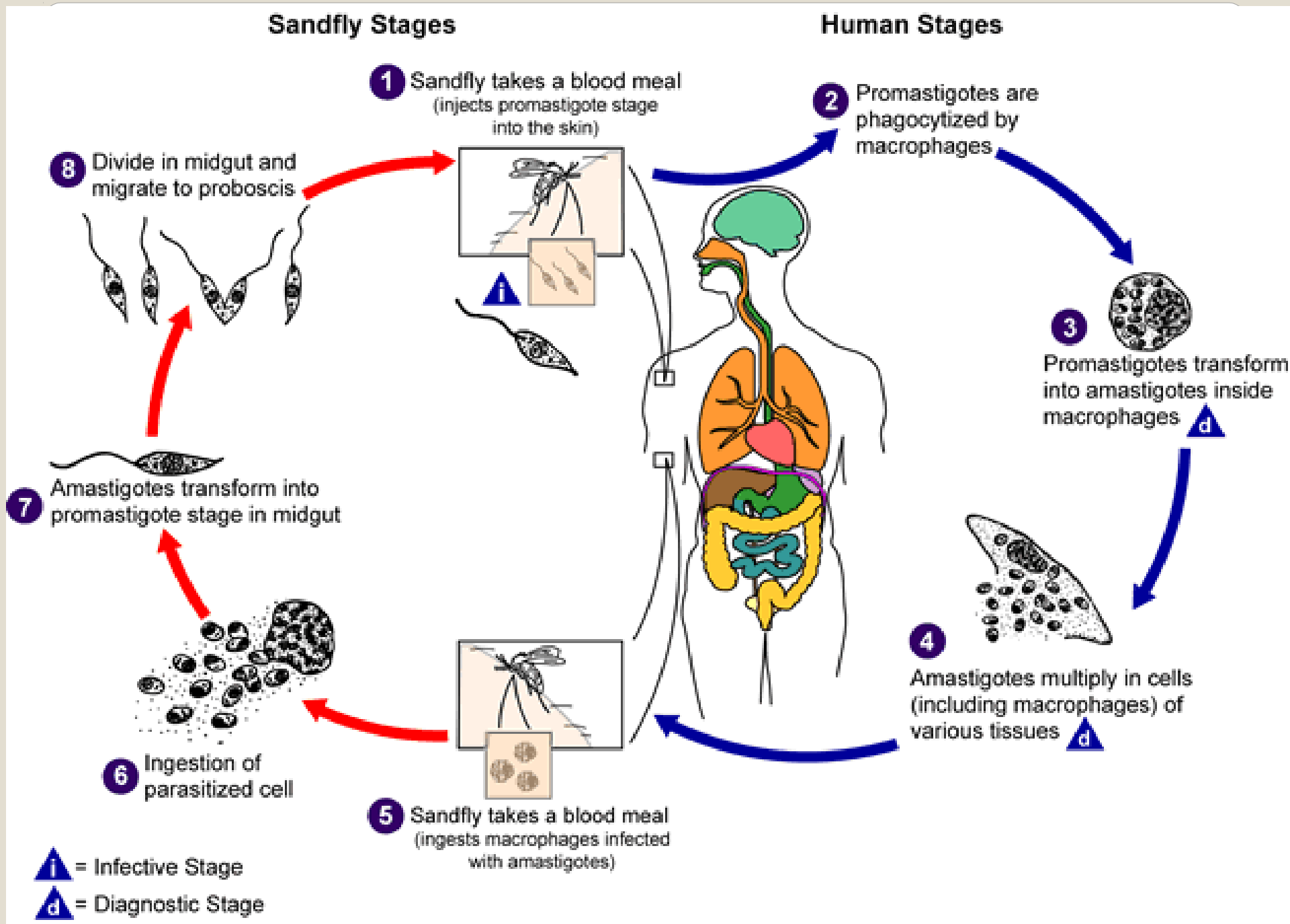
- **Mainly;** sand flies.

- **Rarely:** _ Congenital.
  _ Blood transfusion.
  _ Sexual.
  _ I.V. drug abusers’ .

LIFE-CYCLE



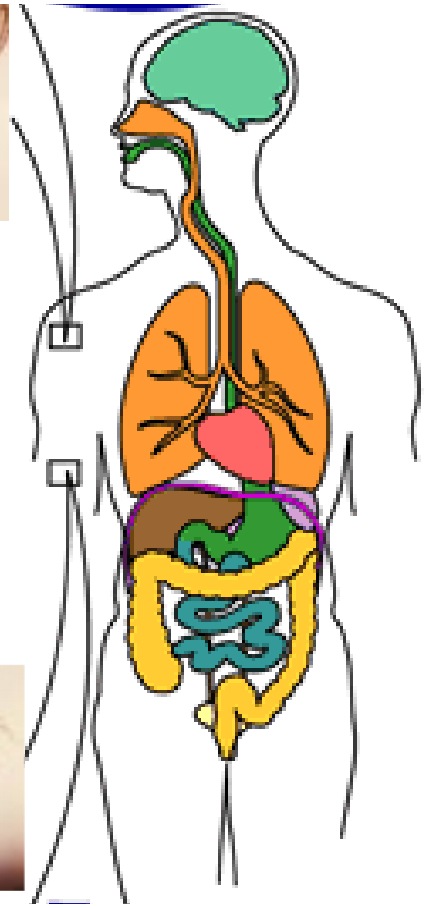
cycle


Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage
into the skin)
2 Promastigotes are
phagocytized by
macrophages
3 Promastigotes transform
into amastigotes inside
macrophages
d
4 Amastigotes multiply in cells
(including macrophages) of
various tissues
d
5 Sandfly takes a blood meal
(ingests macrophages infected
with amastigotes)
6 Ingestion of
parasitized cell
7 Amastigotes transform into
promastigote stage in midgut
8 Divide in midgut and
migrate to proboscis
i
i = Infective Stage
d = Diagnostic Stage

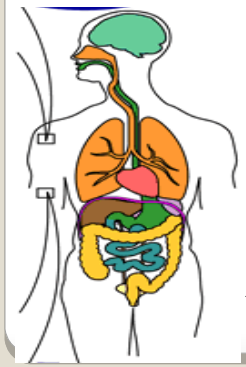
Life Cycle

1- Sandfly bites animal and ingests blood infected with *Leishmania*

2- Sandfly bites human and injects *Leishmania* into skin



3- Another sandfly bites human and ingests blood infected with *Leishmania*

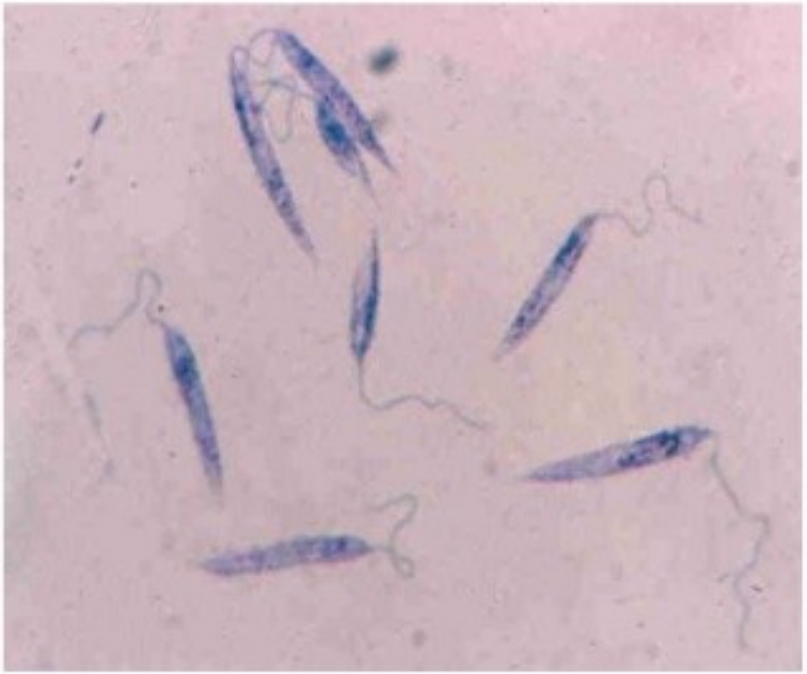


4- Cycle continues when sandfly bites another human or animal reservoir

Digenetic Life Cycle

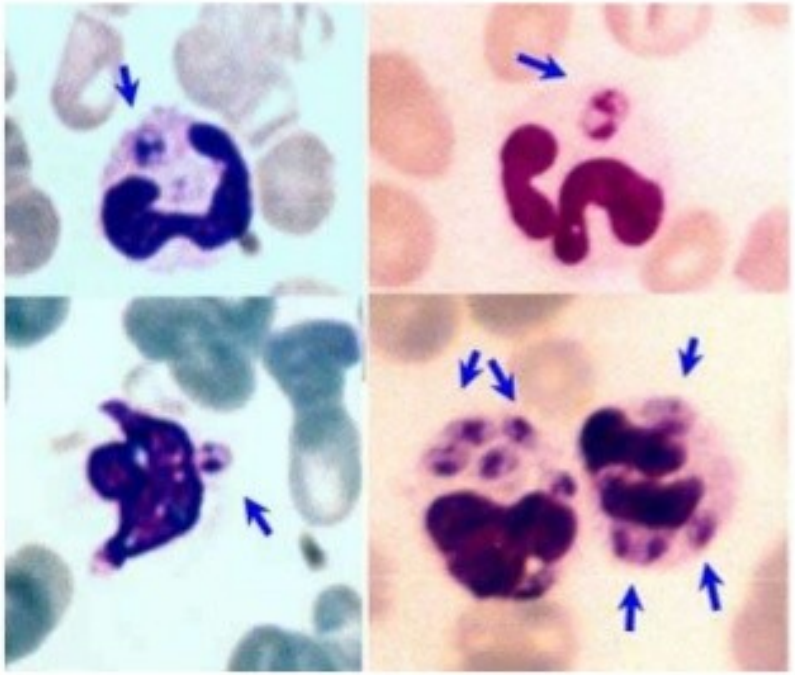
Promastigote

- Insect
- Motile
- Midgut



Amastigote

- Mammalian stage
- Non-motile
- Intracellular



CLINICAL FEATURES

:CLINICAL FEATURES

- **Incubation period**: 2 - 6 month

). but may range from 10 days to several years (

- Asymptomatic & subclinical infection in 30- 50 person for every case of V. Leishmaniasis.

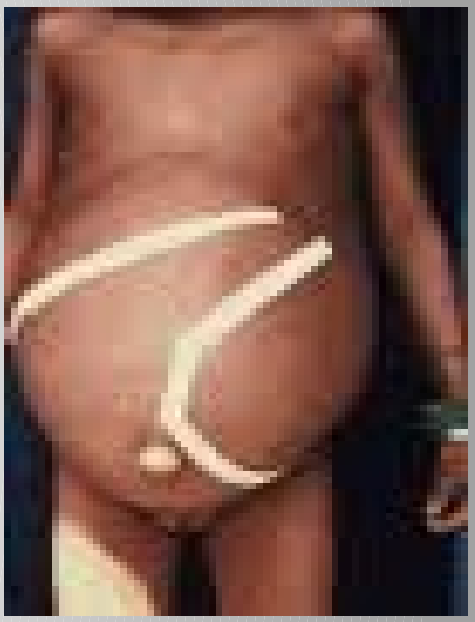
PRESENATION:

- **SYMPTOMS:**
  - Fever ; insidious , intermittent with double or triple rise /day.
  - Weight loss.
  - ↑appettite.
  - Symptoms of anaemia.
  - Epistaxis + gum bleeding.
  - Diarrhoea (gut ulceration).
  - Dry cough.
  - Darkness of the skin(india).
- The disease has been described in india at the end of the 19th century as KALA-AZAR = BLACK FEVER.

PRESENATION:

Signs:

- **Fever** ; 100% of cases.
- **Splenomegaly** (firm ,painless , with time);early sign ;variable.

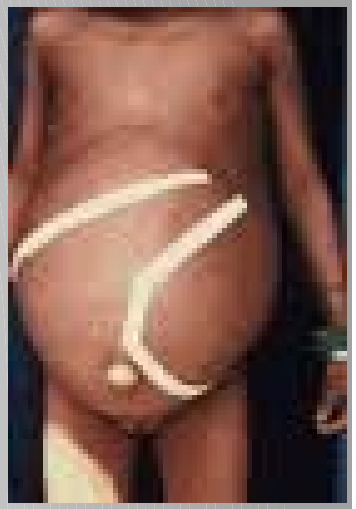


- **Hepatomegaly**; less frequent , occur late.
- **Lymphadenopathy** (Epitrochlear L.N.); small , firm , painless ,mobile L.Ns.

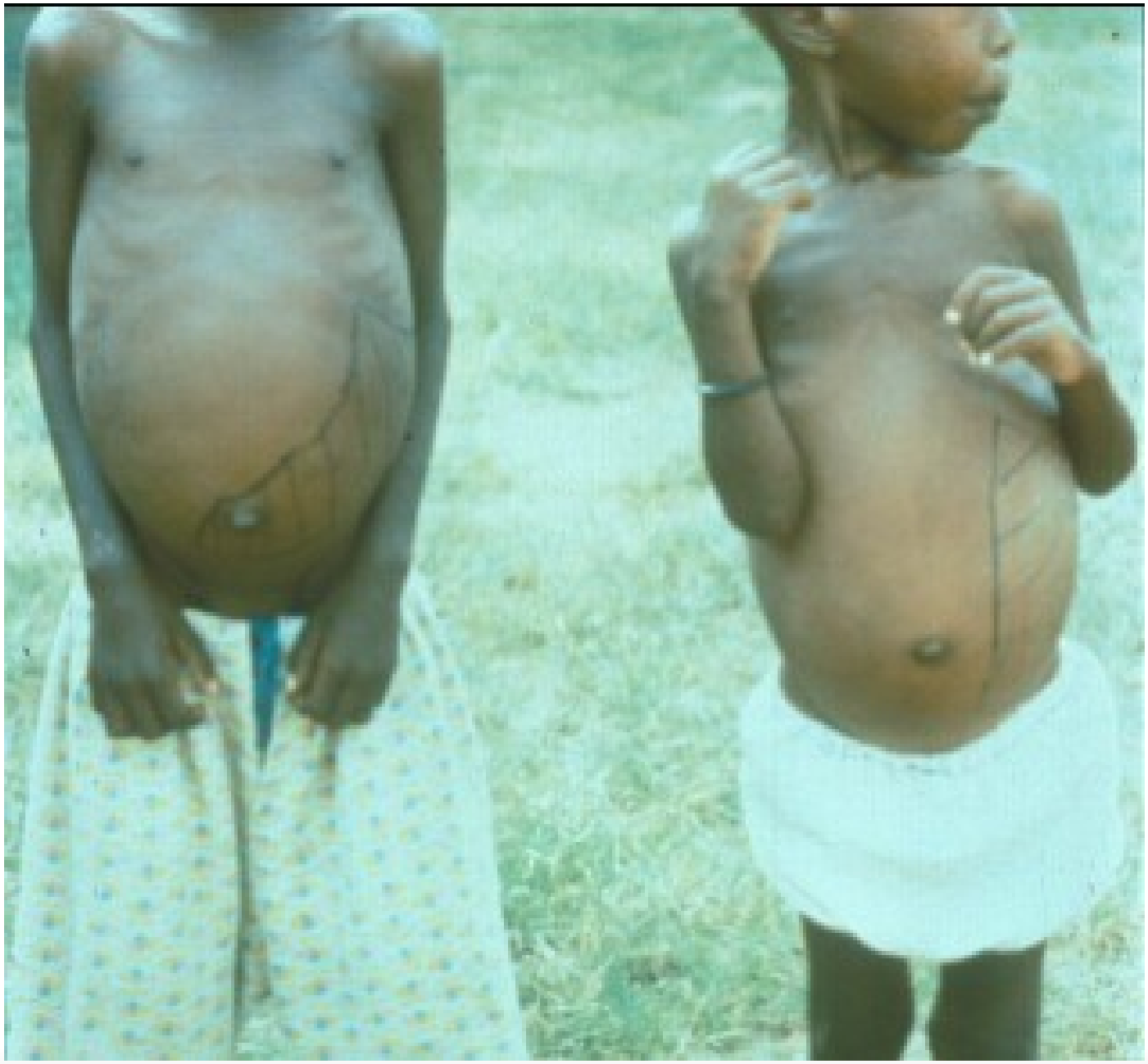
PRESENATION:

Late signs:

- Due to **hypoalbuminaemia** from direct liver insult, nutritional deficiency & protein loosing enteropathy:
- Ascitis.
- Edema
- Pleural effusion.

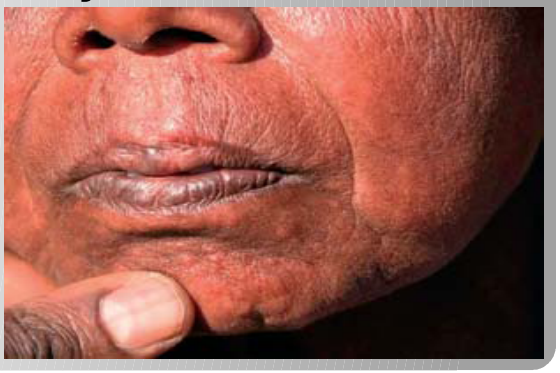


- Renal involvement due to immune complex deposition & proteinuria.



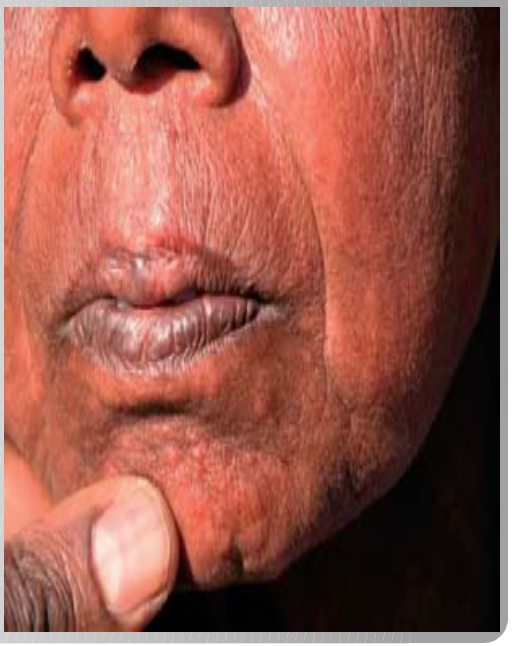
PARA KALAZAR DERMAL :LEISHMANIASIS (PKDL)

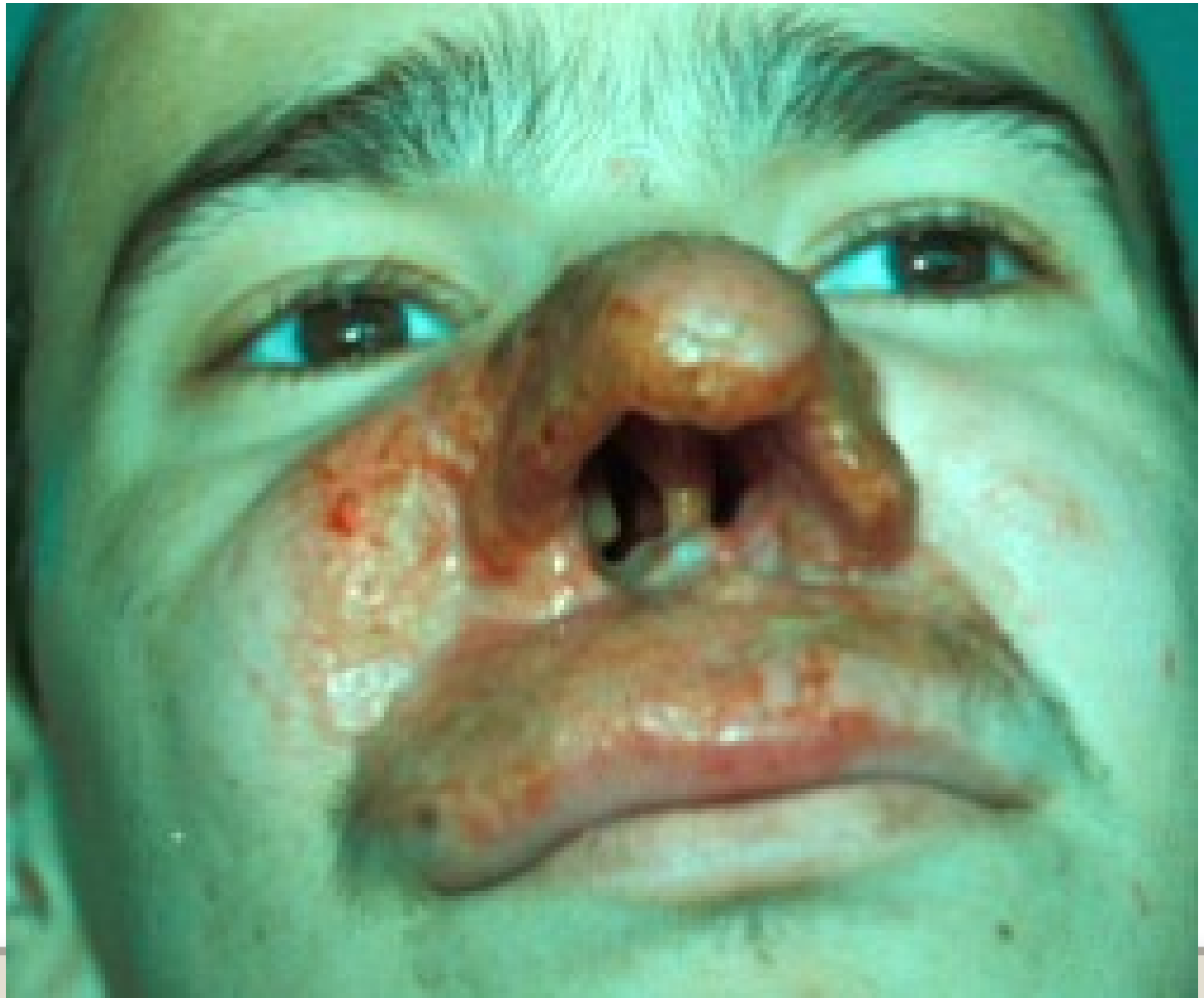
- Frequently observed after treatment in Sudan (**56%**) and in the Indian subcontinent (**20%**).
- Start with hypopigmented macular→ papules or nodules that become hyperpigmented.
- Appear in the face, upper limps , whole body.



PARA KALAZAR DERMAL :LEISHMANIASIS (PKDL)

- The interval between treated VL and PKDL is :
  - 0–6 months → Sudan.
  - 6 months to 3 years → India.
- It can occur in immunosuppressed individuals in *L. infantum*-endemic areas.
- PKDL cases are highly infectious (nodular lesions contain many parasites) and such cases are reservoir for anthroponotic infection.





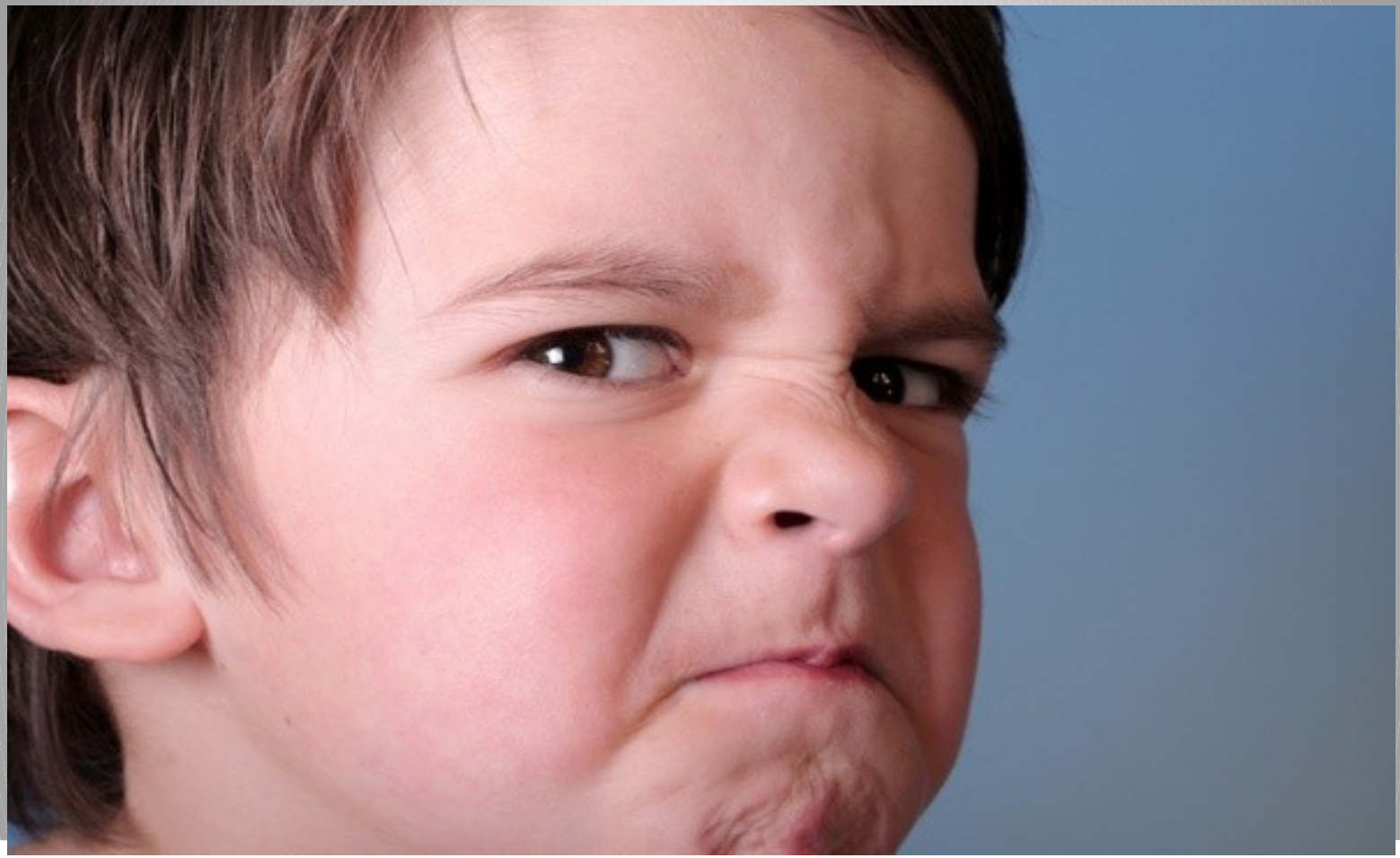
بعد سبعة أشهر من العلاج

:DIFFERRENTIAL DIAGNOSES

Chronic febrile illnesses:

- Brucellosis.
- Tropical splenomegaly (HMSS).
- T.B.
- HIV.
- Haematological malignancies.

COMPLICATONS



:COMPLICATIONS

- **Fatal (100%) if left untreated; die with**:
  - Intercurrent infection.
  - Bleeding.

- **2ºinfections**:
  - Lobar pneumonia.
  - TB.
  - Dysentry (amoebic - bacillary).
  - Cancrum oris(anaerobic infection of oral mucosa).

- **Co-infection between leishmaniasis & HIV.**

DIAGNOSIS

- **Based on:**
  - Clinical picture.
  - Epidemiological factors.
  - Non-specific parameters
  - parasite isolation &/ or Ab. detection.

INVESTGATIONS

:INVESTIGATIONS

- Specific.
- Non-specific.

:NON-SPECIFIC INVESTIGATIONS

- **CBC**:
  - _ Anaemia (Hb ≃ 4 g/dl).
  - _ leukopenia < 3000; mainly neutropenia.
  - _ leukocytosis with 2° infections.
  - _ Thrombocytopenia < 40,000.

- **Inflammatory markers:**
  - _ ↑ESR > 3 folds.
  - _ ↑CRP.

:NON-SPECIFIC INVESTIGATIONS

- **Hepatic dysfunction:**
  - ↓ Albumin.
  - _ ↑gamma globulins.

- **Formal gel test; false +ve result in:**
  - TB.
  - HMSS.
  - _ Lepromatous leprosy.
  - _ Trepansomiasis.

:SPECIFIC INVESTIGATIONS

- **Parasite demonstration**
- **Serology.**

Parasite :demonstration

- Peripheral blood; in india.
- L.N. Aspiration (66%).
- Bone marrow (80%).
- Spleen aspiration >95%.
- By PCR.

Precautions for splenic aspiration:

- Platelets >50,000.
- Not huge splenomegaly.
- Co-operative pt.
- Leukaemia excluded.

:SEROLOGY

- If parasite scanty:
  - DAT; Direct agglutination test (>80%).
  - ELISA.
  - Western blot.
  - Latex agglutination test (Katex test); detection of Ag in urine (86%).

:Leishmanin skin test (LST)

- Similar to tuberculin test.
- Detect delayed immune response.
- -ve in recent infection.
- Indicate exposure to parasite .
- +ve result 3-6 month after exposure.

DAT Vs LST

INTERPRETATION	DAT	LST
Recent infection	+ve	-ve
Past Hx. of Kala-azar	+ve	+ve
Exposure	-ve	+ve
No infection , No exposure	-ve	-ve

MANAGEMENT

- Supportive:

  - Nutritional.
  - Blood transfusion.
  - Treatment of secondary infection.

- Specific treatment.

TREATMENT

SPEECIFIC TREATMENT:

- Pentavalent Antimony Compounds.
  - Na stibogluconate (Pentostam®).
  - Meglumine antimonate (Glucantime®).
- Liposomal amphotericin B.
- Pentamidine.
- Miltefosine.

:Na stibogluconate (Pentostam®)

- Inhibit ATP synthesis in the parasite.
- Poorly absorbed → IM/ IV.
- **Dose:** 20 mg/kg/day for 28 days.
- **Side effects:**
  - Intolerance ; hypersensitivity, fever , shivering , skin rash , myalgia & arthralgia.
  - Toxicity; - Anemia.

.liver enzymes - ↑

.Pancreatitis (↑ S. Amylase) -

.Cardiotoxic : - ECG changes(T, ST, QT) -

Sudden death with big -

.dose

Visceral Leishmaniasis

- Liposomal amphotericin-B (AmBisome®) is the drug of choice
  - 3 mg/kg per day on days 1-5, day 14 and day 21
- Pentostam® is an alternative therapy
  - 28 days of therapy is required
- Although AmBisome® is widely available, the difficulty of accurate diagnosis and the potential severity of visceral infection suggest possible patients be referred to the Leishmania Treatment Center at WRAMC for maximal diagnostic efficiency

Vaccine

- There is as yet no effective vaccine for prevention of any form of leishmaniasis.
- first generation vaccine was prepared using whole killed parasites combined or not with BCG.
- **Live**: including new genetically modified constructs
- **1st generation vaccines**: whole killed parasite with/without adjuvants or fractions of the parasite
- **2nd generation vaccines**: recombinant proteins, DNA vaccines & combinations

Na stibogluconate :(Pentostam®)

- **Precautions:**
  - Before treatment : - Correct anemia.
.Baseline ECG -
  - Bed rest for at least 1 hr after the dose
).to prevent arrhythmia & sudden collapse (

- **Assessment of response to treatment ;**
  - Fever subside (5-7 days).
  - Hematological indices return to normal (1-2 month).
  - LST become +ve (3-6 month).
  - BM –ve in HIV pt.

Na stibogluconate :(Pentostam®)

- **In case of failure of response :**
  - Resistance (60% of cases in india).
  - HIV co-infection.
  - Other disease.

Liposomal Amphotericine B :(AmBisome®)

- Cytotoxic antifungal drug
- Treatment of choice in USA and India .
- **Used for**: kal-azar , PKDL.
- **Dose** : _ Total dose of 7.5 mg/kg over 6day(India). !!! ?
  _ Total dose of 21mg/kg (Mediterranean, Brazelian VL).
- **Side effect:** Nephrotoxic.

:Pentamidine

- Used mainly for PKDL & Trepansomiasis.
- **Dose**: 3-5 mg/kg (IM).
- **Side effect**: hypoglycaemia.

:Miltefosine (Impavido)

- First oral treatment.
- Cytotoxic drug for skin deposits from Ca breast. locally
- **Dose** :one tab daily for 30 days.
- good tolerance (GI upset).
- Cure rate up to 95%.

:UPDATES IN MANAGEMENT

- New antimonial compound (**Urea stibamine**) for treatment of Kala-azar & PKDL.
- Broad spectrum antibiotics (Paromomycin) approved for treating Kala-azar in India.
- Single dose adminstraion of liposomal amphtericin B.
- Combination drug therapy (currently under investigation):
  - ↓ Doses of drugs used.
  - ↓ S.E & toxicity.
  - ↓ Resistance.
  - Cost effective.

ALTERNATIVE TREATMENTS

- Pentamidine
- Amphotericin B
- Allopurinol
- Ketoconaole
- IFN gamma
- BCG
- Rifampin
- Dapsone
- Paromomycin
- Clotrimazole
- Heat
- Cautery/exicion
- IL antimony
- Cryo
- "Shiraz" cream

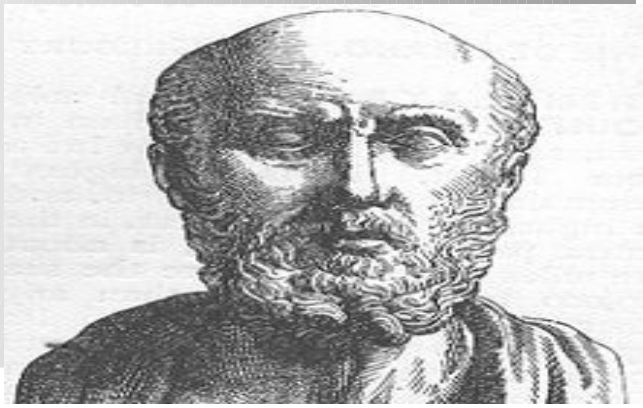
DISEASE CONTROL

Control:

- **Vector control**
- **Reservoir control**
- **Treatment of active cases (mass treatment)**
- **Avoid area of contacts & time of activity.**
- **Vaccination..!!**

I promise that medical knowledge will be used to benefit people’s health. Patients are my first concern. I will listen to them, and provide them the best care I can. I will be honest, respectful, and compassionate towards all.

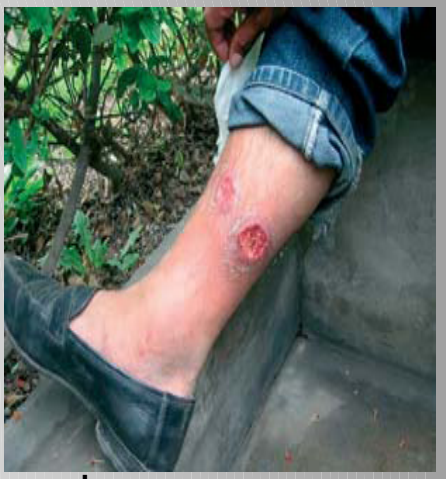
THE NEW HIPPOCRATIC OATH




THANK YOU

:Cutaneous leishmaniasis

- Has variable clinical presentations and prognoses.



- Different species of Leishmania infect the macrophages in the dermis :
  - *Leishmania tropica.*
  - *Leishmania major.*
  - *Leishmania aethiopica.*
  - *Leishmania mexicana.*
- The patient generally presents with one or several ulcer(s) or nodule(s) in the skin.
- The ulcers heal spontaneously — although slowly — in immunocompetent individuals, but cause disfiguring scars.

Muco-cutaneous leishmaniasis:

- Progressively destructive ulcerations of the mucosa, extending from the nose and mouth to the pharynx and larynx.
- Lesions are not self-healing.
- Usually seen months or years after a first episode of cutaneous leishmaniasis, when the macrophages of the naso-oropharyngeal mucosa become colonized.
- *Leishmania braziliensis* is responsible for most of the cases .