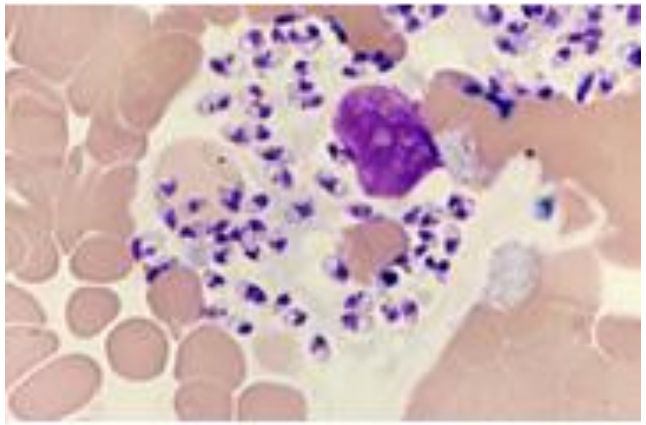
Leishmaniasis



Jarmila Kliescikova, MD

Leishmania spp.

Kinetoplastida

- More than 20 pathogenic species
- Transmission: **inoculative**
- Amastigotes multiply **intracellulary**

Disease

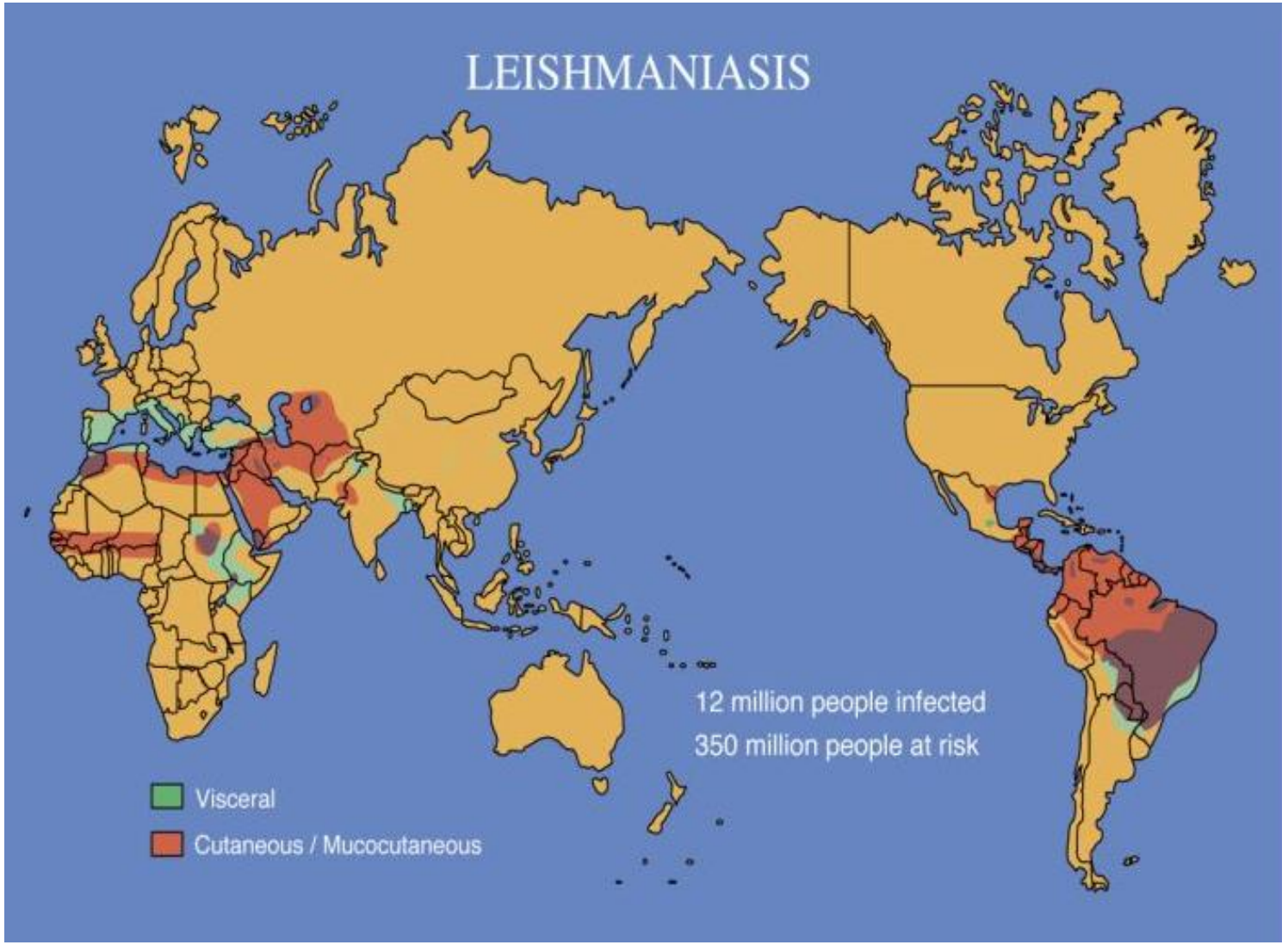
- **Cutaneous**
- **Mucocutaneous**
- **Systemic**

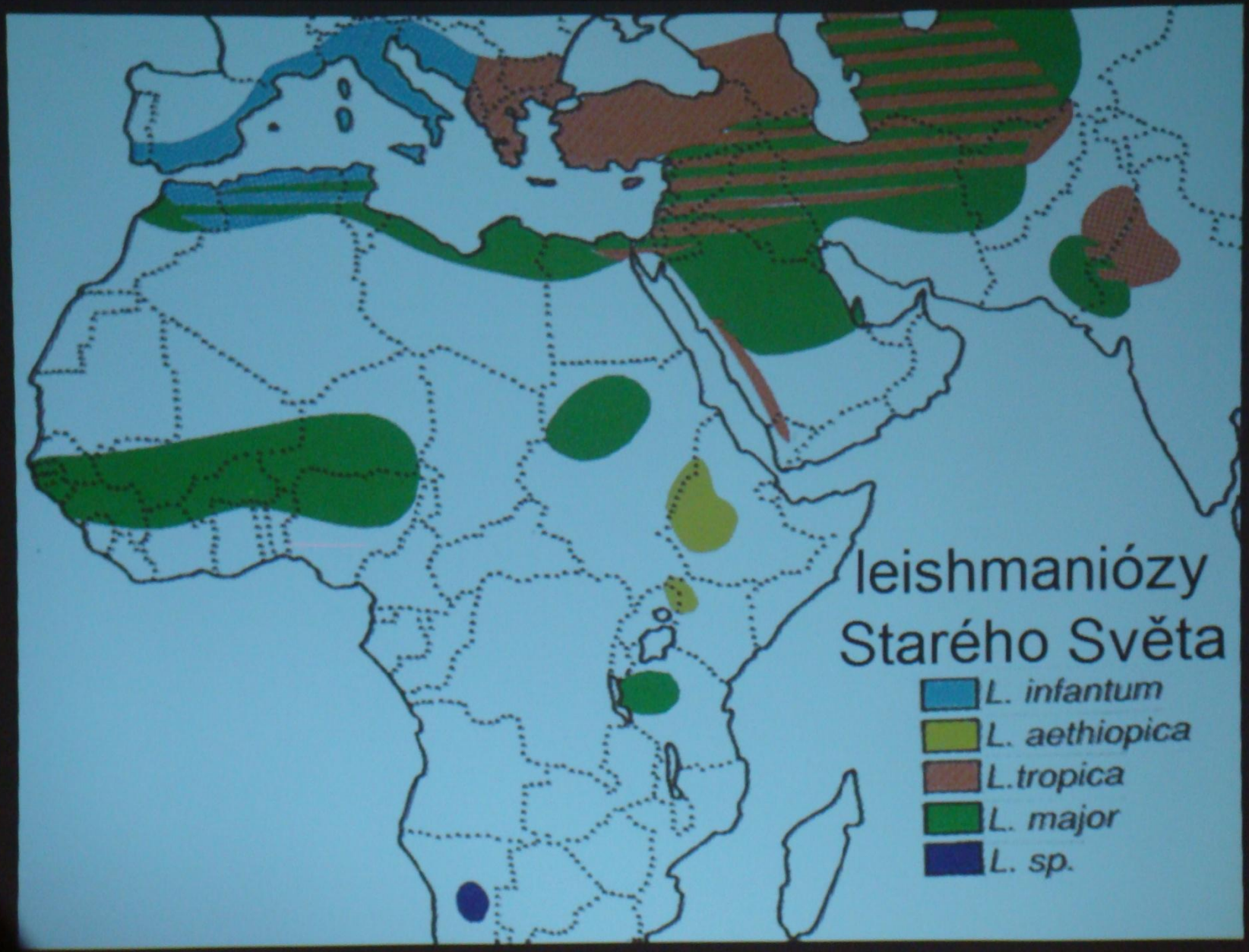
Epidemiology

- Distribution: **tropical and subtropical countries**
- 200 mil. of people at risk
- Endemic in 82 tropical and subtropical countries
  61 countries of Old world
  21 countries of New world
- Higher prevalence in male (2:1)

- 0,5 mil cases of visceral leishmaniasis per year
- 1 – 1,5 mil. Cases of cutaneous leishmaniasis per year
- 2 mil. Clinical infections per year
- **Co-infection with HIV** – new opportunistic inf., increasing incidence

Distribution




leishmaniózy
Starého Světa
L. infantum
L. aethiopica
L.tropica
L. major
L. sp.

Mortality

Localised cutaneous infection

Spontaneous recovery possible after 2-6 months

Mucocutaneous infection

chronic, progressive, highly fatal if not treated

Visceral infection

Untreated - mortality 79-95%; treated 5%

Life cycle

- **Reservoir:**

Old world:

dogs, rodents, foxes..

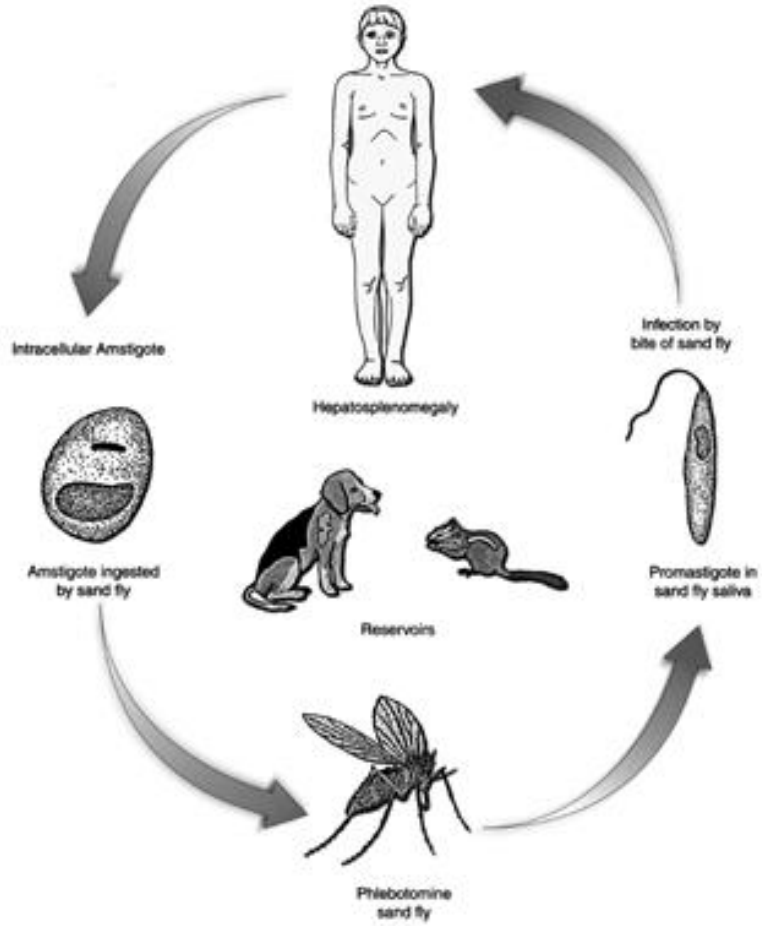
New world:

rodents, sloth, opossum..

- **Vector:**

Phlebotomus/Lutzomia:

In blood intracelullary in makrophages



Animal Reservoirs

Dog

Nile grass rat (*Arvicanthis niloticus)*

Spiny mouse (*Acomys*)

Jackal (*Canis aureus*)

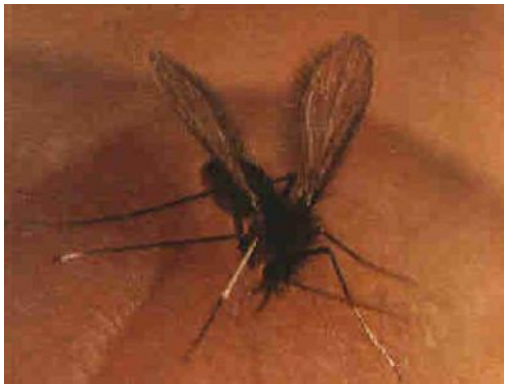
Serval (*Felis Serval)*

Phlebotomus/Lutzomia

Multiplication

- rodent burrows, compost, fallen leaves in the woods
- Dependent on temperature and rainfall

- Transmission by **females** in upper part of the respiratory systém (not salivary glands)
- Biting mainly at **night**
- Infected mosquitos survive about 30 days



Aedes spp vs *Phlebotomus* spp. vs *Culex* spp.

http://www.imr.gov.my/org/idrc/19.jpg

Typical site of multiplication of phlebotomus transmitting *L. Major*

Pathogenesis I.

1. **introduction** to the skin

2. Release of **inflammatory and vasodilatative subst.**

3. **multiplication** in cells of RES (monocytes, macrophages, histiocytes, Kupffer cells, reticuloendothelial cells of spleen)

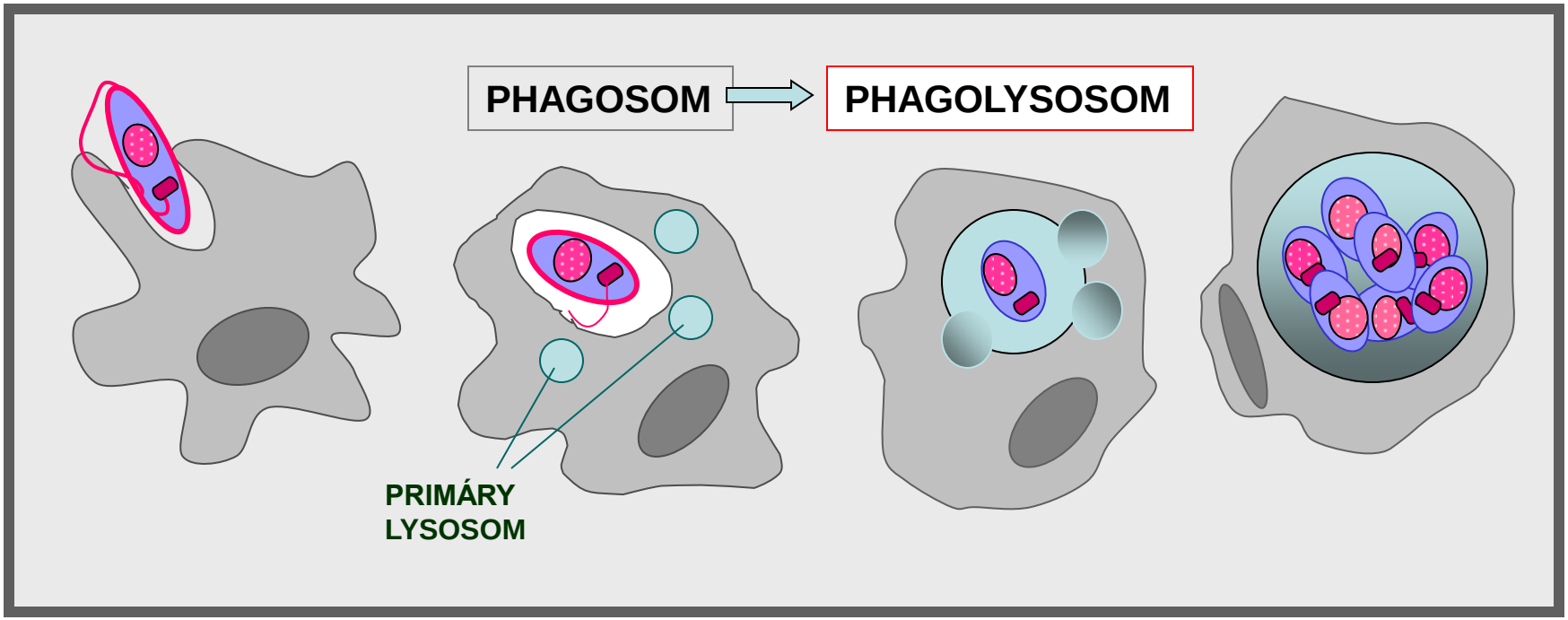
A) **Destruction by IS**
person becomes immune

B) **local infection** – followed by eradication/dissemination

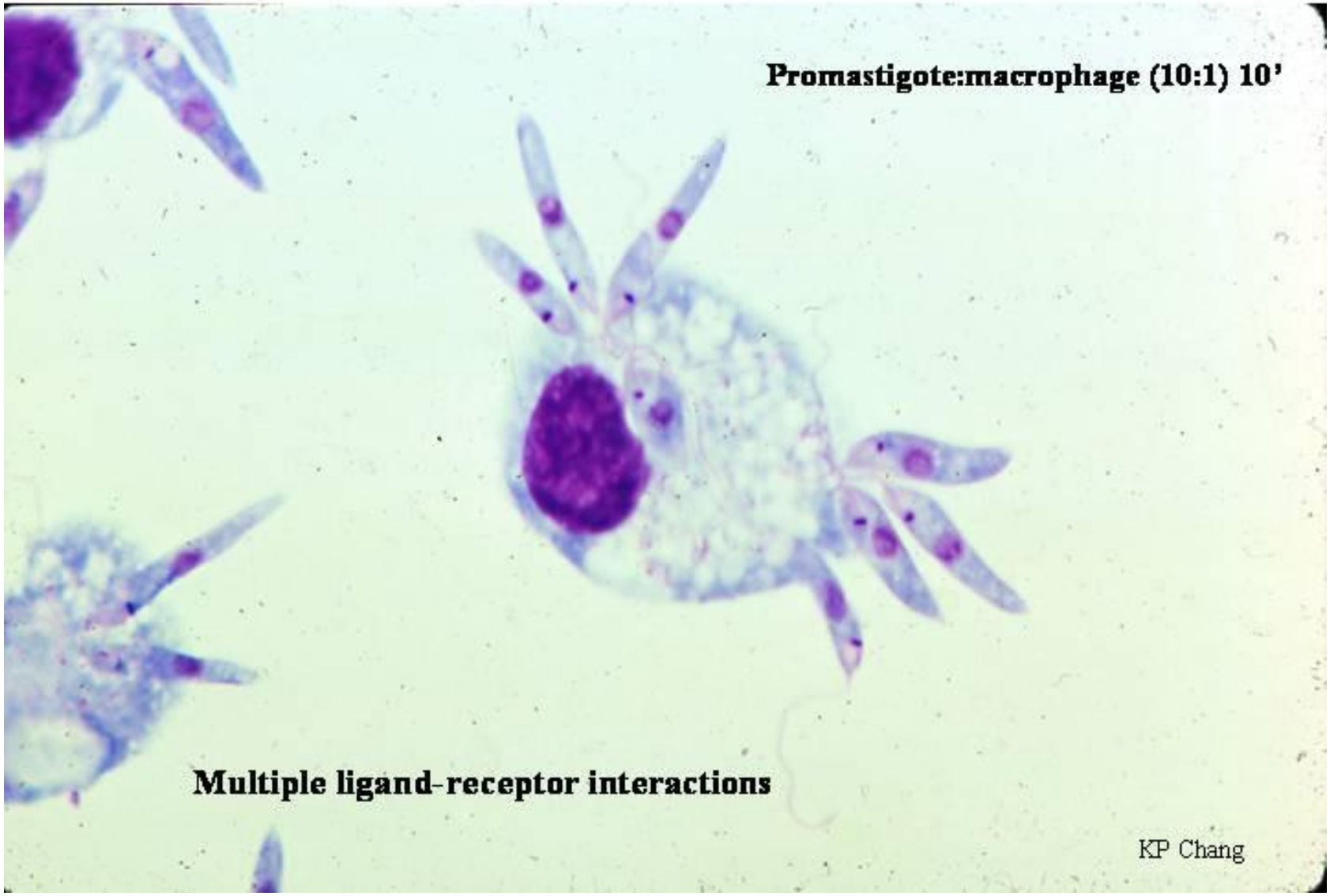
C) **Haematogenous spread** to visceral parts, skin or oronasal mucosa,

ACTIVE ENDOCYTOSIS

ACTIVITY OF PROFESSIONAL PHAGOCYTIC CELLS



Leishmania donovani promastigote-binding to macrophage

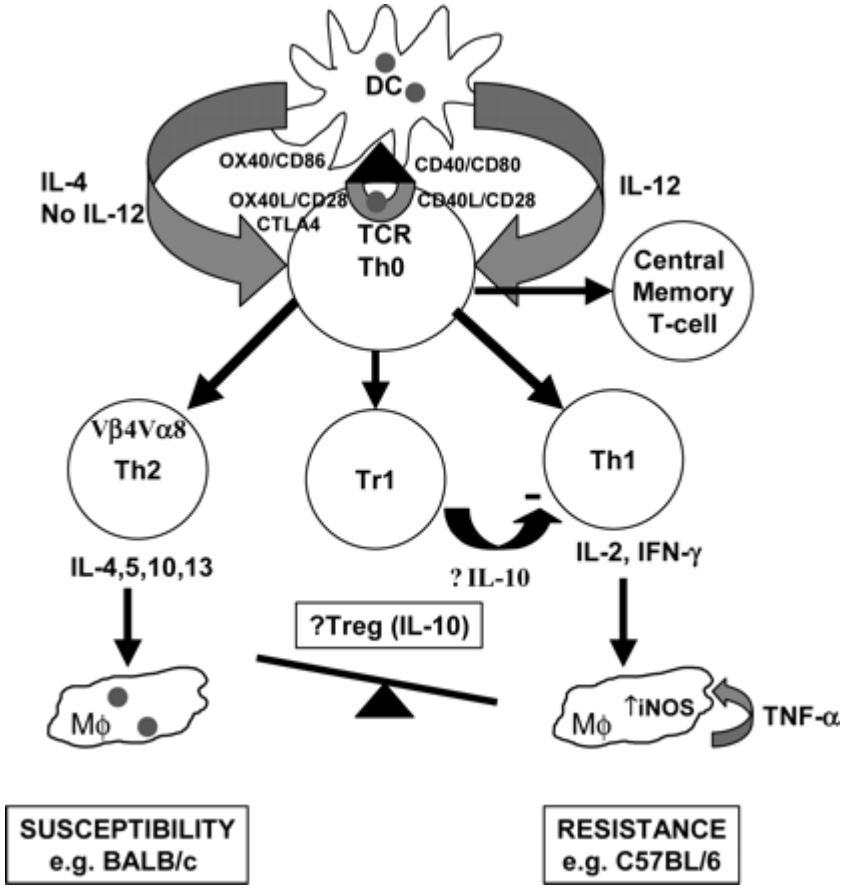


Intracellular survival is dependent on specific immune response

- **Th1: control of the infection**

  (oxidatory burst; elimination of leishmanias)
- **Th2: establishment of the infection and visceralisation**

  (increased level of Ab)



Cutaneous leishmaniosis

- ***L. major, L. tropica***
- IP: several days up to several months

Primary leasion

(chronic, non-dolorous, solitary or multiple)

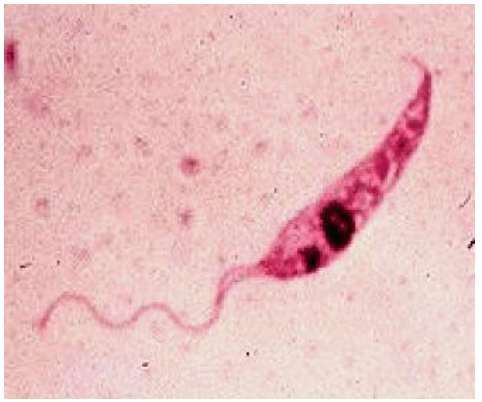
face, neck, limbs

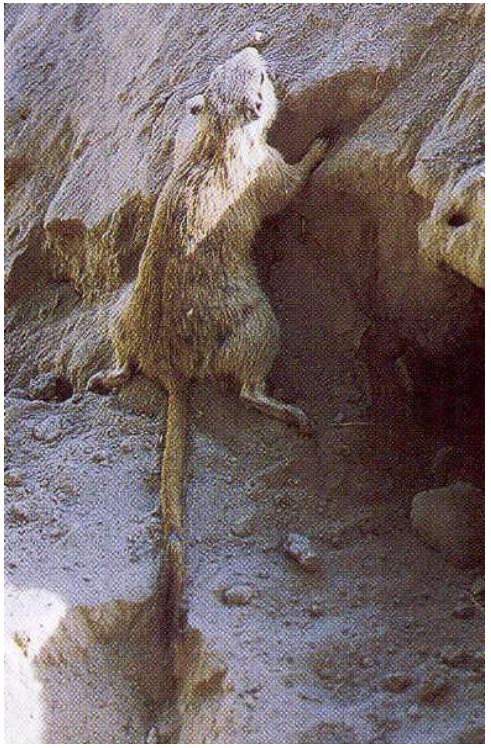
erythematous nodulus – eschar – ulcus

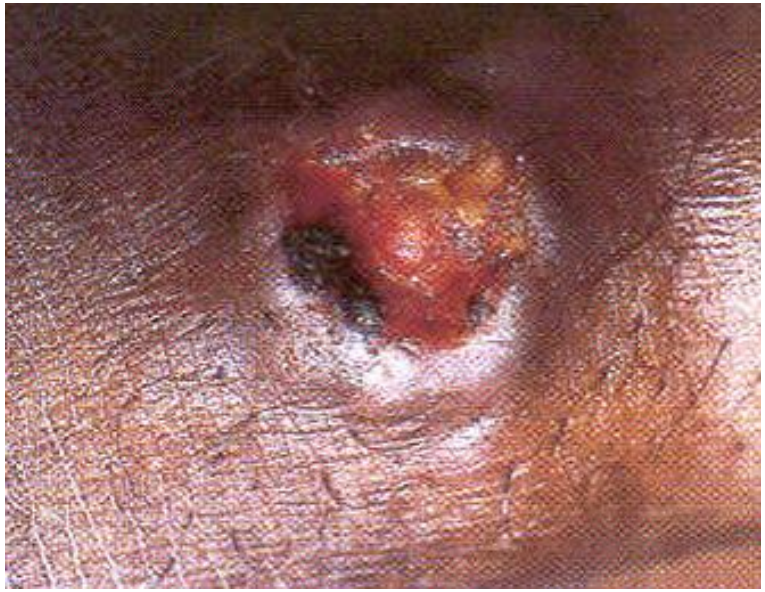
After healing remains **invaginative scar**

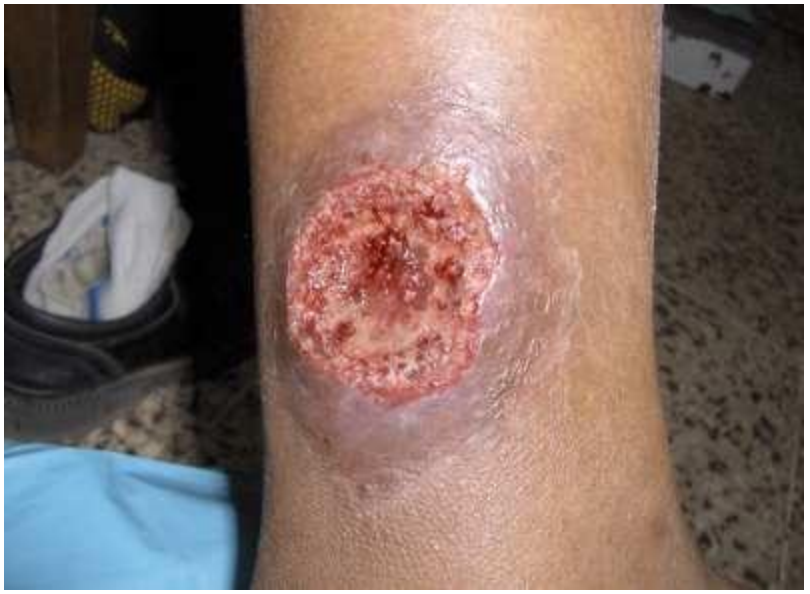
Leishmania Major

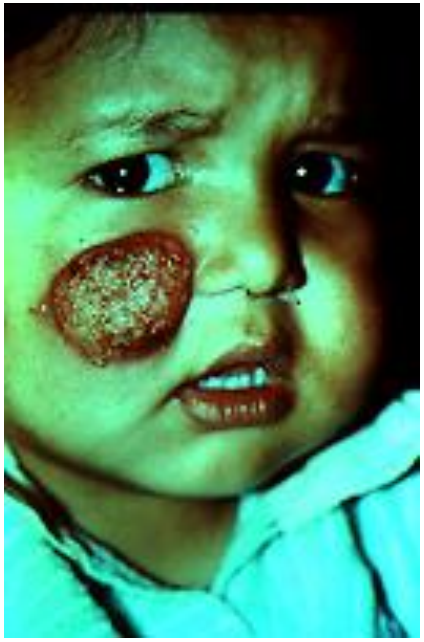
- **IP:** 1 week to 2 months
- **Productive ulcus** with elevated borders
- **Grows 3-6 cm in 3-5 months**
- The limbs are most commonly affected
- Does not heal spontaneously

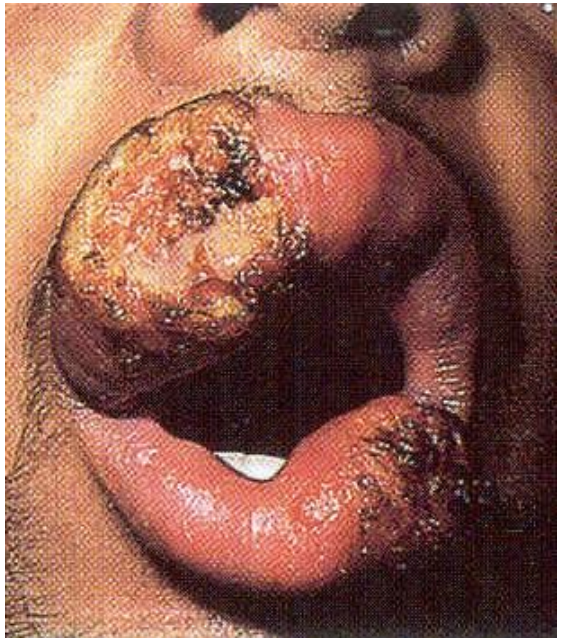


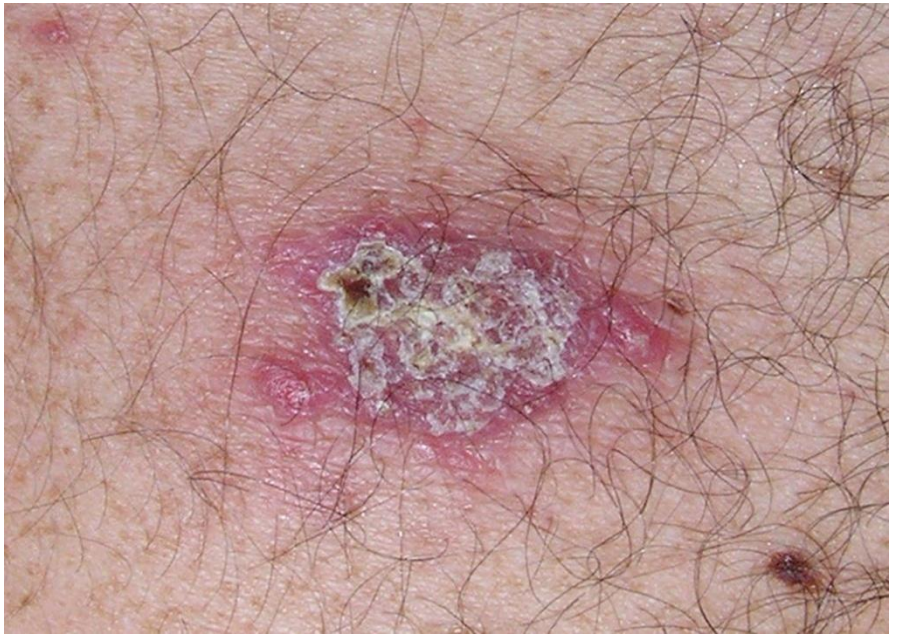






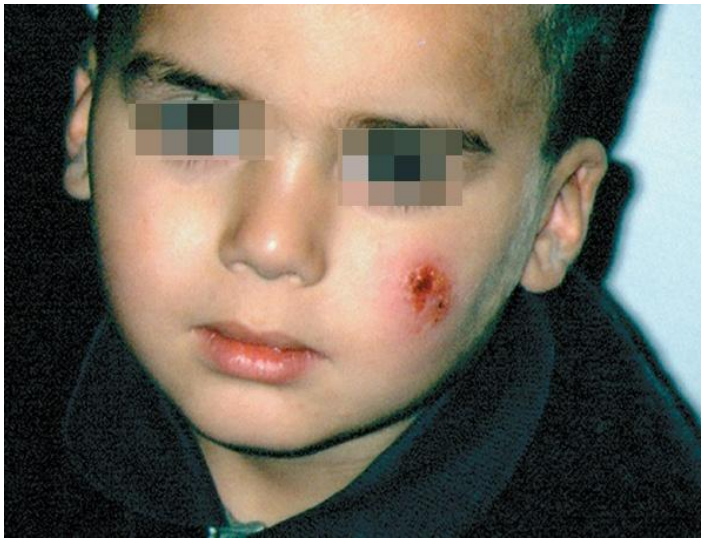


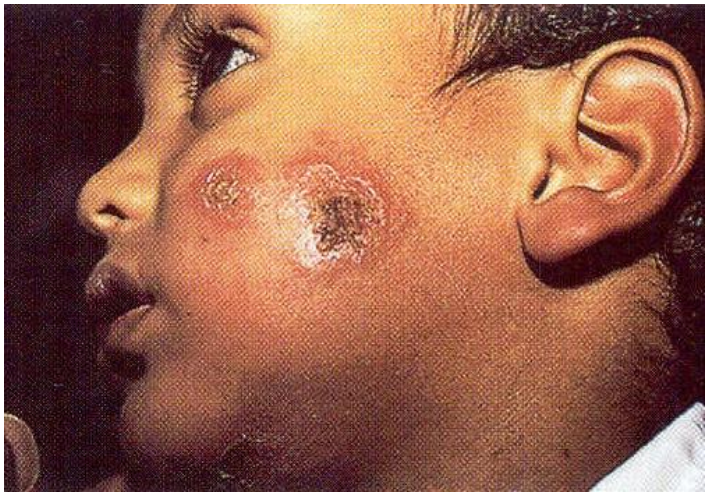


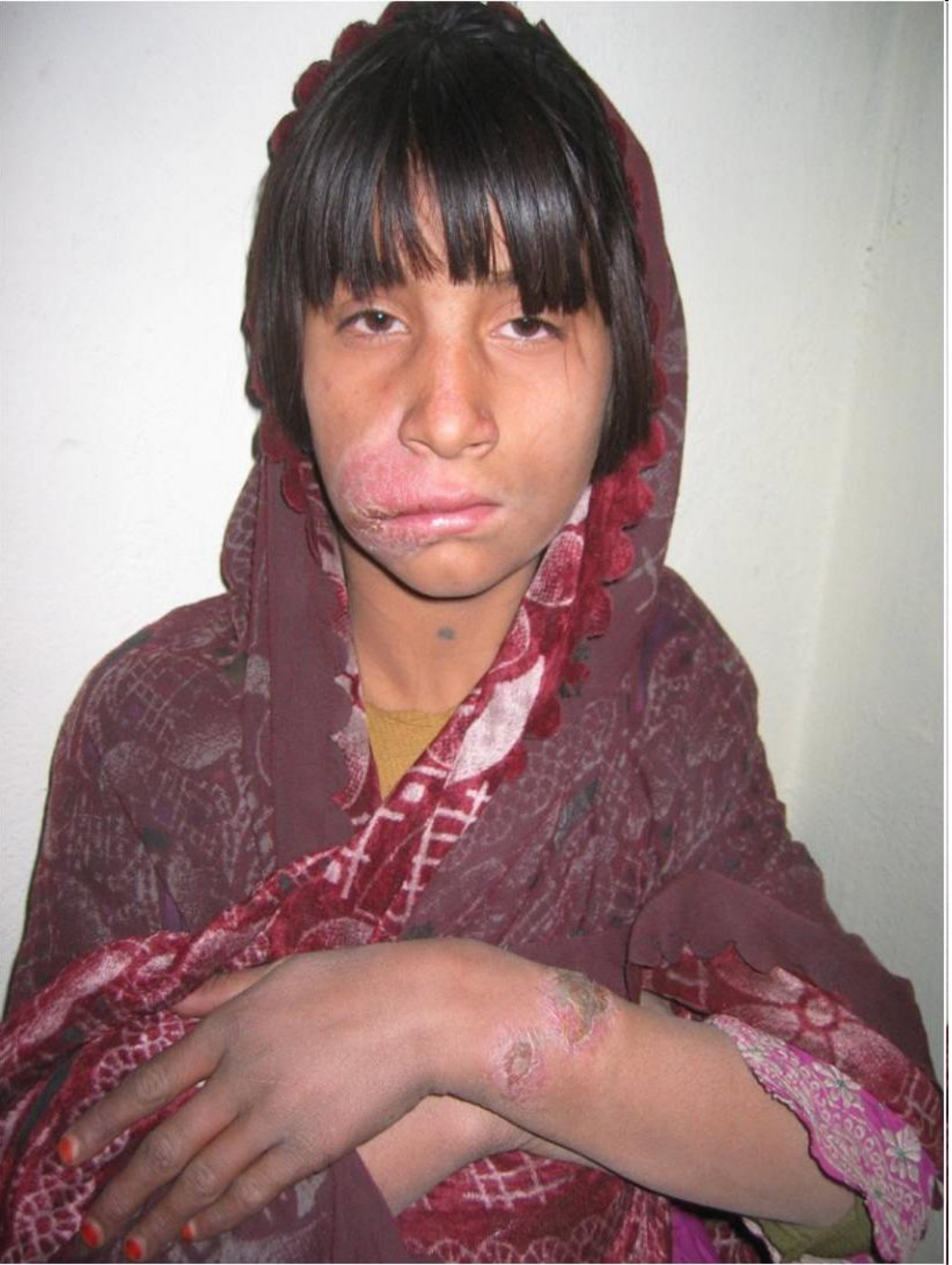


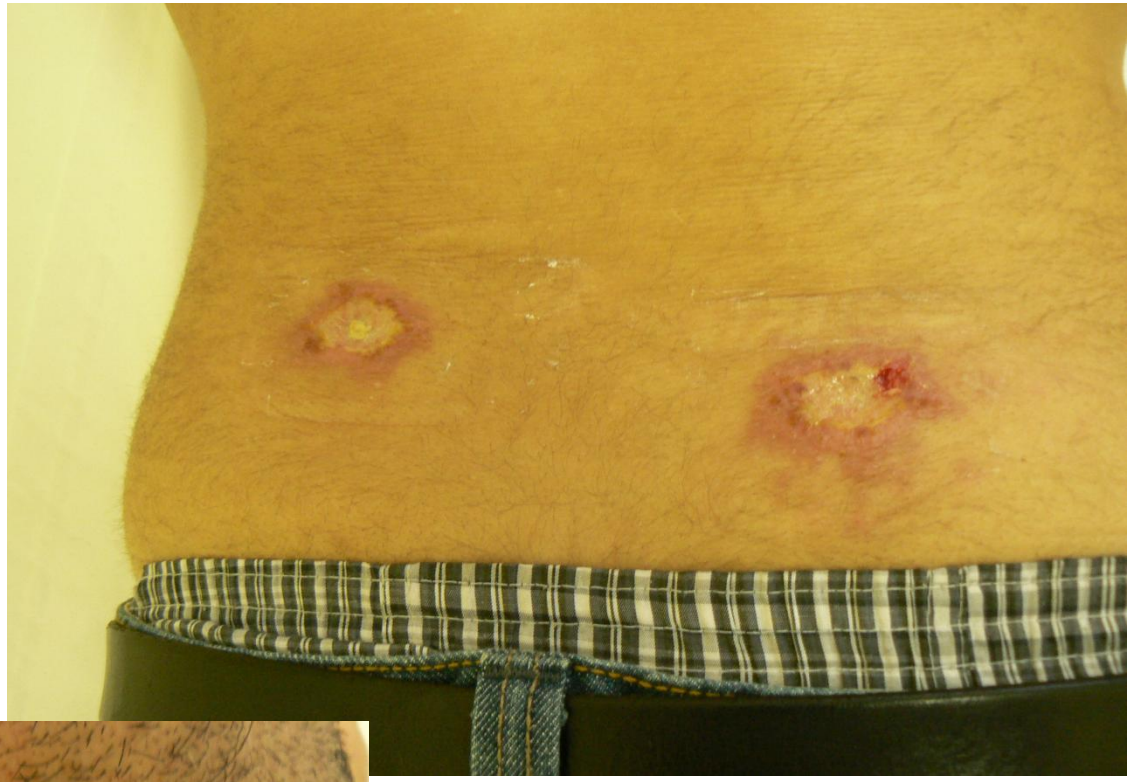
Leishmania tropica

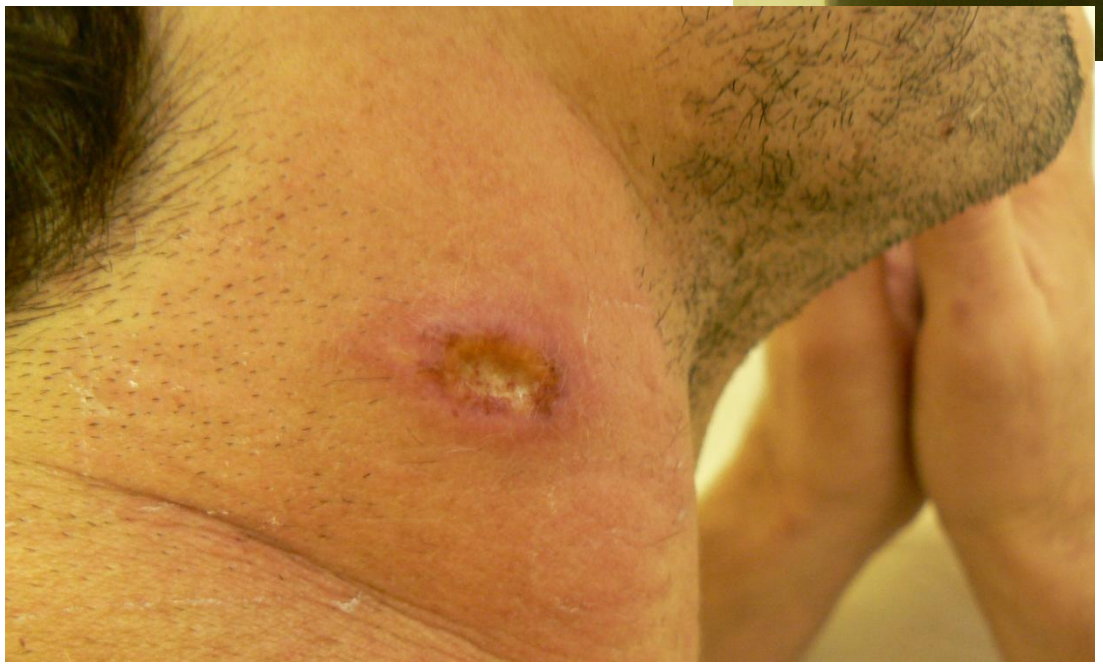
- IP: 2-4 months
- **Dry ulcus**
- Satelite lesions
- Grows 1-2 cm in 8-12 months
- Lesions mostly on face
- Could heal spontaneously





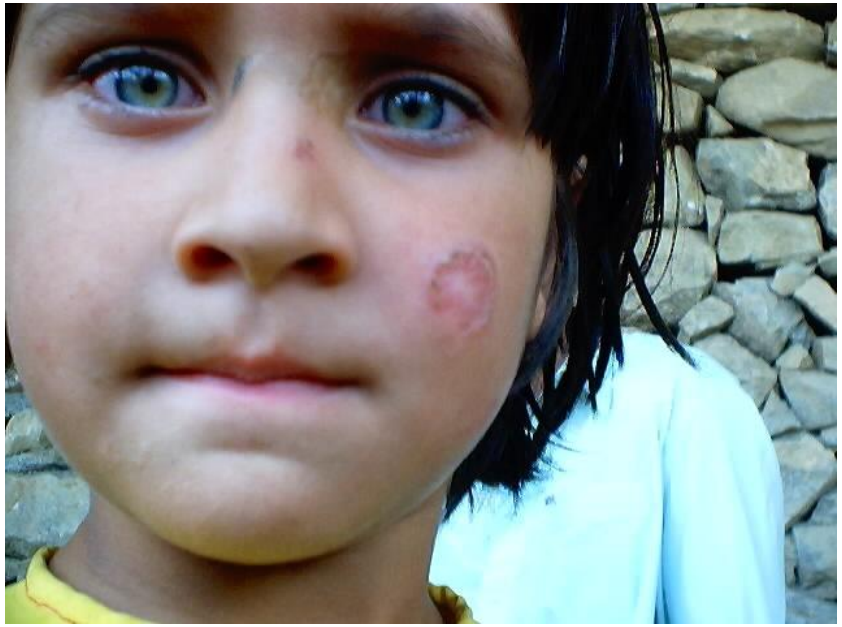


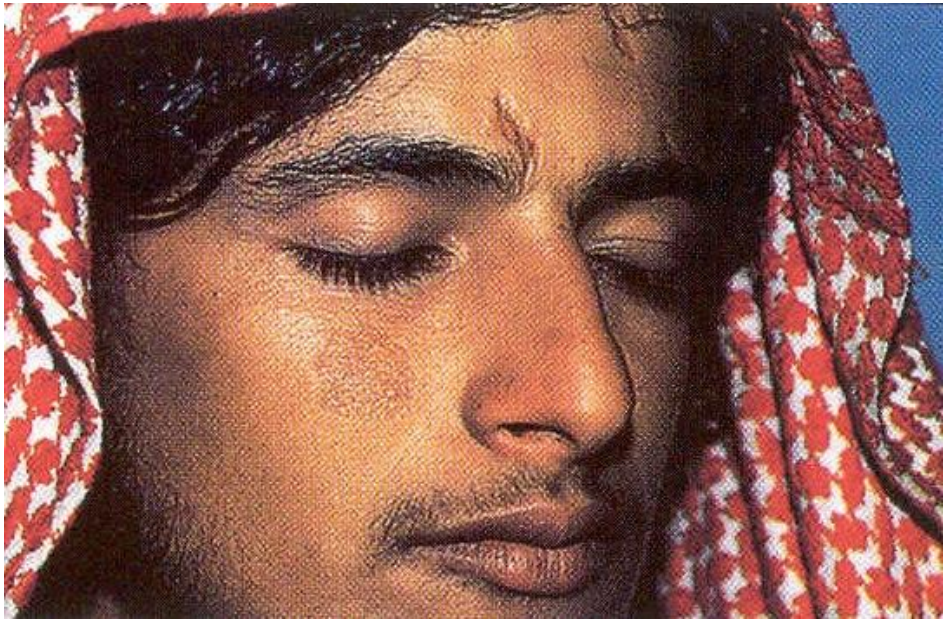




Healed infection of *L. tropica*

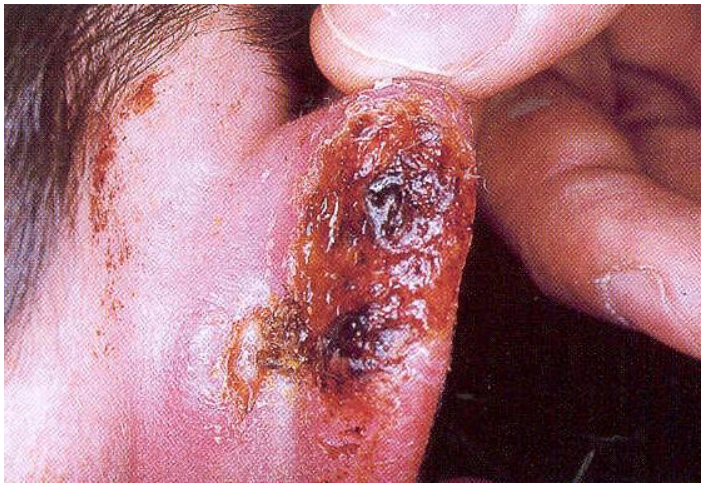
Leaves **scarification**

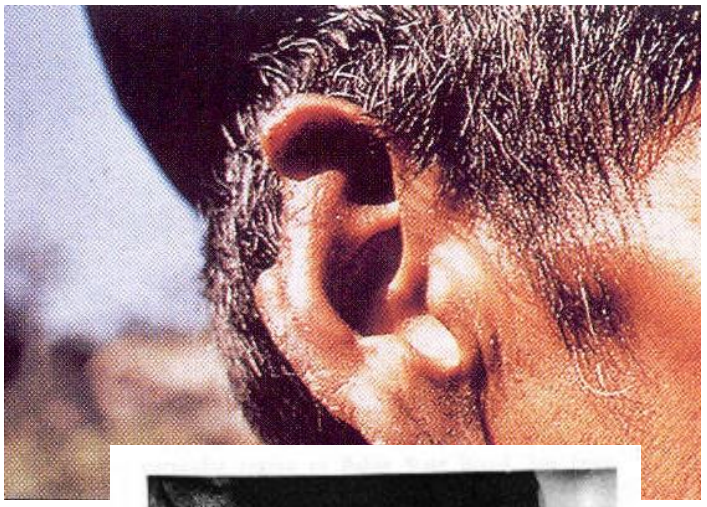




Leishmania mexicana

- Leasions located in the face and ear lobe
- Healing in 6-8 months
- If located at the ear lobe, continuous destruction of the cartilage – **Chickleros ulcer**





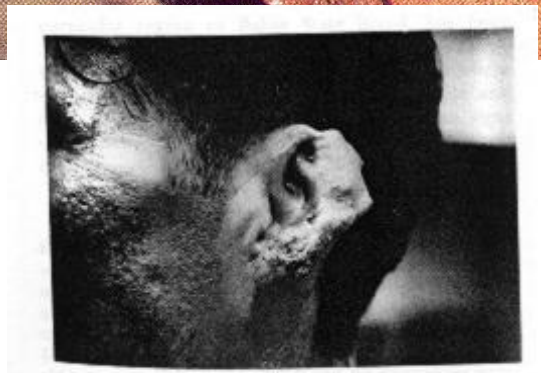


Fig. 13.9 'Chiclero's ulcer', due to *L.* (*L.*) *mexicana*. Almost total destruction of the the external ear in a chiclero from Belize with an infection of many years duration. (From Lainson and Strangways-Dixon 1963.)

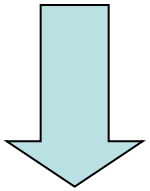
Mucocutaneous leishmaniasis

- *L. brasiliensis, panamensis, guyanensis*

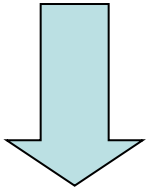
Primary skin leasion (usually 1),
often legs; spontaneous recovery
Secondary mucosal infection
Within 2 years (15% patients no primary lesion)

- Most commonly affected nasal mucosa,
  1/3 cases: pharynx, larynx

Nasal mucosa



Cartilage → perforation of the nasal septum



Mouth mucosa (palate and lips) → perforation of palate

Symptomatology

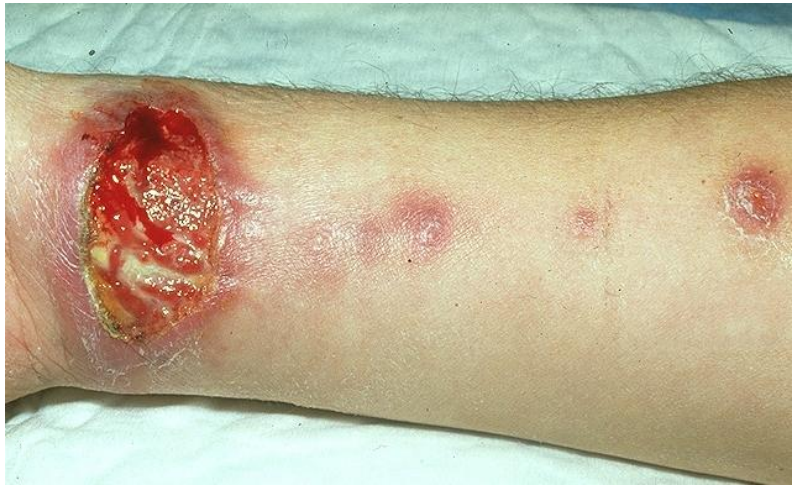
- Nasal obstruction, epistaxis
- Local lymphadenopathy

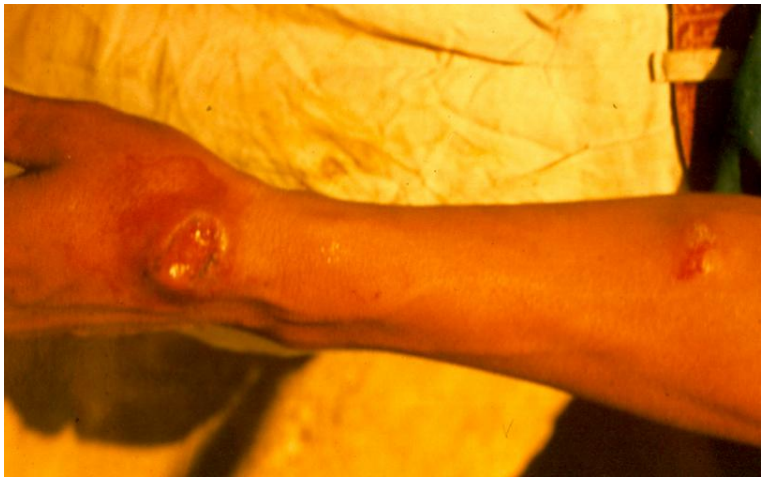
Two different forms:

hypertrofic: Espundia

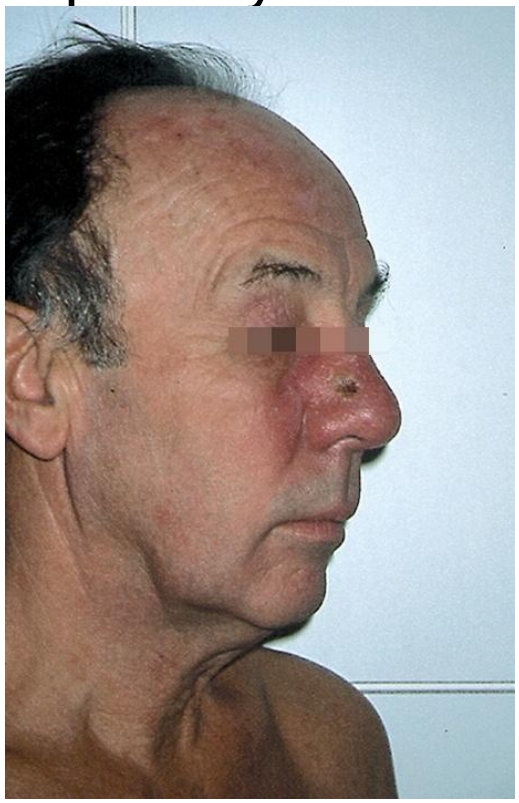
ulcerative

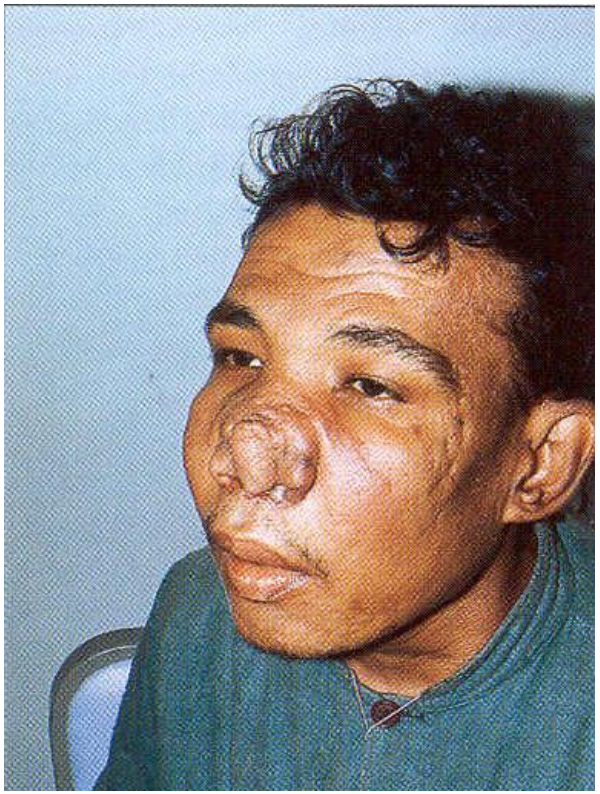
- Not treated is fatal due to the secondary bacterial infection



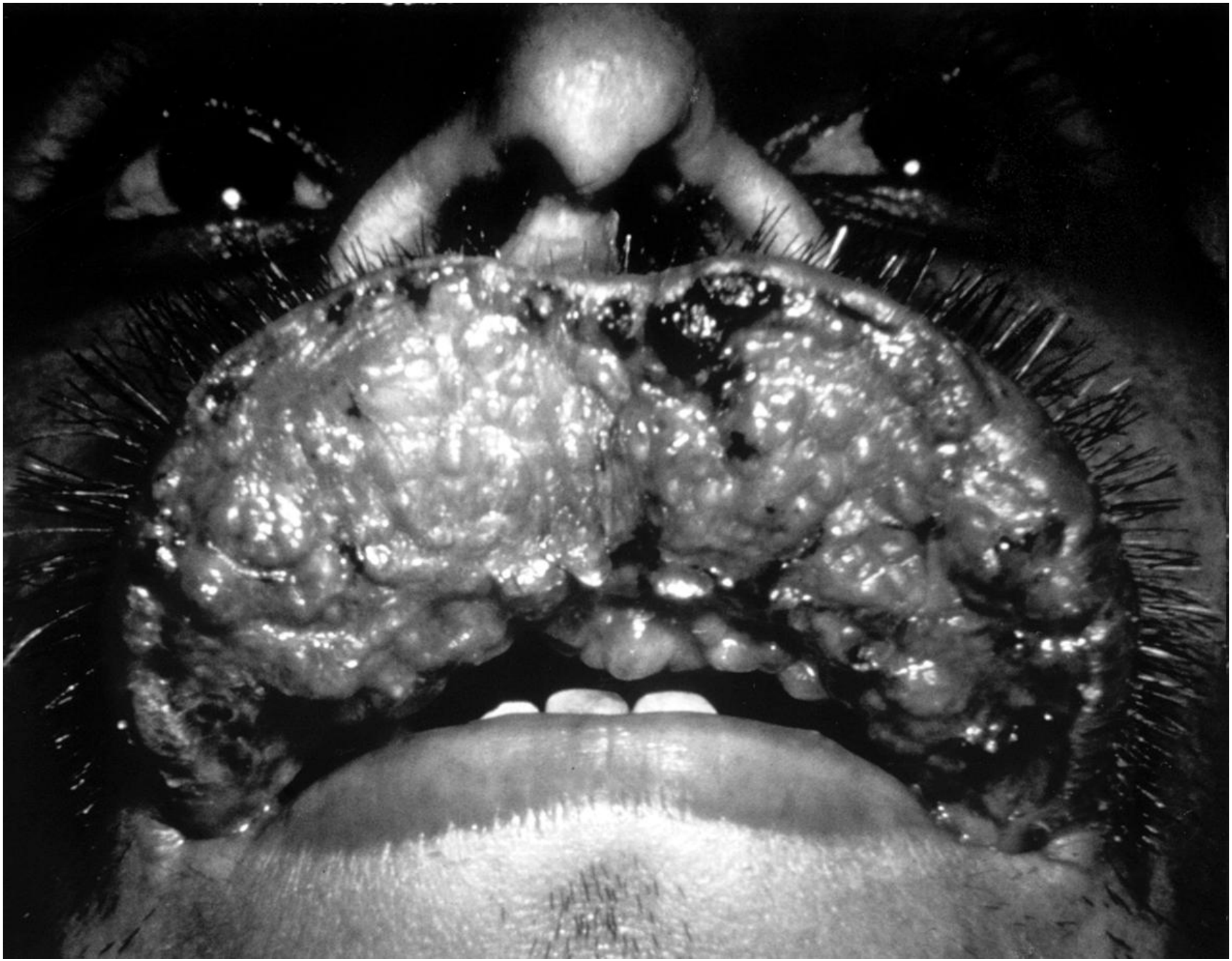


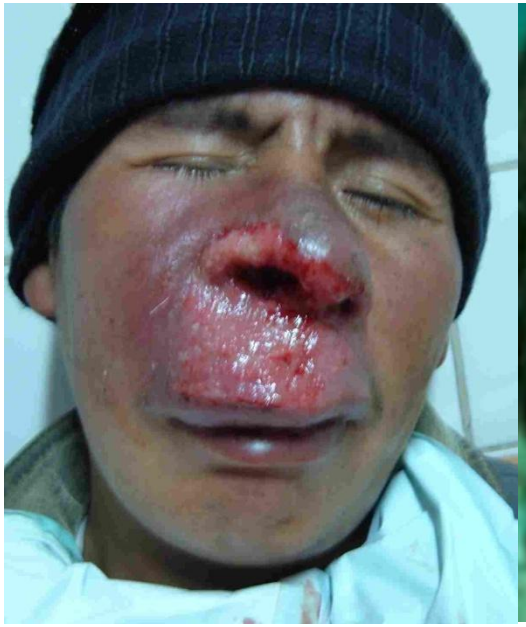
primary lesions

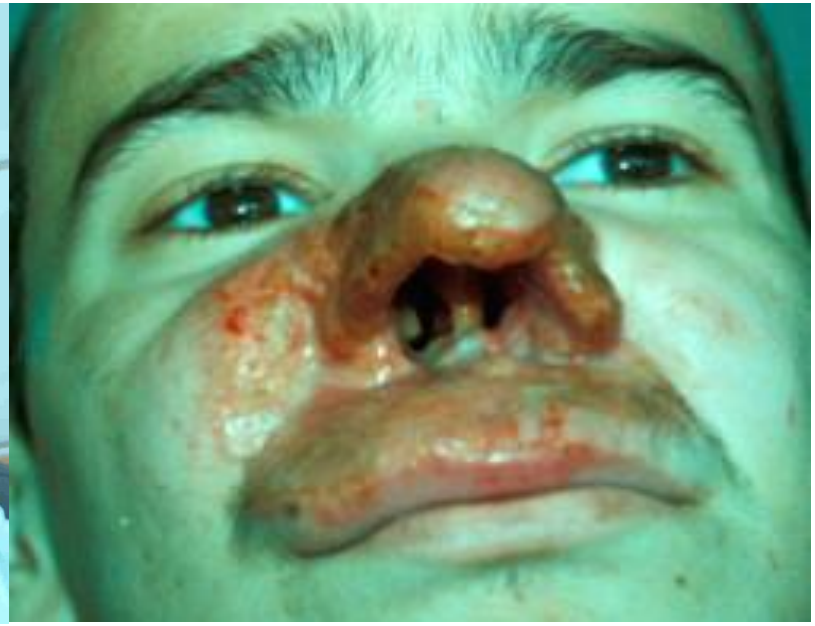




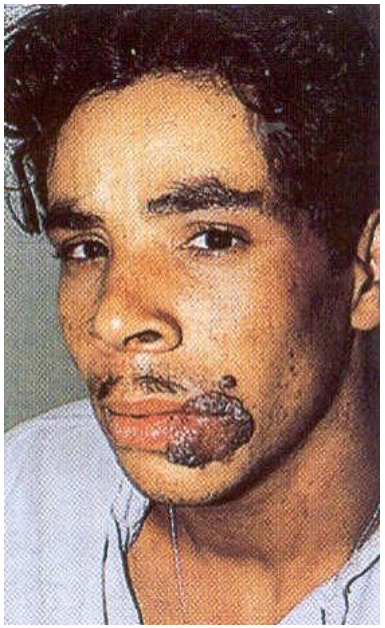
secondary lesions
(early stage)



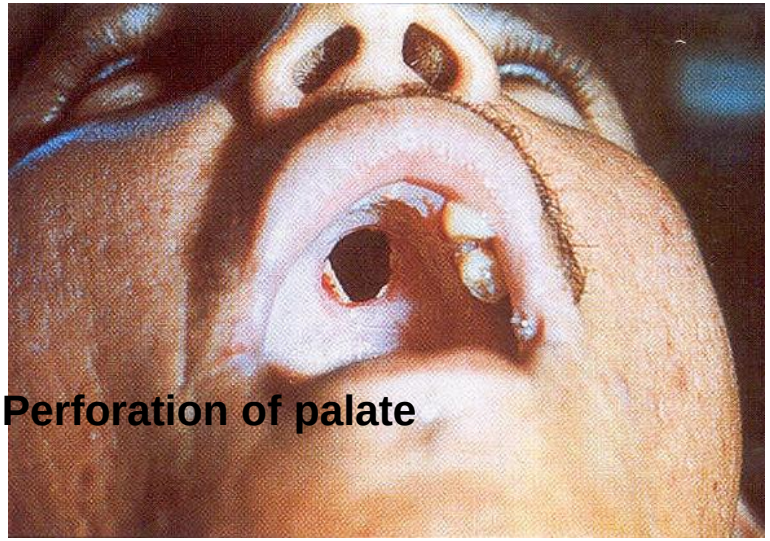


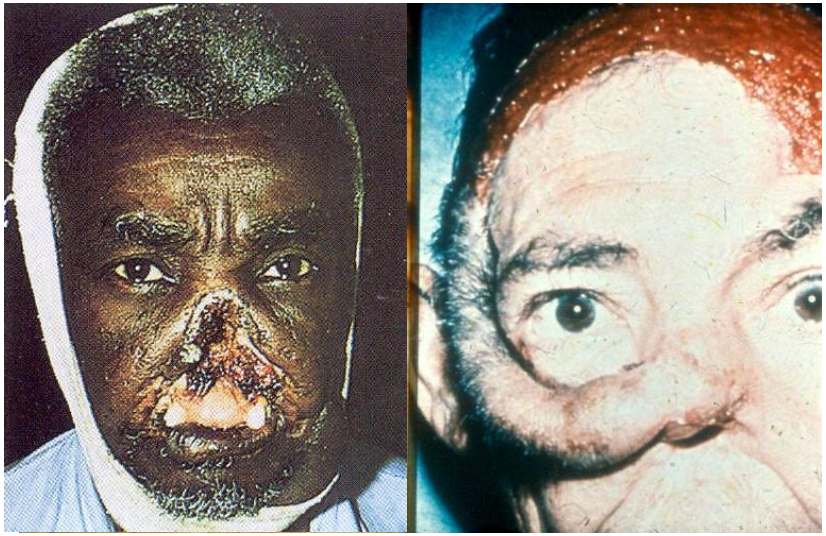


Sec. lesions (late stage)



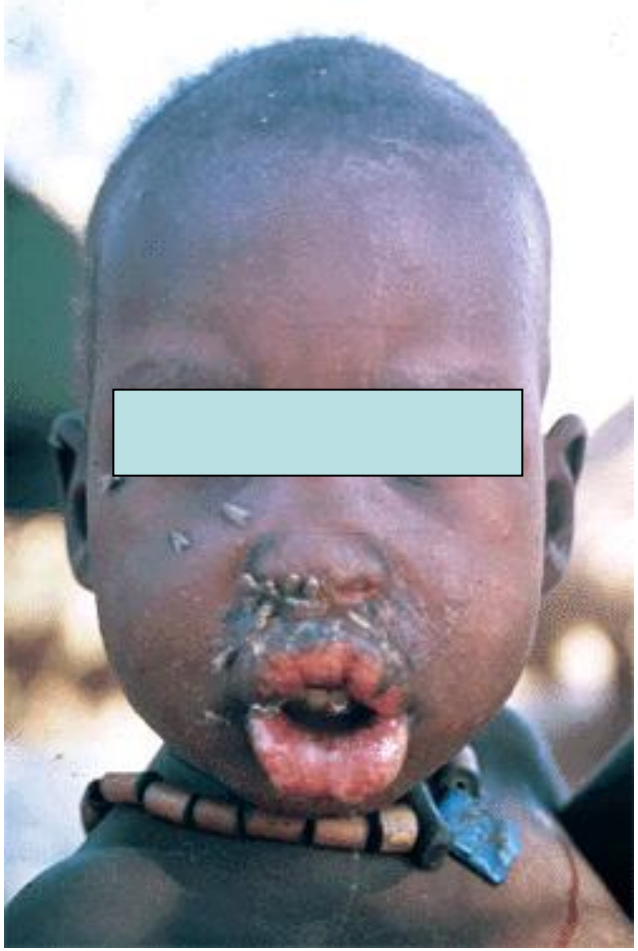
Espundia (early stage)





Espundia (late stage)

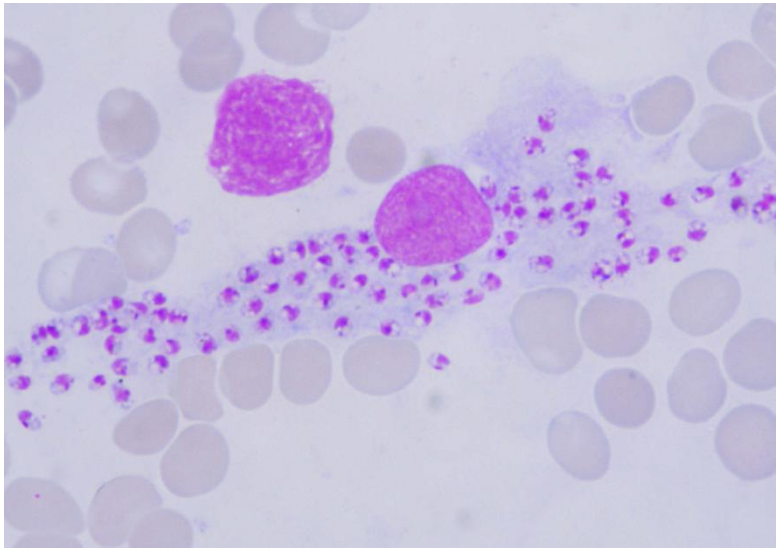
MUCOCUTANEOUS LEISHMANIASIS is believed to be found in some African countries such as Sudan



Association with HIV positivity?

Visceral leishmaniasis

- Caused by: ***L. donovani,*** *infantum, chagasi*
- Chronic disease
- Kala-azar, „black fever“



- **Failure of the immune response** ⇨ dissemination into spleen, bone marrow and lymph nodes

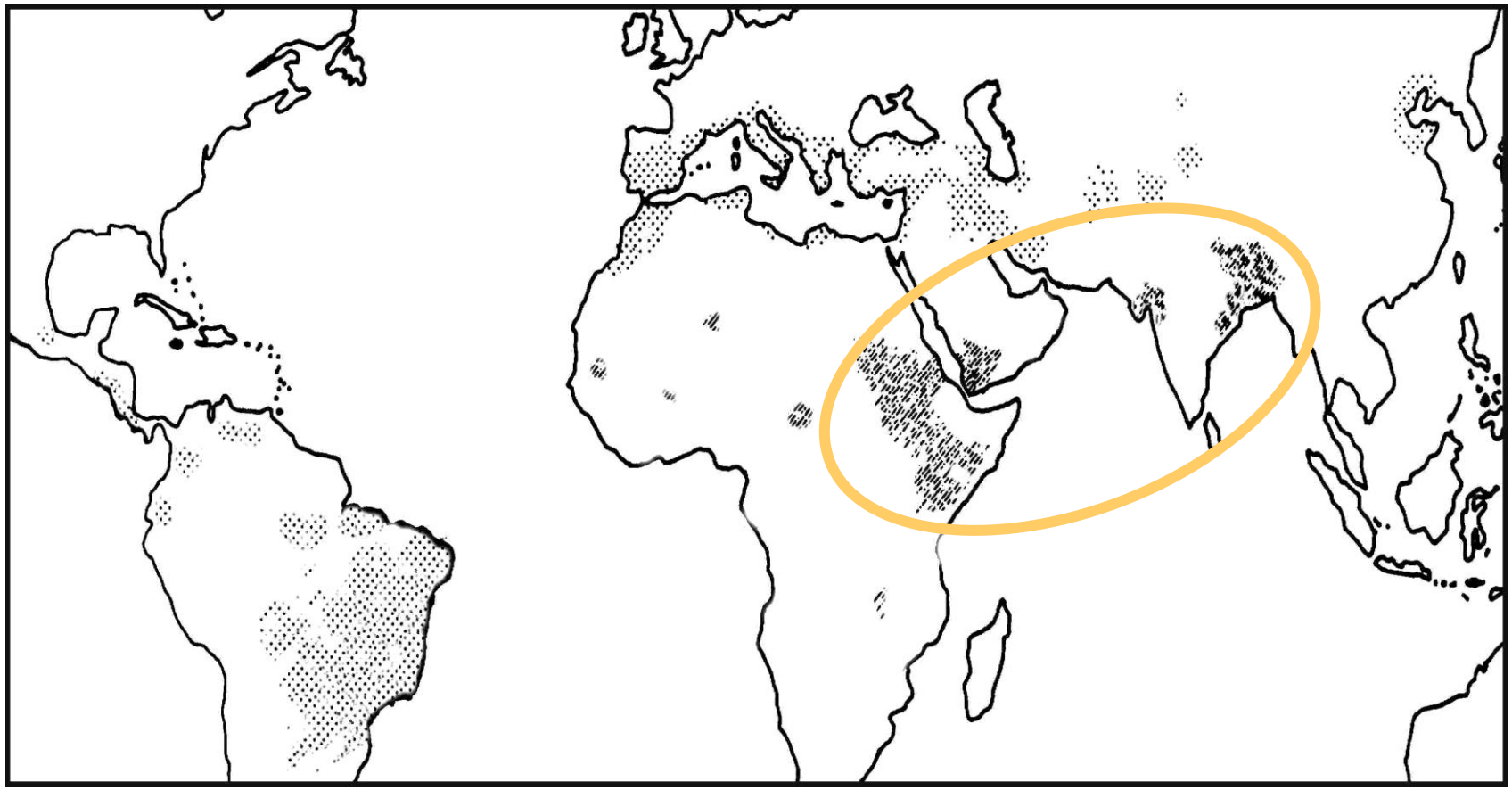
- Risk factors:

Malnutrition

Imunosupression

(HIV, transplanations, neoplasia, corticosteroid therapy)

Most cases in East Africa and Indian sub-continent



EPIDEMIOLOGY OF VL IN ETHIOPIA

Breeding sites for the sand flies

Balantine Trees

Acacia Forests

Black cotton soil or Termite Hills

Favorable Environmental conditions

Altitude below 1500 meters (low land)

High level humidity (T^o 25-32 ^oC)

Increasingly serious public health problem (1)

Increased world-wide prevalence of KA since 1993 (WHO) due to

-massive rural-urban migration and

-agro-industrial projects that bring non-immune urban people into endemic rural areas

Expansion of AIDS pandemic in KA endemic areas

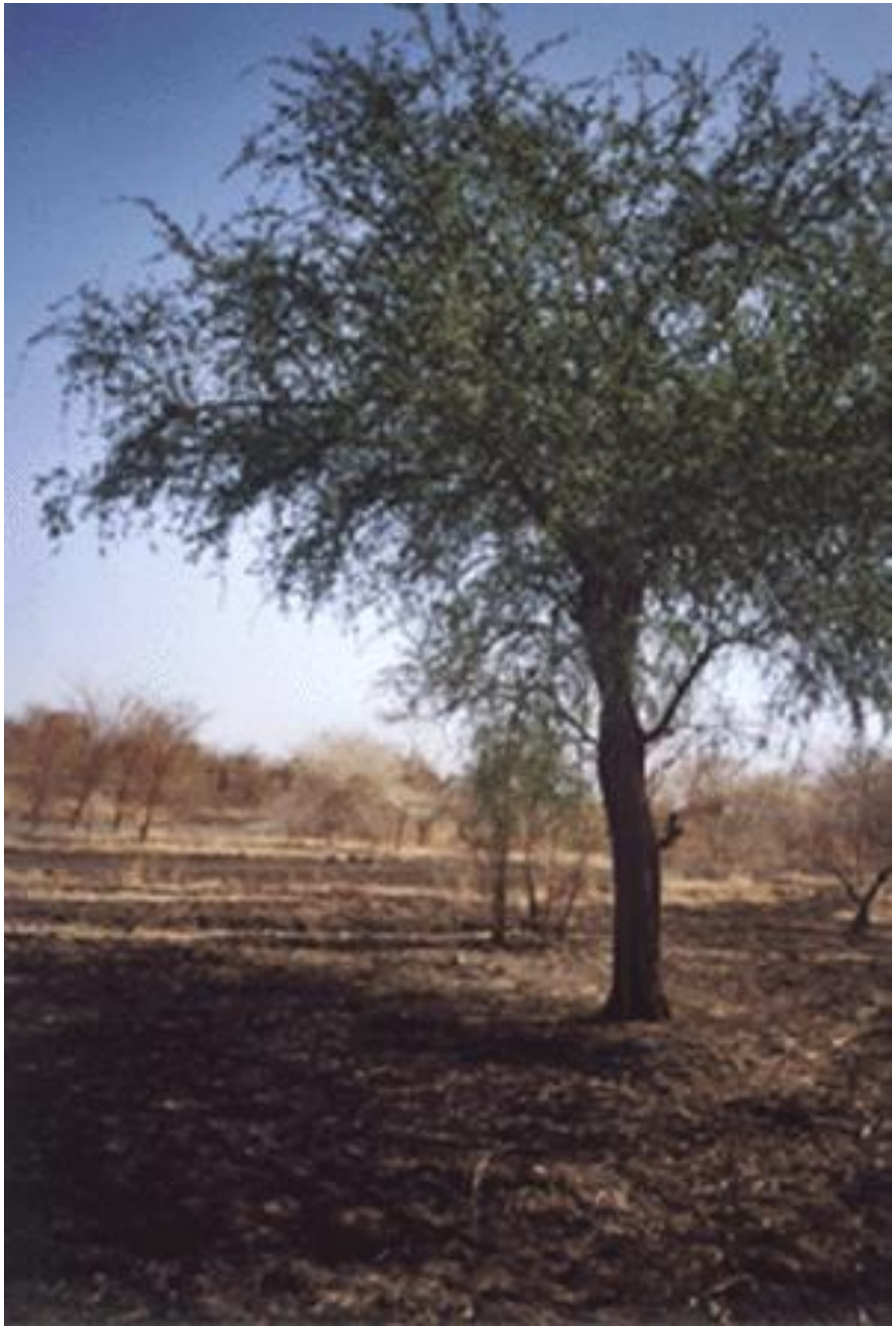
Increasingly serious public health problem (2)

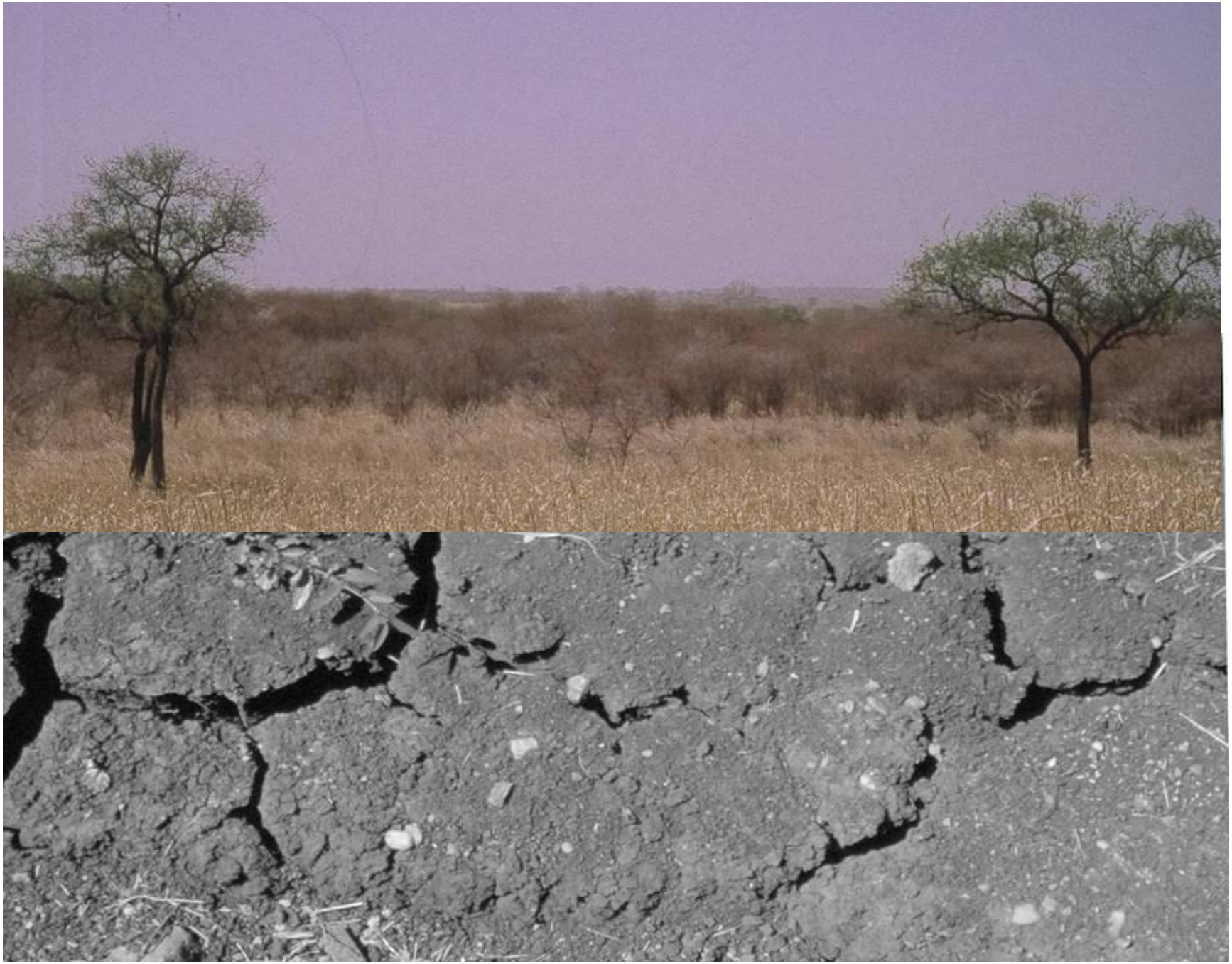
HIV/KA co-infection reported in 35 countries.

Most *reported* cases from the **Mediterranean area.**

Unknown, high, numbers in India, Sudan and Ethiopia

Co-infected patients **act as reservoir** (no parasite clearance)





Involved organs

Lymph nodes
Spleen
Hepar
Bone marrow

Mucosa of duodenum and jejunum
Lungs
(Interstitial pneumonitis)

Immune system:

Cellular:

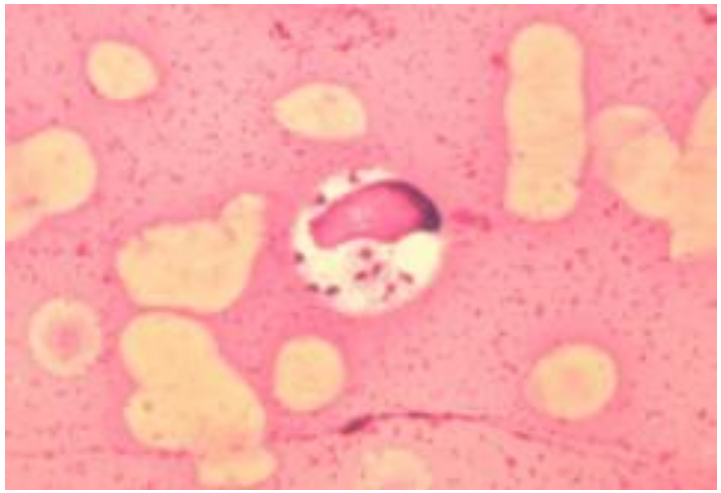
Dyserythropoesis in bone marrow

Humoral:

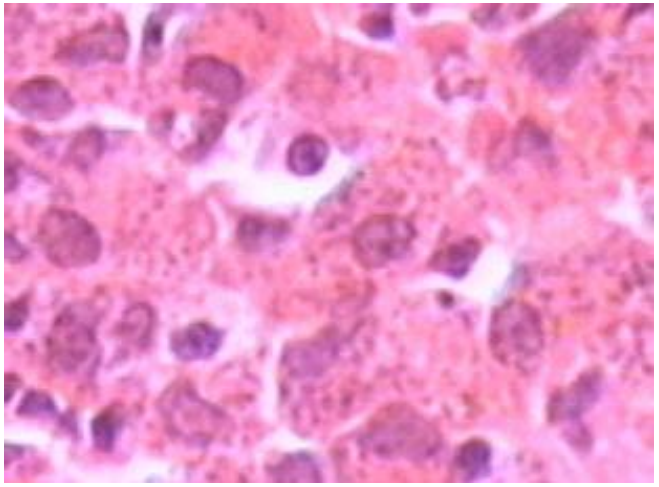
- Overproduction of IgG a IgM (polyclonal activation, autoantibodies)
- Decreased level of complement:

Immunocomplex formation in ren (nefritis)

Pathology



Infected macrophage in liver



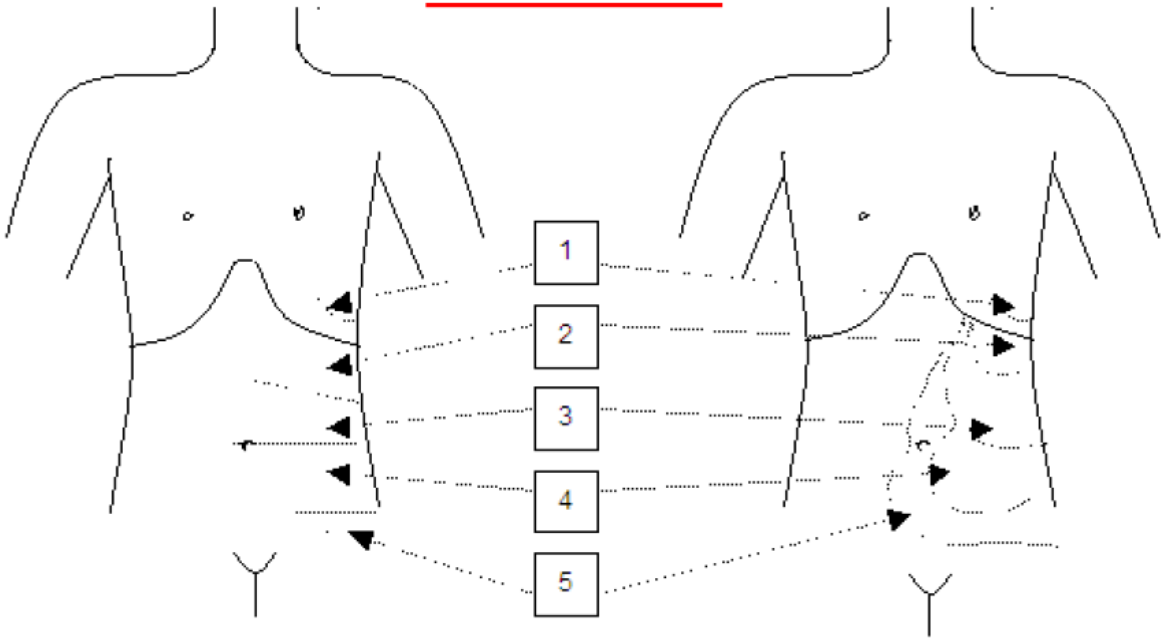
Infected macrophages in spleen

Symtomatology VL

- IP: 2-4 months, very slow progress
- Majority of infections - asymptomatic seroconversion
- **Non-regular fevers**, weakness, fatigue, headaches, anorexy, dry non-productive cough, diarrhoea, weight loss, nasal bleeding,
- **Hepatosplenomegaly**

  (firm spleen, non-dolorous, extremely enlarged)
- **Generalised lymphadenopathy**
- **Epistaxis,**
- **Skin changes**: hyperpigmentation (India: kala-azar); post-kala-azar dermal leishmaniasis
- Oedemas – rather due to the malnutrition
- Cause of death: secondary infections: TBC, pneumococcus, bronchopneumonia, measles….

SPLEEN SIZE



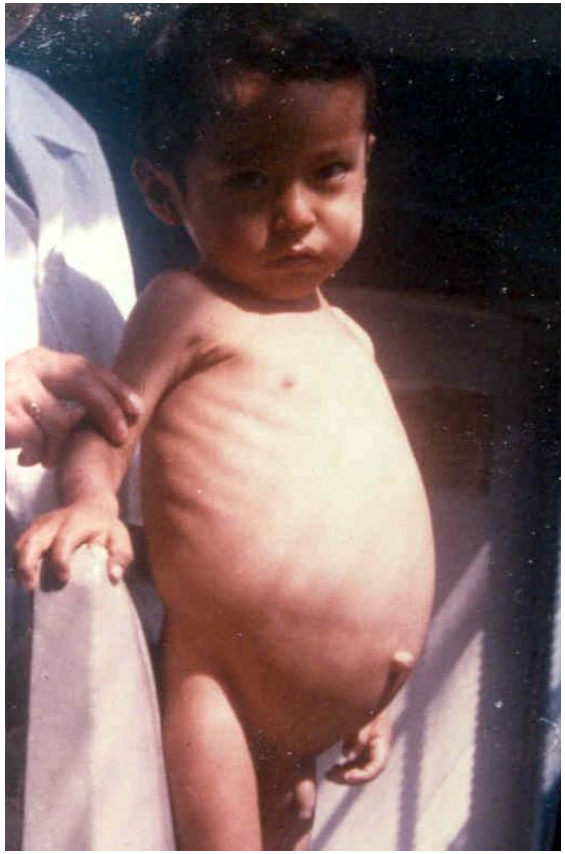
HACKETT SPLEEN SIZES

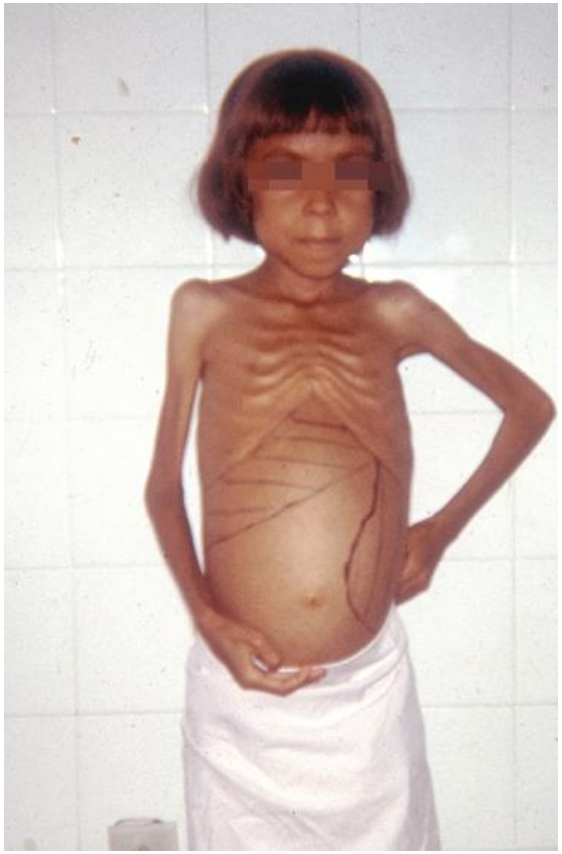
SPLEEN 1:	This is a normal spleen. It is not palpable even after a deep breath.
SPLEEN 1p (palpable):	The spleen is palpable after a deep breath.
SPLEEN 2:	The spleen is palpable below the ribs.
SPLEEN 3:	The lowest point of the spleen is almost at the umbilicus.
SPLEEN 4:	The spleen goes below the umbilicus.
SPLEEN 5:	The spleen goes all the way down to the bones of the pelvis.

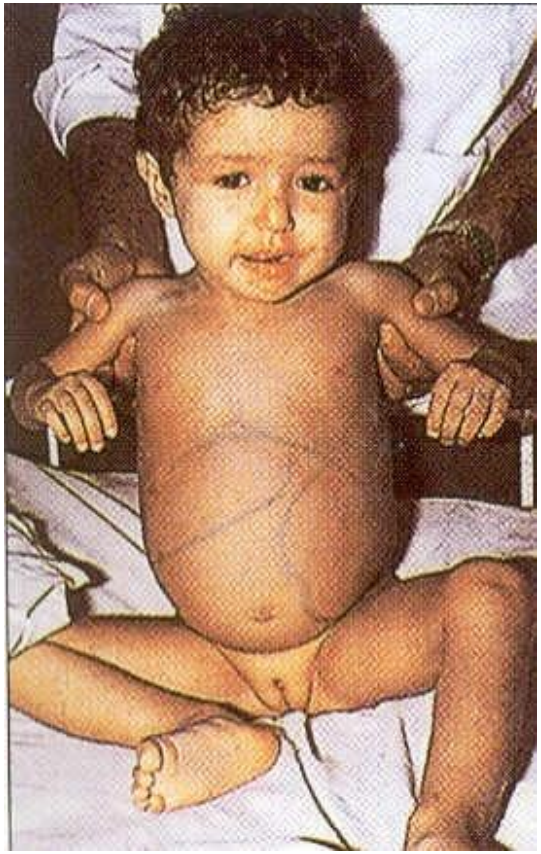
Different *Leishmania* spp = different prevalence of symptoms

Signs/Symptoms	Sudan	Brazil	India
Fever	95	95	99
Splenomegaly	95	99	98
Uncomfortable spleen	85	50	50
Weight loss (wasting)	80	98	87
Anaemia	75	98	96
Lymph node enlargement	75	30	90
Loss of appetite	70	20	30
Cough	75	40	50
Hepatomegaly	60	90	98
Epistaxis (nosebleed)	50	30	10
Diarrhoea	40	60	50
Vomiting	15	infrequent	infrequent
Jaundice	5	10	
Oedema	5	40	

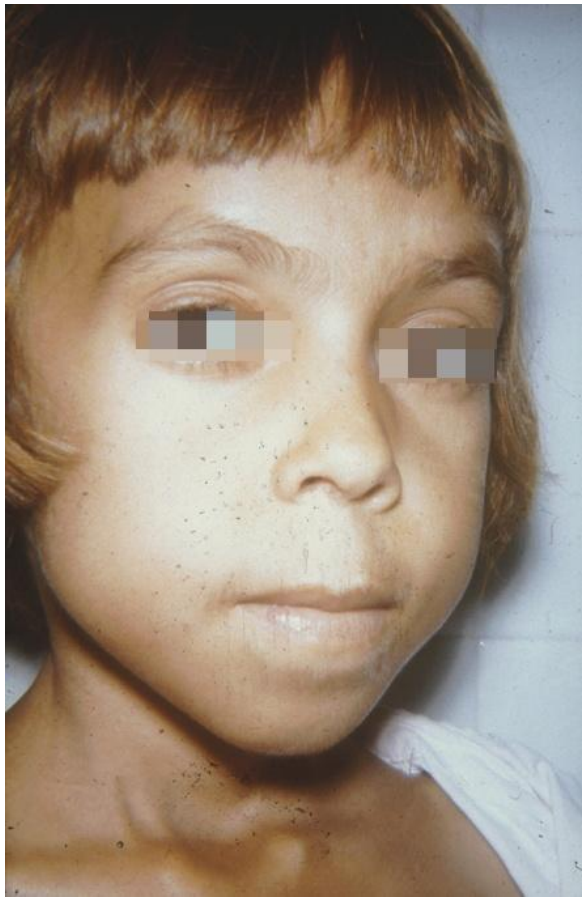
Hepatosplenomegaly



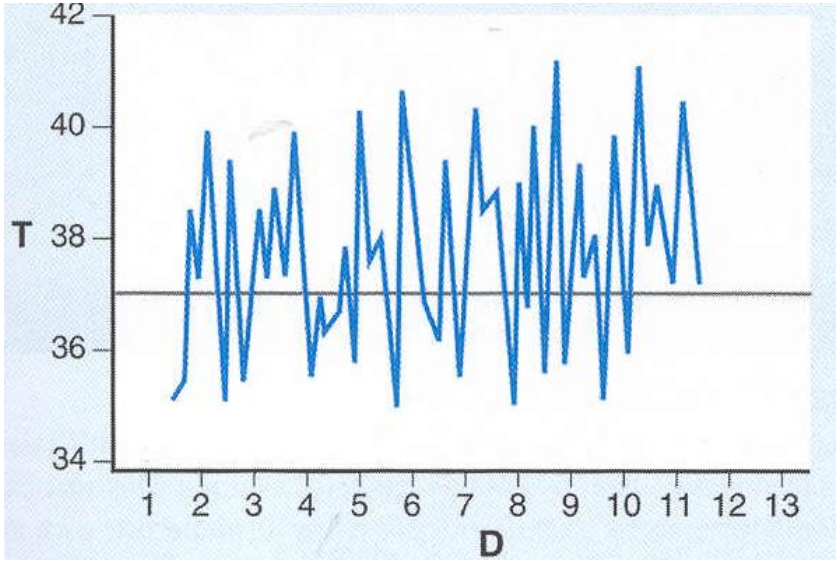




Kala-Azar is rather affects people with SAM and leads to severe weakness and wasting



Anaemia



Temperature monitoring

Laboratory

- Elevated CRP, increased sedimentation rate
- Hepar:
- Normal level of transaminases,
- Decreased level of albumin (below 2g/l), but hyperglobulinaemia, hypergamaglobulinaemia
- Blood:pancytopeania

anaemia (normochormal, normocytosis)

(sekvestration of ery in the spleen, hemolysis, ineffective erythropoesis)

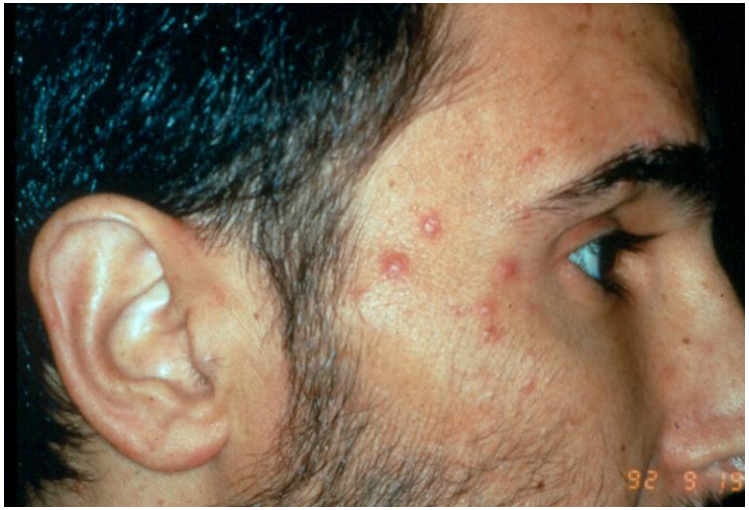
neutropenia (sekvestr.)

trombocytopenia (sekvestr.)

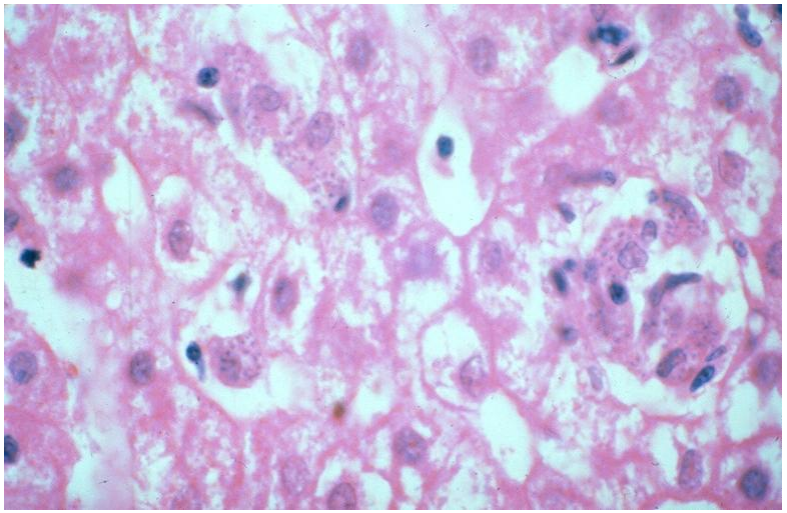
- Hb below 70g/l
- Elevation of RF

VISCERAL LEISHMANIASES AND AIDS

- Spain, France, Italy, Brazil, Ethiopia, Sudan
- **Activation of asymptomatic infection** *L.infantum, L.braziliensis* in late stage of AIDS ($CD4^+$ 50-100/mm^3)
- Amastigotes in many different organs, positivity in bone marrow or buffy coat
- Status complicated by aplastic anaemia, often skin dissemination
- Challenging therapy, relapses very often



L. infantum - Spain



Amastigotes in hepar

HIV/KA co-infection: a strong and dangerous association

AIDS increases the risk of KA by 100-1000 times in endemic areas

- HIV induced immunodeficiency prevents control of Kala-Azar, despite treatment
- KA accelerates HIV replication and AIDS progression

$\Rightarrow$**vicious circle of mutual reinforcement**

Lack of scientific knowledge African *L. donovani* Kala-Azar

Research on co-infection mainly from the Mediterranean region: not representative for Ethiopia/Sudan:

-Different parasite (*L. infantum* vs *L. donovani*)

-Different patients (IV drug users vs normal population)

-Different transmission (zoonotic and needle sharing vs anthroponotic)

-Different effect of HAART? Milder illness ?

-Different resources (expensive treatments)

Clinical characteristics of HIV/KA co-infection

Parasitic dissemination

Lower cure rates

Higher treatment failure rates

Higher drug toxicity

Increased risk of drug resistance

Higher death rates

High relapse rates

Post Kala-Azar Dermal Leishmaniasis (PKDL)

- *L. donovani*
- 6-20% India, 2-5% East Africa
- 1-2 years post infection

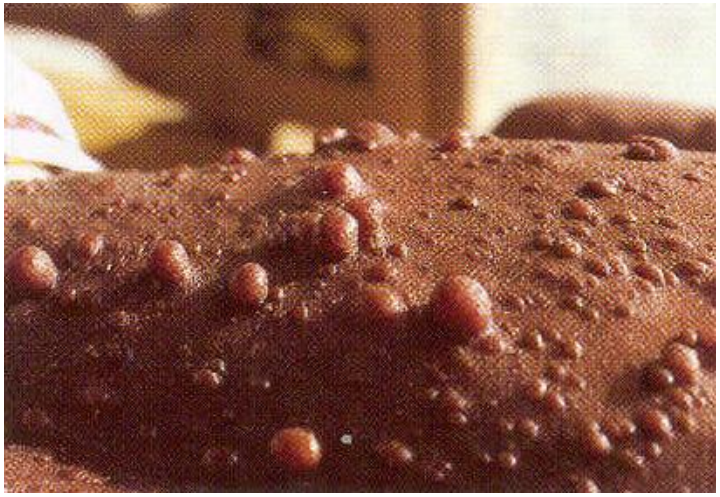
Hypopigmented lesions

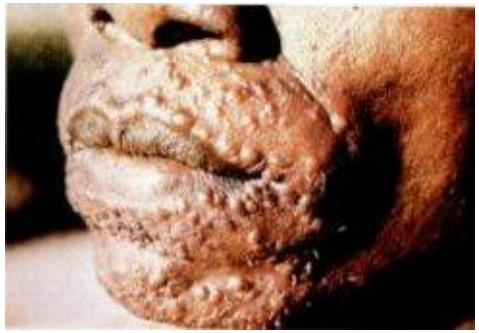
(chin, lips, neck, extensor parts of the limbs…)

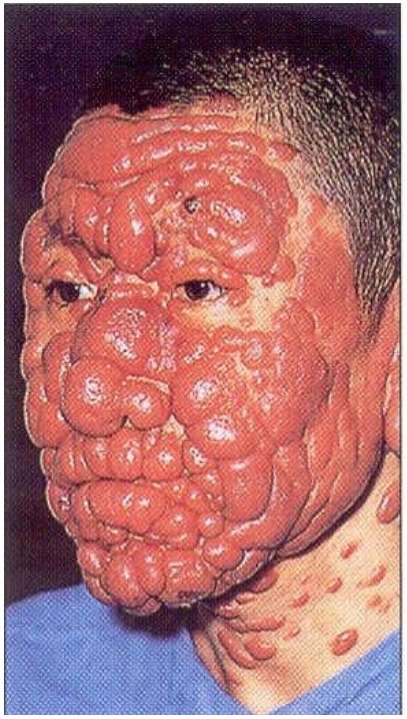
Nodules

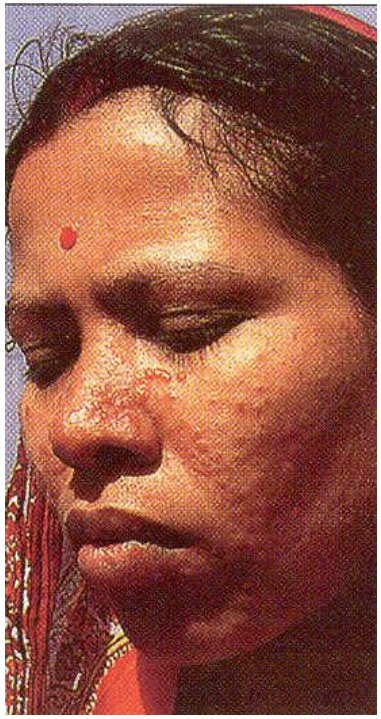
(veruccal, papillomatous..)

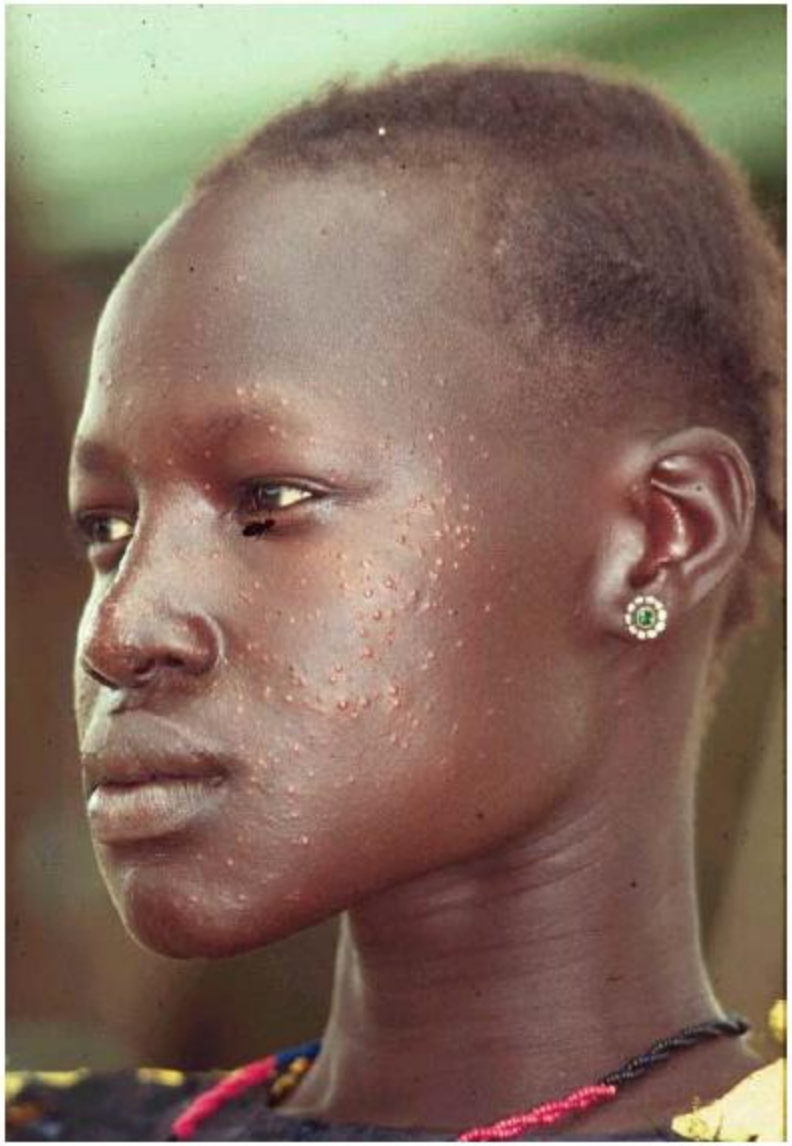
- Dif. Dg.: leprosy, sarcoidosis, TBC





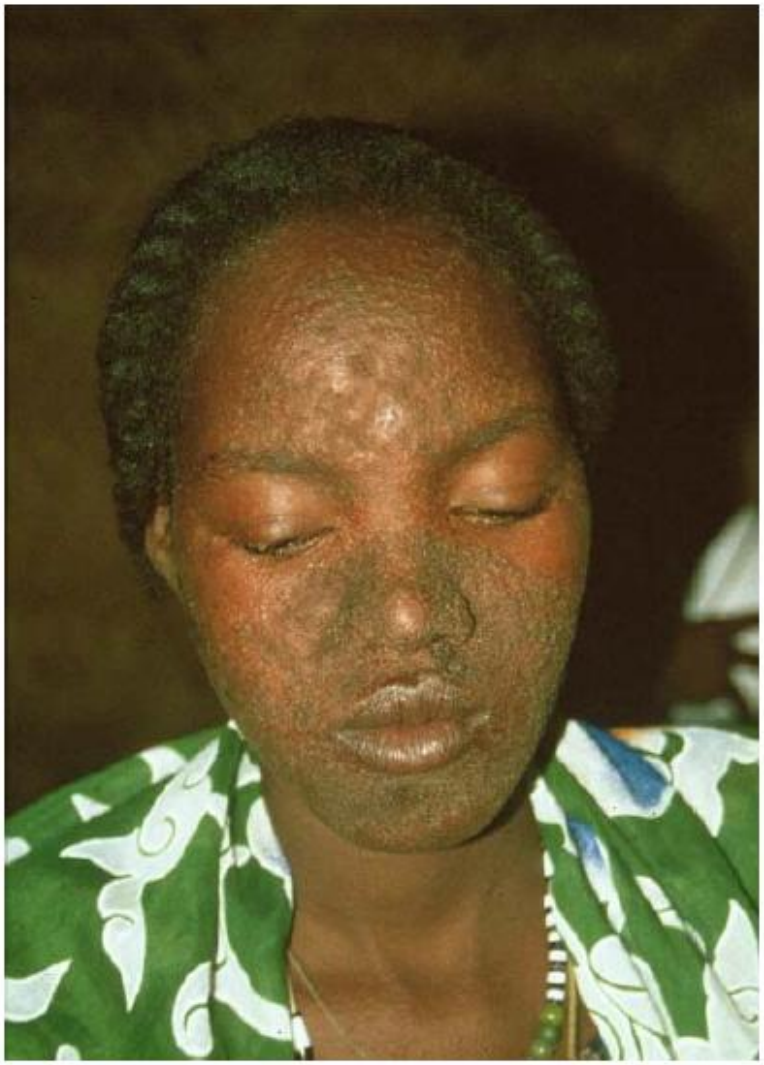




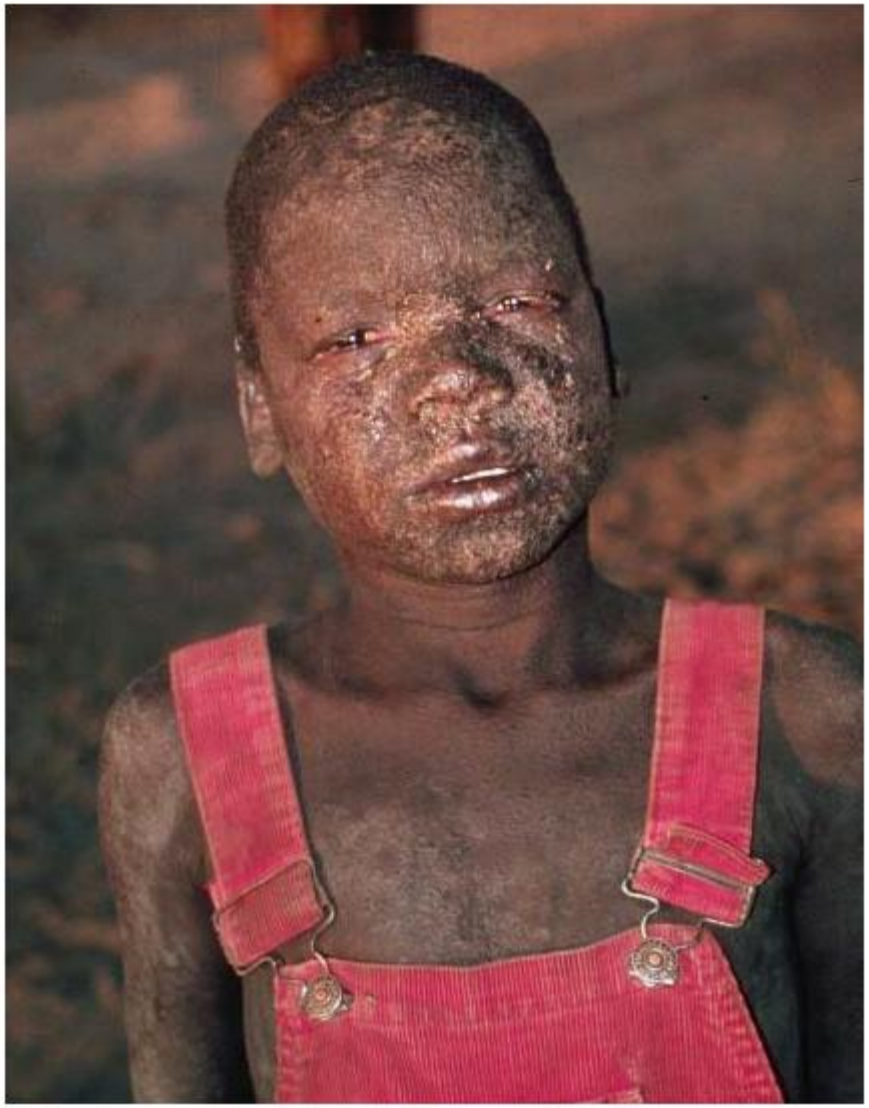


Early grade one PKDL – note the scattered hypopigmented papules. This may improve without treatment.

Now the lesions are becoming more dense, almost confluent. She has a mild macular rash extending beyond her face, this is grade 2, but may include the conjunctiva (grade 3) and so it is good to treat.



The lesions are dense and hyperpigmented, this needs treatment. (Most all blackened lesions need treatment to resolve.) It does not extend much beyond her face but is otherwise grade 2.



This is confluent, peeling, extends throughout the body, and includes the mucosa (see the eyes and nose). This is grade 3 PDKL and needs treatment. This person is sick.

Kal

This child has grade 3 PKDL including mucous membrane involvement and has VL. She has had 10 days of treatment; her skin is peeling and her fever is gone. She was almost moribund on admission.

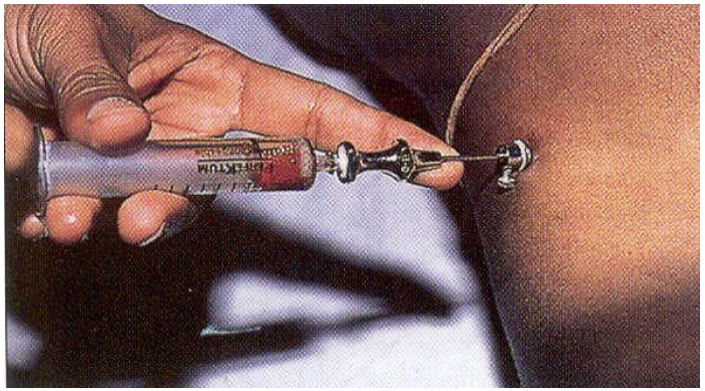
DIFFERENTIAL DIAGNOSIS

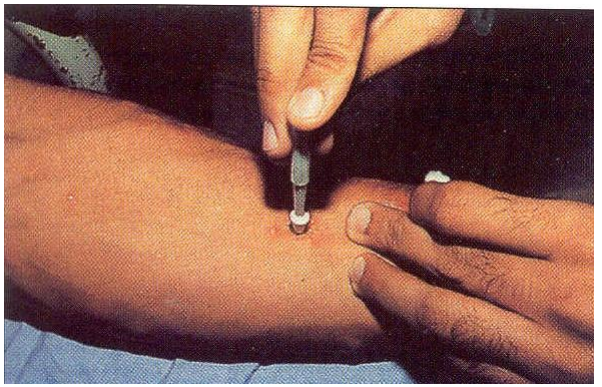
	Kala Azar	Typhoid	Brucella	Schistosomiasis – liver	Tropical splenomegaly
FEVER	YES > 2 weeks Mostly in afternoons, evenings It can last months	YES – it is a high fever up to 40. It is constant; it does not go up and down It lasts 3 – 4 weeks.	YES – intermittent up to 2 years. Can be days without fever	NO - unless there is another infection	NO – unless there is another infection
WASTING	YES, severe	Maybe – a little	Yes, slowly	Rarely (except end stage)	No
SPLENOMEGALY	YES – most have a big spleen	YES, not all patients have a big spleen, and the spleen is only a bit enlarged	Only 1/3 of patients have a big spleen	Sometimes – in the late stages	YES – usually a huge spleen that has been growing for years, usually it is firm
BIG LIVER	Some, but usually not huge	Not often	Less than 1/3 of patients have a big liver	YES, this is the classic sign	NO
SPECIAL SIGNS OR SYMPTOMS	Very sick	Very sick, very high fever – and can be talking crazy	A swollen joint	Always a big liver, non-tender.	Always a big spleen – usually for years
Will you likely need a DAT (If they haven't had KA before)?	YES	Yes, if it has been 2 weeks of fever	Maybe – make sure the person has a fever before you test!	No – there is no fever	No – there is no fever

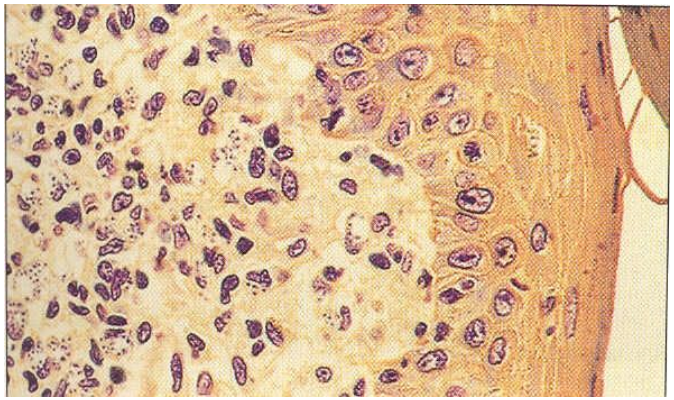
Diagnostics: skin and mucosal

Direct detection of the parasite: **biopsy of ulcer**

(material taken **from peripheral part of ulcer**)

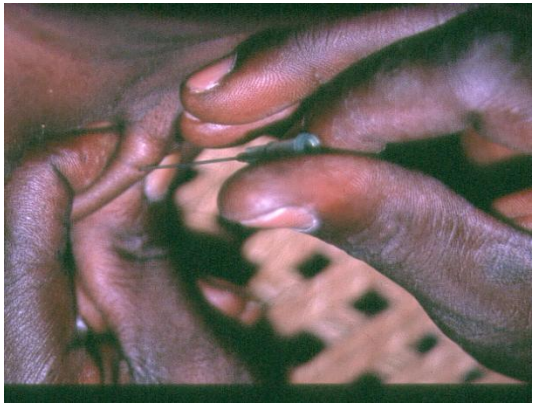






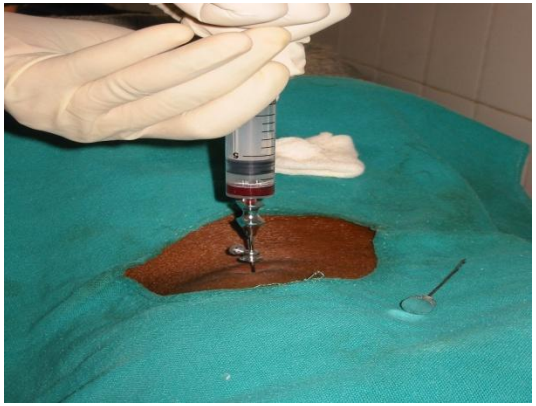
Parasitology

Lymph node



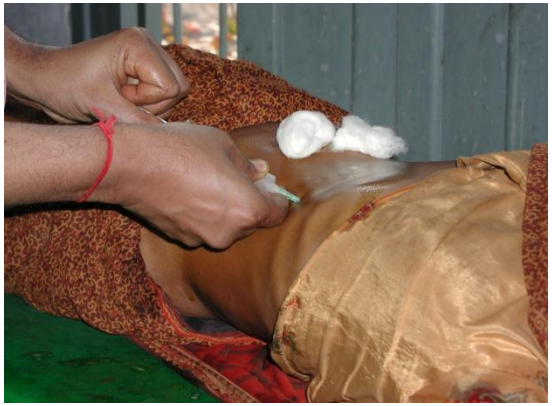
- Lack sensitivity

Bone marrow



- Lack sensitivity
- Painful
- Sterilisation !
- Medical procedure

Spleen



- Gold standard
- Needs expertise
  - Procedure
  - Reading
- Medical procedure
- Risk of bleeding

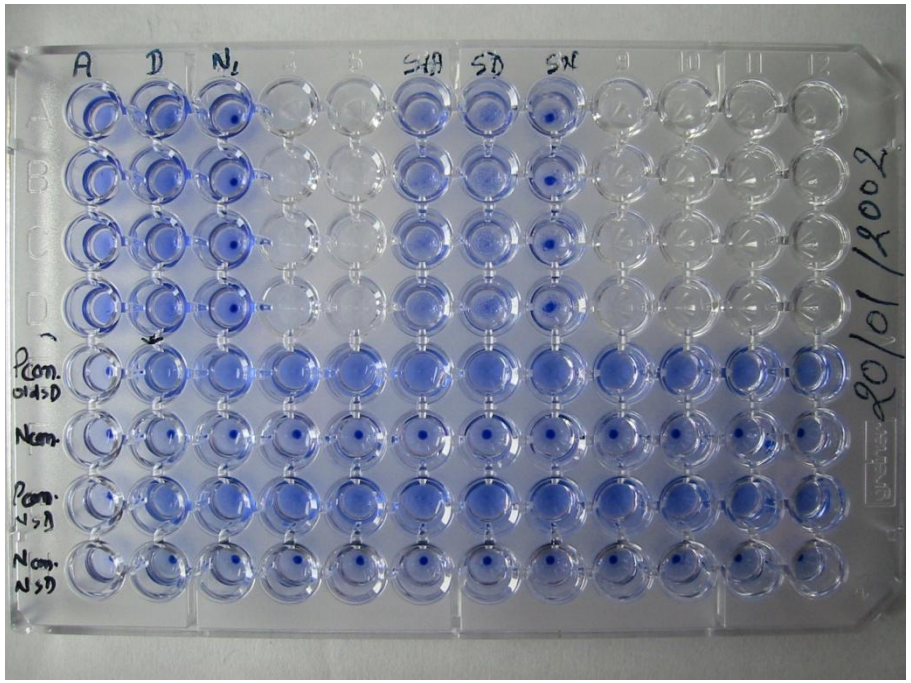
Not satisfactory for remote field use

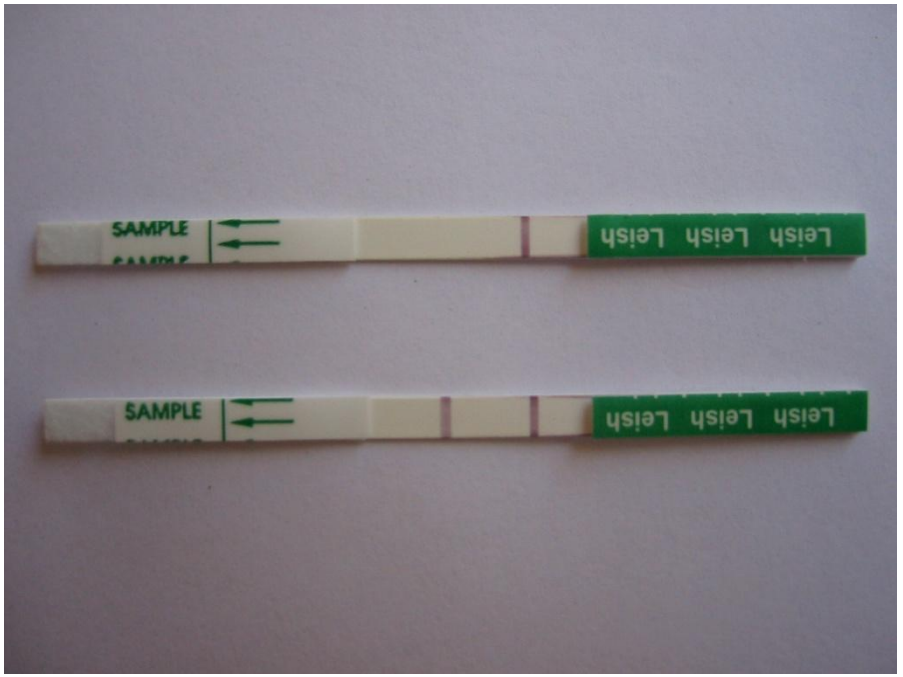
Diagnostics VL

- **Biopsy and spread on the glass**
  (Giemsa) or histology:
  - Bone marrow (sensitivity 54 – 86 %)
  - Spleen (98 %)
  - Hepar, lymph nodes (64%)
- Cultivation on special agars (blood agar SNB-9, NNN; 7-10 days)
- Inoculation of the laboratory animals
- Buffy coat or xenodiagnostics in HIV + patients
- **Serology,** skin tests
- Molecular diagnostics, PCR: RFLP possibility to differentiate the species

Serological tests

- **The DAT and rK39 dipsticks are being used in the field**
- **Both tests have been well validated**





IMUNODIAGNOSTICS

- **Serology**
  - Direct Agglutination (DAT), latex agglutination
  - ELISA, dotELISA
- Intradermal skin tests – positive even in asymptomatic individuals

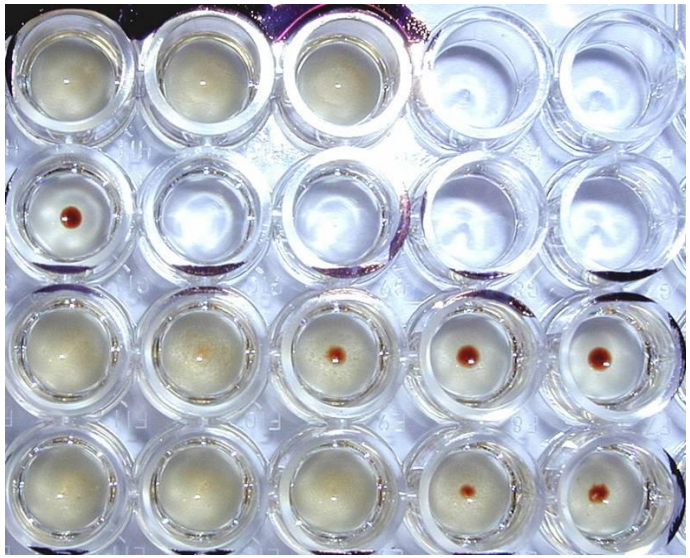
Indirect agglutination

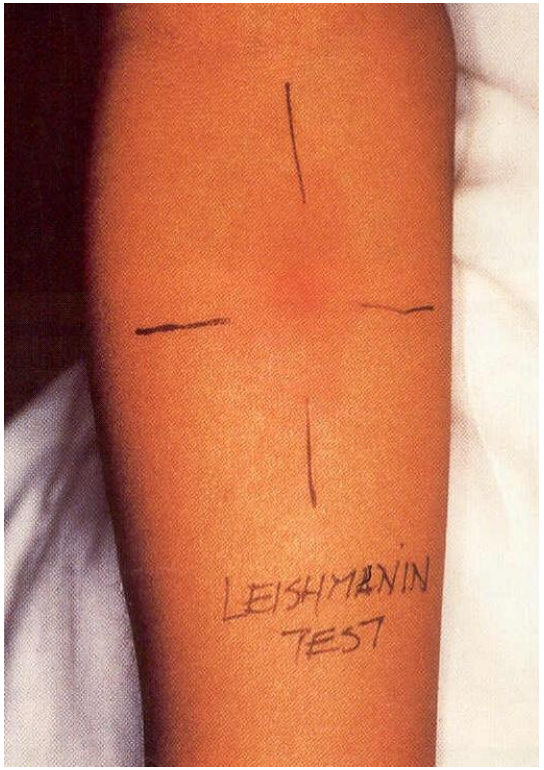
Positive control

Negative control:

Patient A:

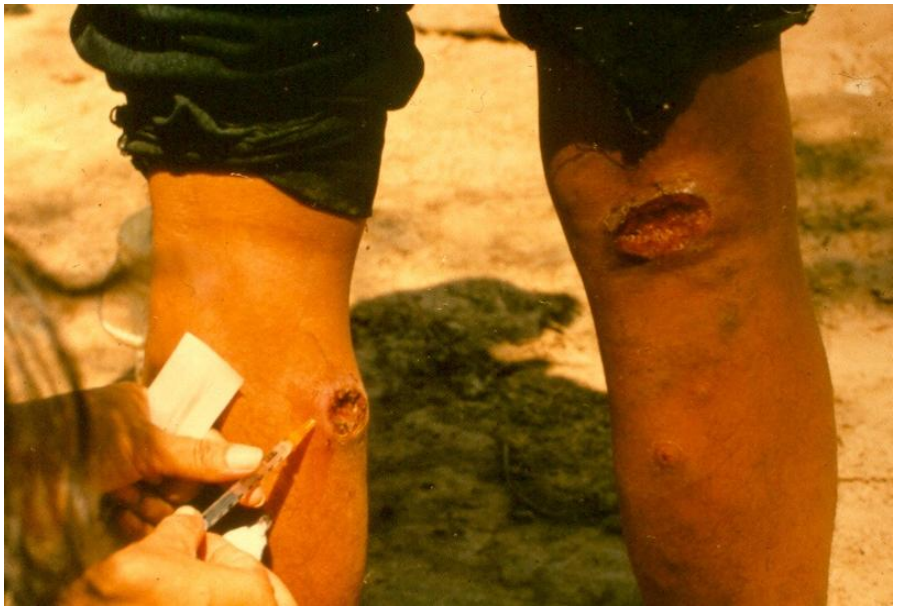
Patient B:





Skin infection is treated systematically or locally

- Sb^V i.v or locally - Glucantime, Pentostam
  (*L.tropica, L.braziliensis*)
- Amfotericin B i.v.
  (*L.tropica, L.braziliensis)*
- Ketokonazol (Nizoral) 600 mg/day p.o.
- Terbinafin (Lamisil) 300 mg/day p.o.
- Paromomycin ung. 15% (*L.major*)
- Surgical treatment, kryotherapy, thermotherapy

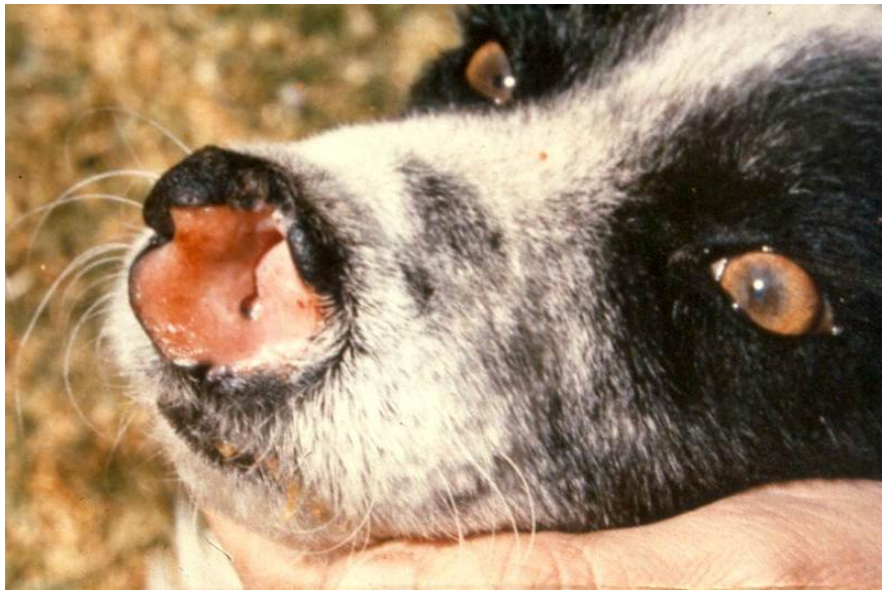


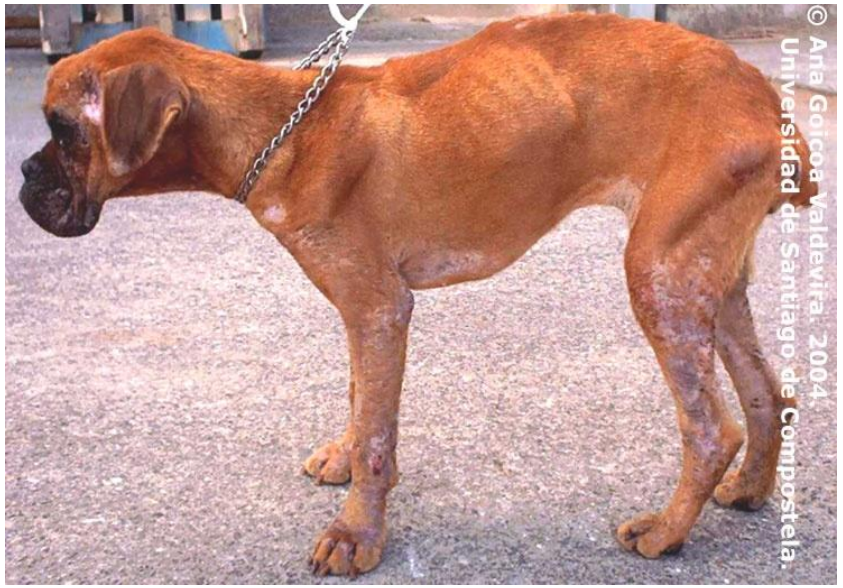
L. braziliensis complex Bolivia, local treatment

THERAPY VL

- Stibium Sb^V
  - Sodium stiboglukonate (Pentostam, SKB) – 100 mg Sb^V/ml
  - Meglumin antimoniate (Glucantime, Aventis) - 85 mg Sb^V/ml
  - 20 mg/kg Sb^V i.v. or i.m.for 20 – 28 days
  - Good effect on *L.infantum, L.chagasi* and *L.donovani* from Africa, common relapses in *L.donovani* from India
  - Side effects: pankreatitis, cardiotoxicity (sudden death), nephrotoxicity
- Amfotericin B
  - 0,3-0,5 mg/kg/day (1mg/kg ob day) i.v., 21 days
  - Liposomal 2-3 mg/kg/day, altogether 21 mg/kg during 7-10 days
- Pentamidin isethionát (Pentacarinate)
  - 4 mg/kg/day i.m. or i.v. 3 times per week for 5-25 weeks
- Paromomycin/aminosidin (Humatin)
  - 15 mg/kg/day i.v. or i.m. during 10-21 days
- Miltefosin (alkyl phospholipid derivate for p.o. therapy)
  - 100 mg/day p.o. for 4 weeks
- Clinical response expected after 7-10 days, controls after 3, 6 and 12 months

LEISHMANIASIS IN DOGS





Rezervoar of *L. infantum* in Mediteran regions