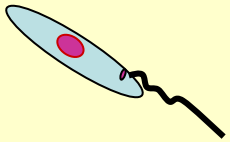
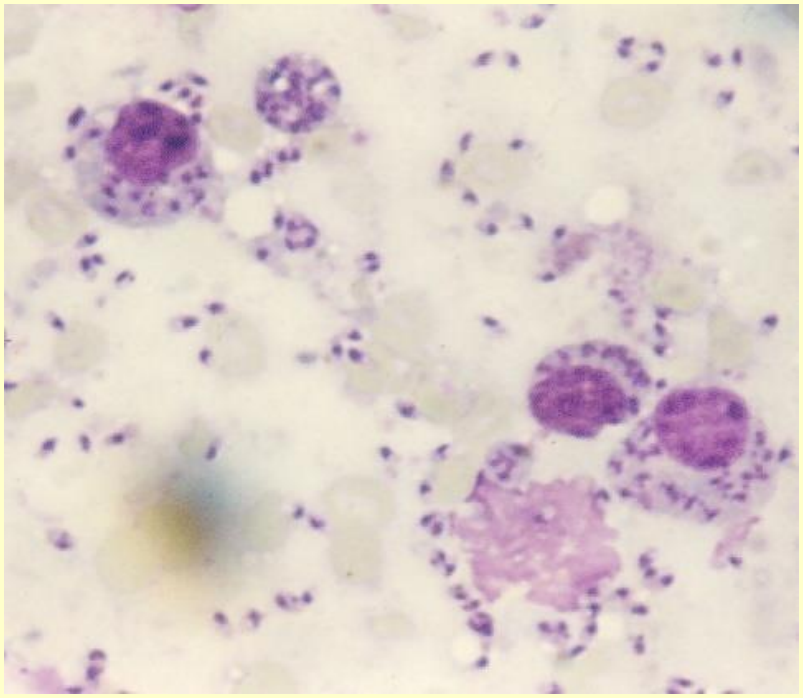


# Leishmaniases



## DEFINITION

Leishmaniases are parasitic diseases caused by protozoan flagellates of the genus *Leishmania*. These are characterized with febrility, splenomegaly, and anemia (visceral leishmaniases) and cutaneous and mucocutaneous lesions (cutaneous and mucocutaneous leishmaniases).

# DISTRIBUTION AND IMPACT

***According to WHO data:***

***Leishmaniases*** are endemic in 88 countries on four continents: Africa, Asia, Europe and the Americas, where 350 million people are at risk of being infected.

***An*** estimated 700 000 to 1 million new cases and 20 000 to 30 000 deaths occur annually.

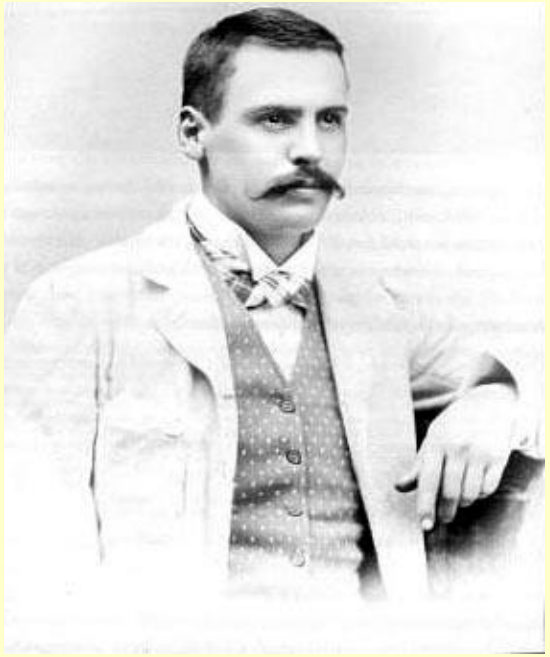
***Every*** year about 50 000 to 90 000 new cases of visceral leishmaniasis are registered in 9 countries - Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan.

***Most*** of the patients (90%) with cutaneous leishmaniasis are registered in Afghanistan, Algeria, Brazil, Colombia, Iran, Syrian Arab Republik.

***Most*** of the patients with mucocutaneous leishmaniasis are seen in Bolivia, Brazil, Ethiopia and Peru.

***The*** social relevance of leishmaniases is determined by their high prevalence in tropical and subtropical countries, as well as the severe clinical manifestations and high-cost damages.

**William Leishman**



**Charles Donovan**

The parasites were detected in the spleen of a patient with kala-azar disease (black fever) in India, and were first described by W. Leishmann and C. Donovan in 1900-1903.

# ETIOLOGY

The *Leishmania genus* includes about 30 different species, most of which are infectious for humans.

According to their geographical distribution, the *leishmania species* are divided into two main groups:

- ***spread in the Old World*** (*Leishmania donovani, L. infantum, L. tropica, L. major, L. aethiopica*);

-***spread in the New World*** (*L. mexicana-complex, L. chagasi, L. braziliensis, L. panamensis, L. guynansis and L. peruviana*).

According to their isoenzymes, antigens and the composition of the nucleic acids the genus *Leishmania* is divided also into two subgenera:

-***Leishmania sensu stricto***, distributed in both the Old and the New World;

-and ***subgenus Viannia***, seen only in regions in South America.

***Each subgenus is further divided into the so-called complexes.***

***Order Kinetoplastida***

***Family Trypanosomatidae***

***Genus Leishmania***

***Subgenus Sensu Strictu*** includes:

***L. donovani complex - (causes visceral leishmaniasis in the Old and the New World)***
*L. donovani;*
*L. infantum;*
*L. chagasi.*

***L. tropica complex - (cutaneous leishmaniasis in the Old World)***
*L. tropica;*
*L. major;*
*L. aethiopica.*

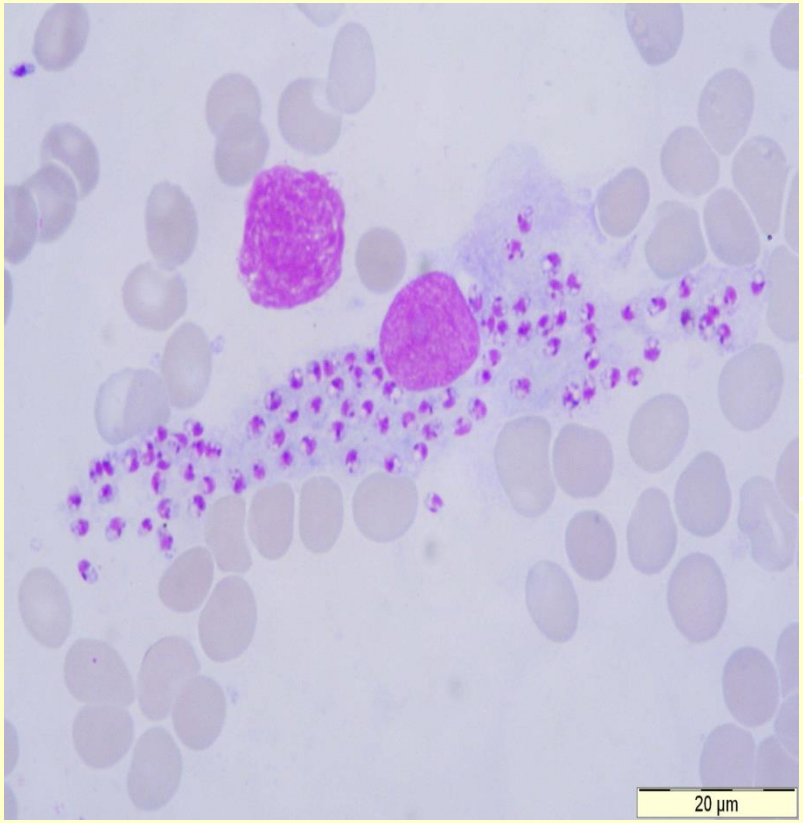
***L. mexicana complex - (cutaneous leishmaniasis in the New World)***
*L. mexicana;*
*L. amazonensis.*

***The subgenus Viannia*** *is presented by the complex* ***L. braziliensis*** *including four species:*

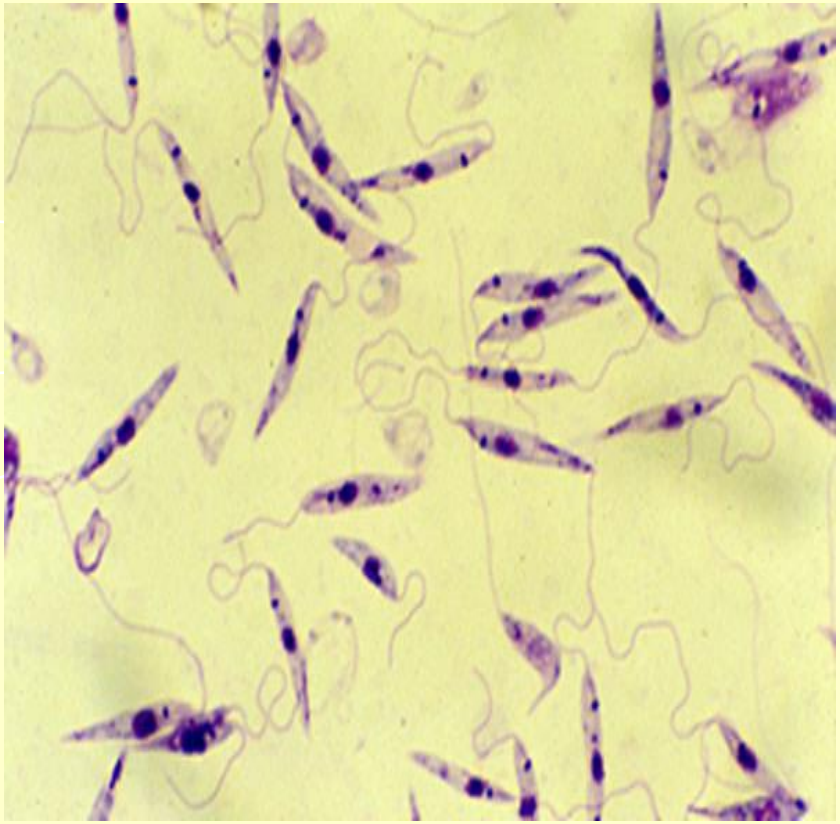
***L. brasiliensis complex-(causes cutaneous and mucocutaneous leishmaniasis in the New World)***

*L. braziliensis*
*L. guyanensis;*
*L. peruviana;*
*L. panamensis;*

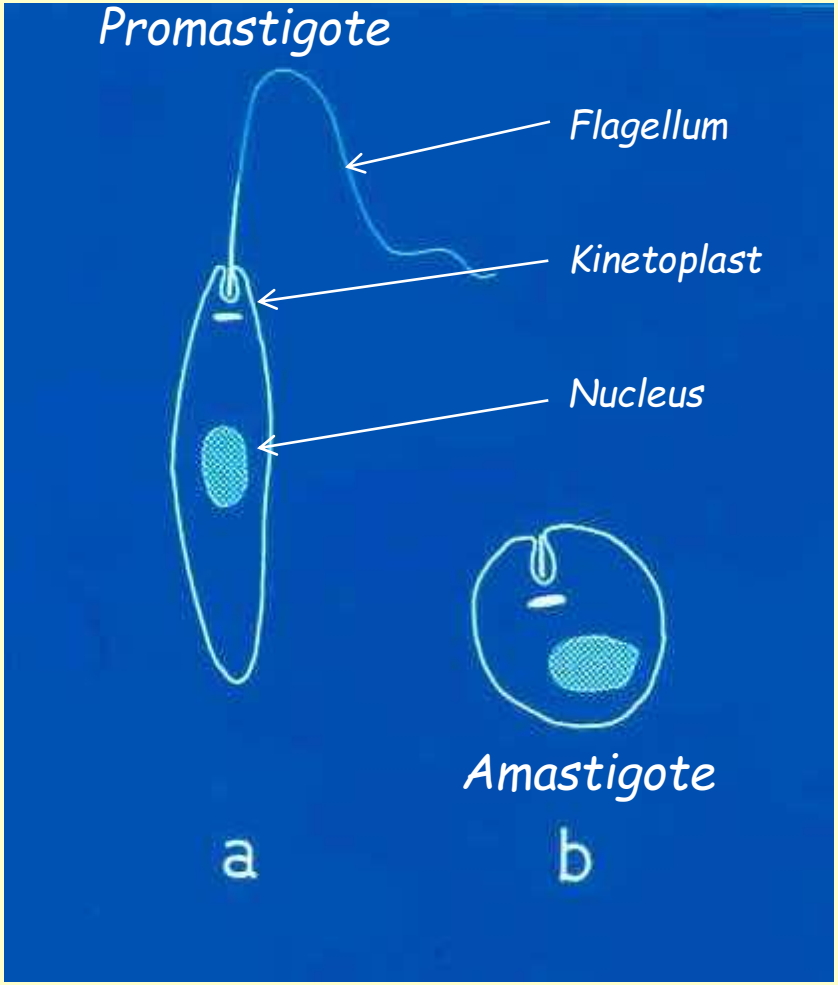
Regardless of what species they are, leishmania parasites are dimorphic parasites, presented as two principal morphological forms:




The intracellular amastigote, within the mononuclear phagocytic system of mammalian hosts (humans and animals)

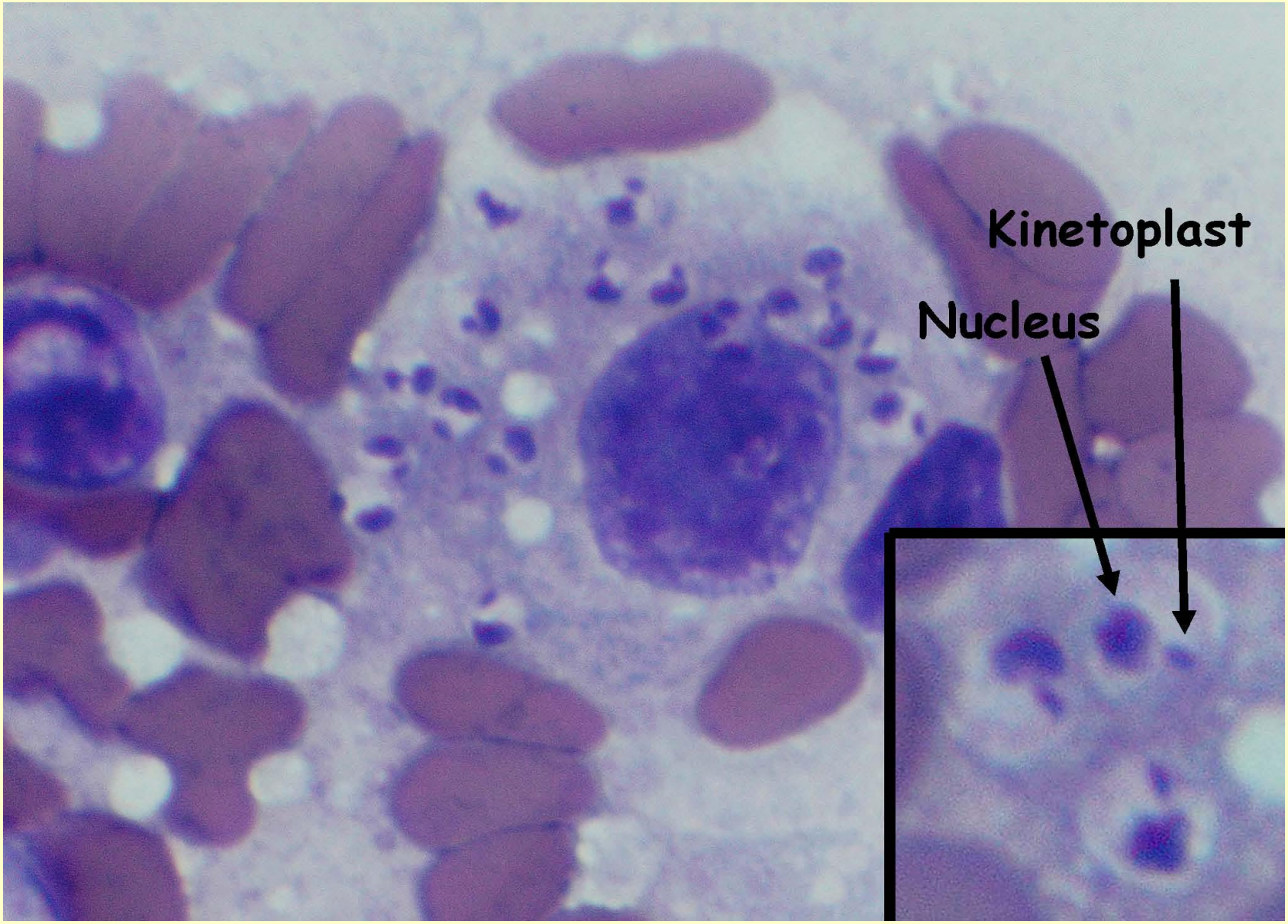


The flagellated promastigote within the intestinal tract of insect vector and in culture media



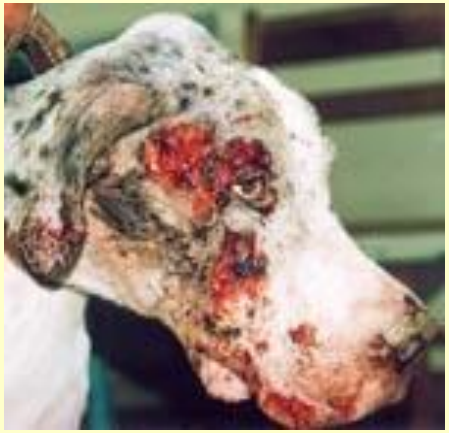

**The amastigote stage** is a round or oval body about 2–6 μm in diameter, containing a nucleus and a kinetoplast. Nearly 15% of the cellular DNA is in the kinetoplast. By means of a variety of receptor mechanisms, macrophages trap the leishmania and amastigotes multiply within the parasitophorous vacuoles of macrophages by binary division. The number of amastigotes in a single cell may be as high as 20-30.

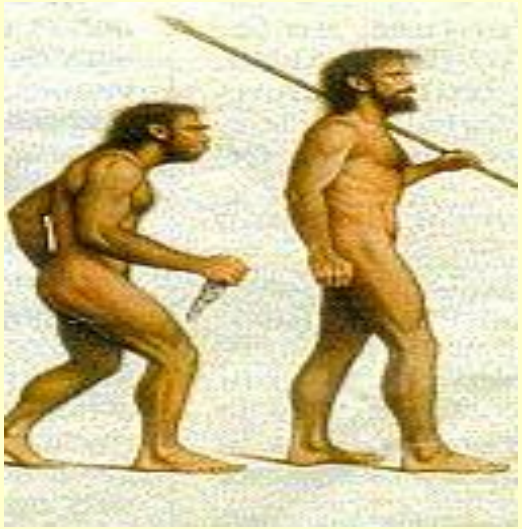
**The promastigote stage** has a long and slender body (about 15–30 μm by 2–3 μm), with a central nucleus, a kinetoplast and a long free anterior flagellum.



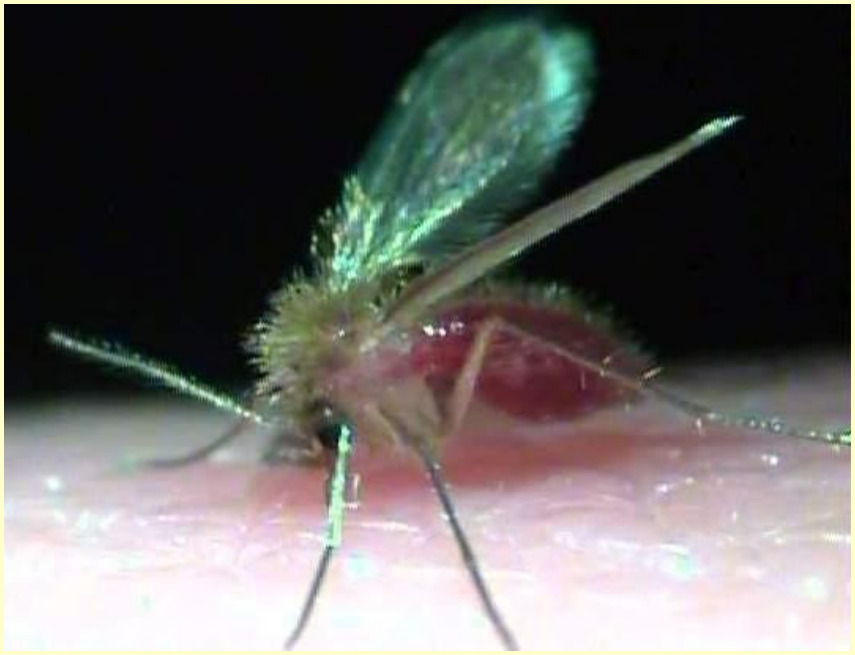

Amastigotes in a macrophage at 1000× magnification. Inset shows the cell membrane and points out the nucleus and kinetoplast, which are required to confirm that the inclusion seen in a macrophage is indeed an amastigote.

**Hosts and reservoirs** of the parasite include various species of wild and domestic animals (dogs, foxes, wolves, rodents and other.



An **infected human** individual can also be a **host and a source** of infection.

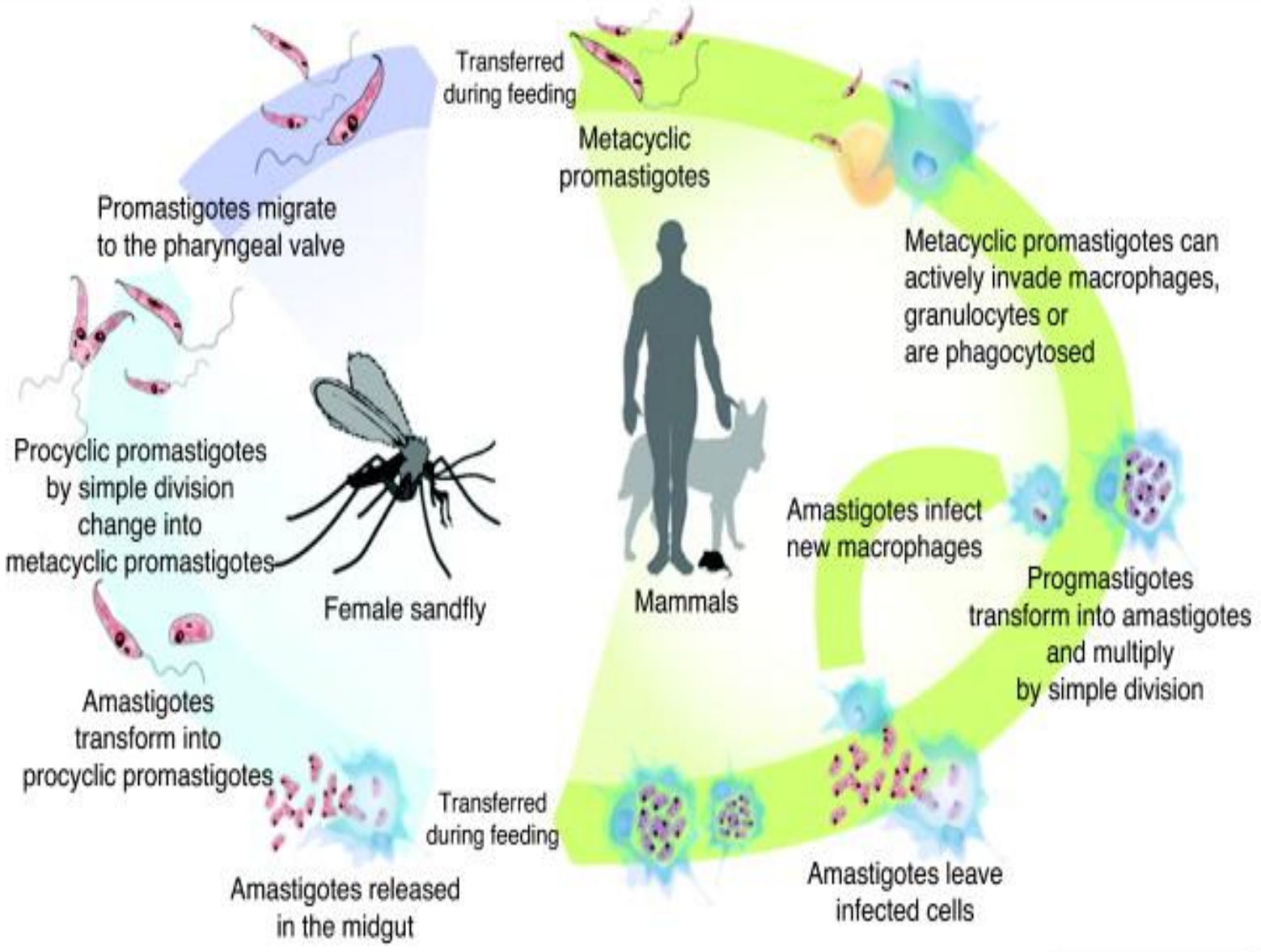


The disease is transmitted by over 800 blood-sucking insects of the genera: ***Phlebotomus*** and *Sergentomyia* in the Old World, and ***Lutzomyia***, *Brumptomyia* and *Warileya* in the New World.

Among these species, about 70, belonging to the genera ***Phlebotomus*** and ***Lutzomyia***, are proven vectors of *Leishmania* for humans.

*Lutzomyia longipalpis*

# LEISHMANIA SPP. - LIFE CYCLE



***Leishmaniases*** are divided into the following groups:

1. Visceral leishmaniasis.
2. Cutaneous leishmaniasis of the Old World.
3. Cutaneous leishmaniasis of the New World.

## *Visceral leishmaniasis*

Visceral leishmaniasis is a transmissive protozoosis, which takes a chronic course characterized by fever, splenomegaly, hepatomegaly, progressive anaemia, thrombocytopenia, leucopenia and cachexia.

*Visceral leishmaniasis* is caused by species of ***L. donovani complex:***

- *L. donovani* - causes the Indian visceral leishmaniasis (kala azar);
- *L. infantum* - causes the Mediterranean-Middle-Asian type;
- *L. chagasi* – causes the American type of leishmaniasis;

## PATHOGENESIS AND PATHOLOGY

- On the site of the insect bite, where the promastigotes are inoculated, a small granuloma forms, containing multiple histiocytes that are full of amastigotes.

- Later, the parasites may reach the regional lymph nodes and enter the blood stream with the lymphocytes. They reach the spleen, the liver, the bone marrow, lymph nodes and other organs.

- Depending on the immune response of the host, they either die or multiply in the cells of the reticuloendothelial system (RES) to cause disease.

- The spleen is enlarged due to hyperplasia of the retuculoendothelial system (RES) , and a great number of amastigotes are found in the pulp.

- The liver is also enlarged, and many sarcoid granulomatous nodules are detected, however the parasites are not that many.

- Similar changes occur in other organs too: in the kidneys, lungs, bone marrow and others.

- Blood formation is impaired and granulocytopenia and thrombocytopenia develop.

# CLINICAL PRESENTATION. CLINICAL FORMS.

Incubation period - varies in length, but is usually 4 to 10 months.

There are three stages in the clinical course of leishmaniasis:

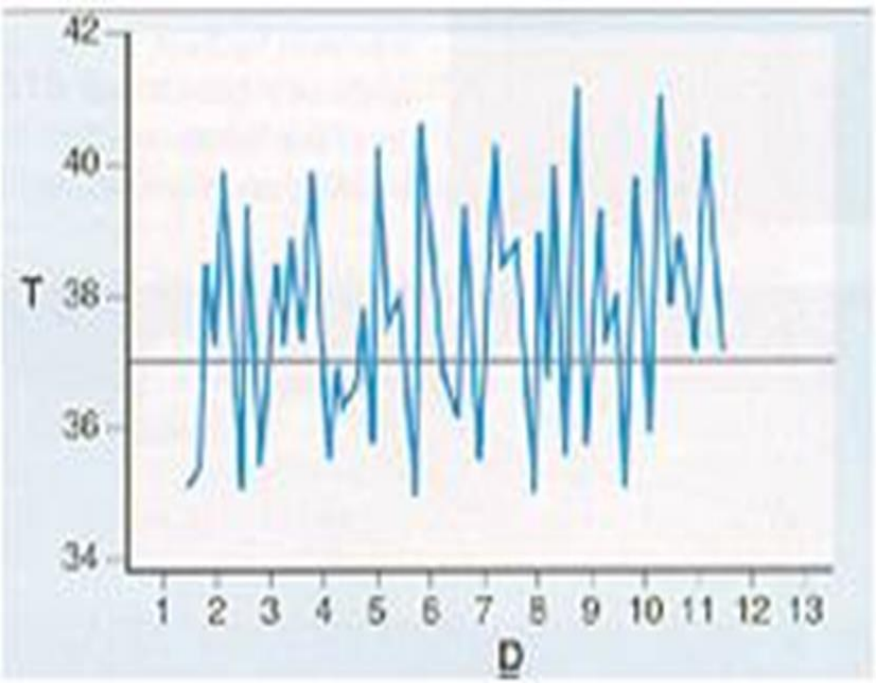
**1.Early stage.**

Initially, there is the first sign – a skin papula which appears several days or weeks after the insect bite which heals spontaneously.

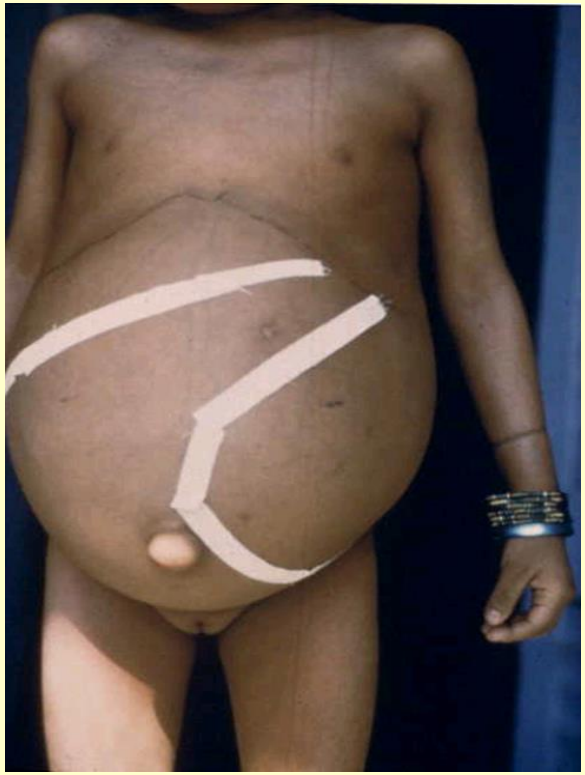
After the incubation period, there are general symptoms such as fatigue, muscle weakness, fever, smaller appetite, pale skin, and mild splenomegaly. This stage usually lasts 2 to 6 weeks.

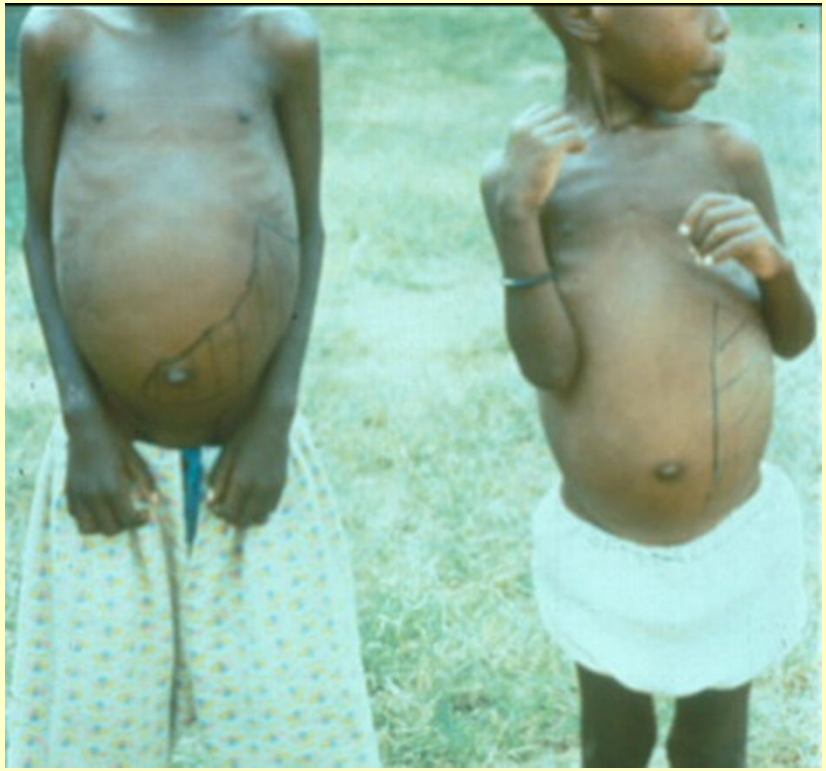
**2. Stage of fulminant disease** (splenomegaly and anaemia).
This stage is characterized by the following main symptoms:

- high fever with an irregular peak pattern, sometimes subfebrility to hyperfebrility (up to $40^0C$), often with 2 or more peaks in 24 hours (Roger's type febrility);




- marked splenomegaly, which develops quickly, while the spleen is thick and non-tender and can enlarge as far as the symphysis;
- hepatomegaly is less marked and occurs later on;
- generalized lymphadenopathy (especially in the African type of visceral leishmaniasis);

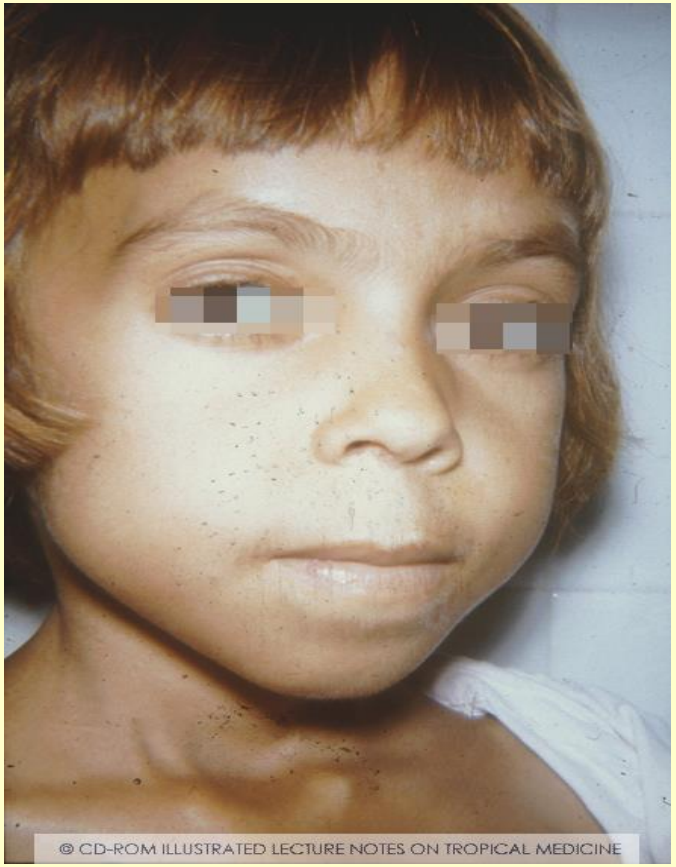





Girl suffering from visceral leishmaniasis – a potentially fatal condition, if untreated - with markers showing signs of liver and spleen enlargement. Libo Kemkem district, Ethiopia.

- skin changes – in many cases of the Indian type of the disease the skin becomes grayish-brownish (kala-azar – black fever derives from the skin colour seen).

- anaemia - develops rapidly and as the disease progresses; with mild lymphocytosis and monocytosis, lack of eosinophils, thrombocytopenia (causing hemorrhages) and high erythrocyte sedimentation rate (ESR).

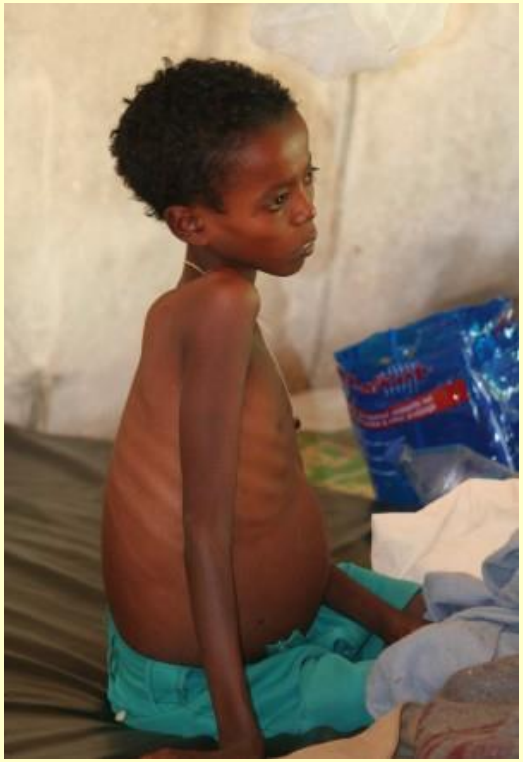


## 3. Cachexic (terminal stage).

This is characterized by:

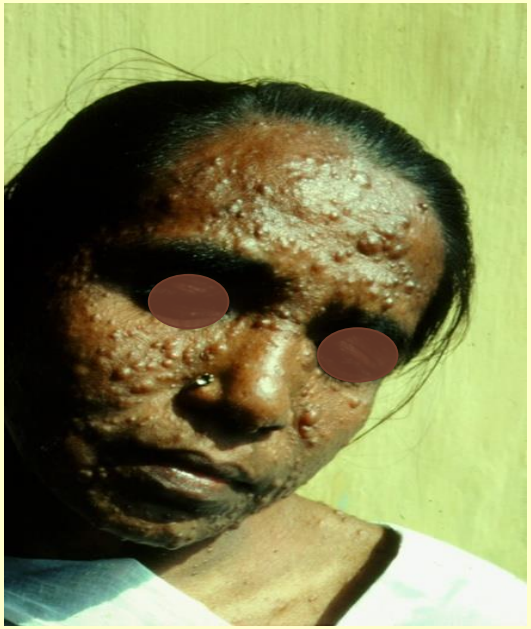
marked splenomegaly

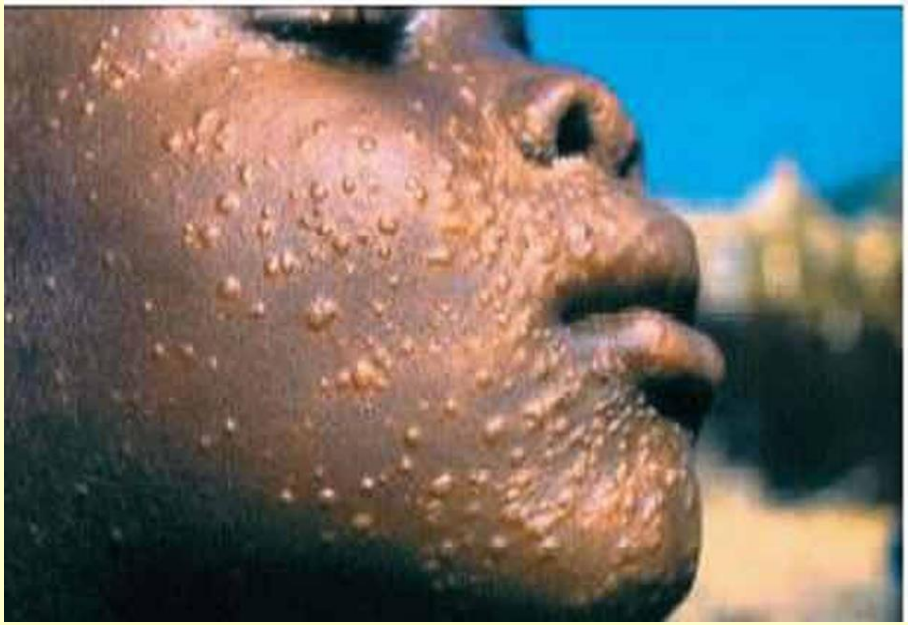
general emaciation, reduced body mass and muscular tone.



## COMPLICATIONS.

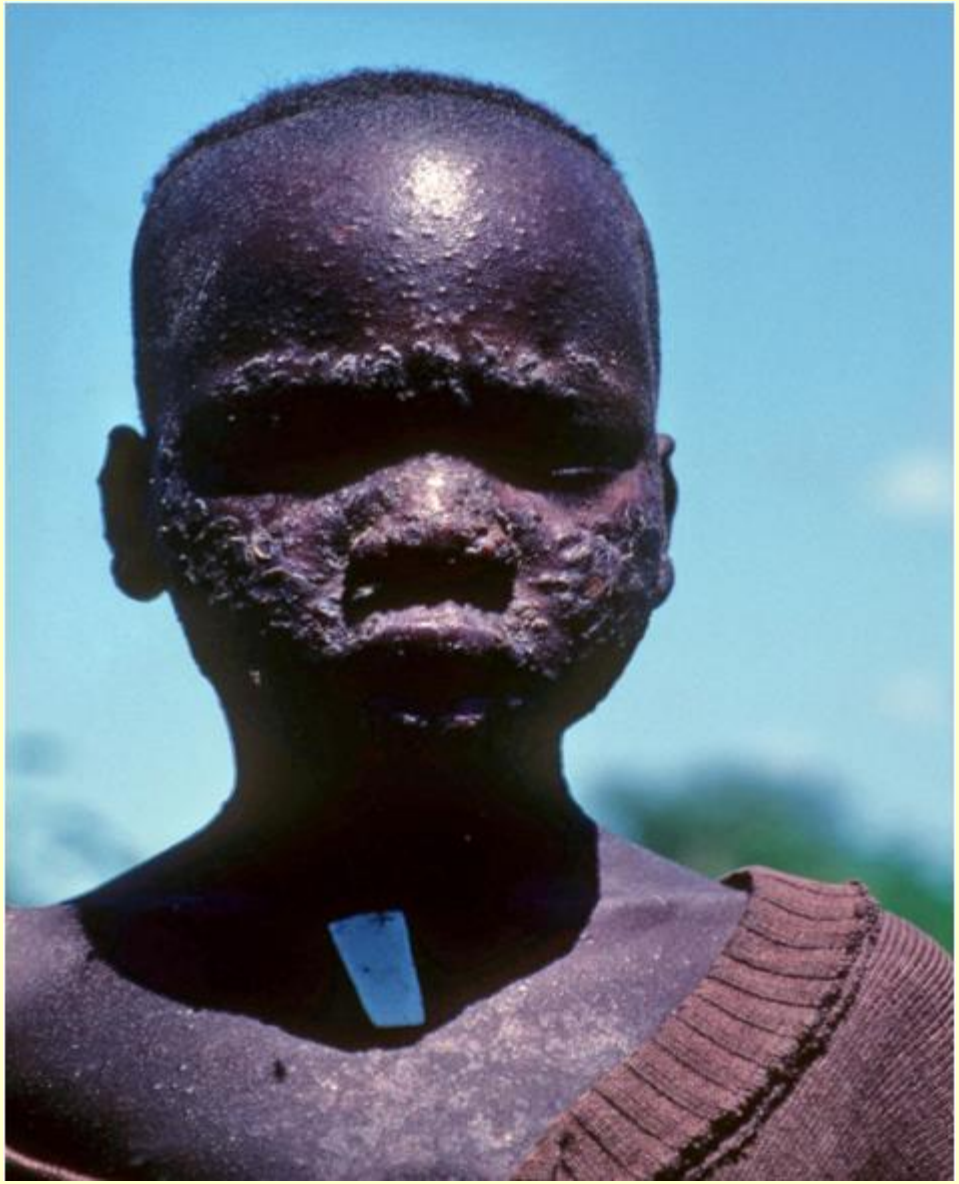
Post kala azar diffuse leishmaniasis (PKDL). In India, leishmania – containing multiple leishmanoids (i.e. nodules, papillomata, erythematous spots or depigmented spots) occur in about 10% of the cases.





In undiagnosed and untreated cases - pneumonia, enterocolitis, nephritis, diathesis to hemorrhages etc. develop.


Patient with post-kala-azar-dermal leishmaniasis. Was earlier treated and cured for visceral leishmaniasis. Libo Kemkem district, Ethiopia.



Post kala azar diffuse leishmaniasis (PKDL).

## DIAGNOSIS

The diagnosis is based on clinical, parasitological and epidemiological (travel to tropical and subtropical countries) data.

**The materials investigated** include: bone marrow aspirate (the material of choice), splenic aspirate or lymph node tissue sample, blood serum, or samples collected on autopsy.

**Methods of investigation.**

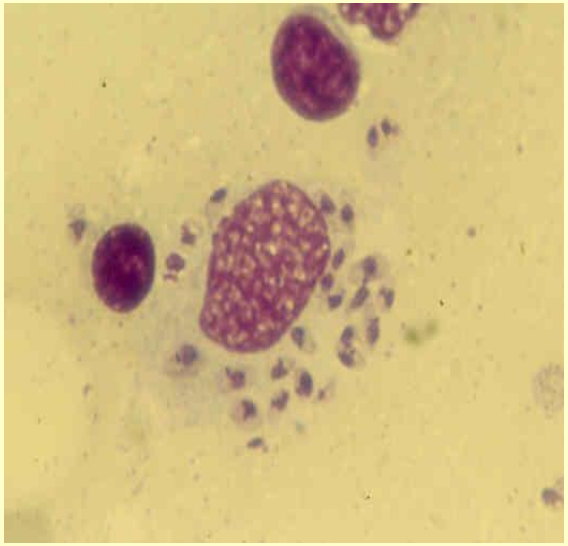
**Microscopy:**

- staining after Romanowsky-Giemsa in fixed smears;
- culture on artificial media (NNN or others);

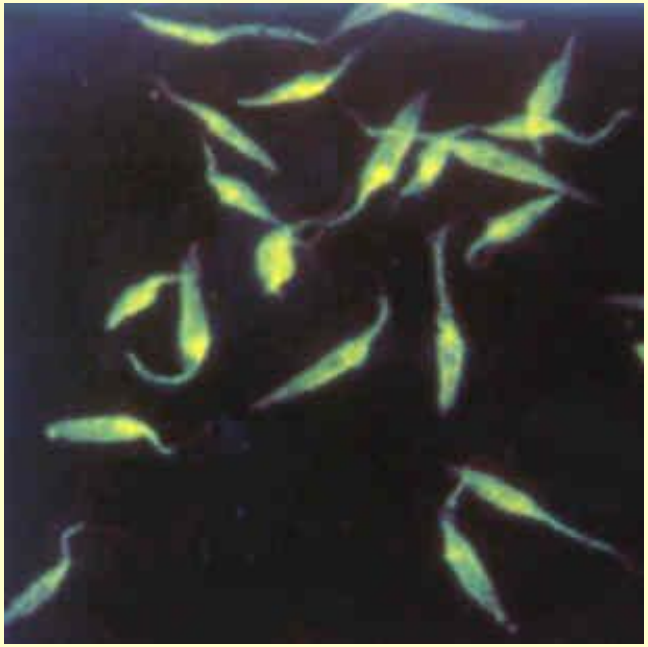
**Serological methods:**

- blood serum is investigated using Direct Agglutination Test (DA), immunofluorescence reaction (RIF) and ELISA;

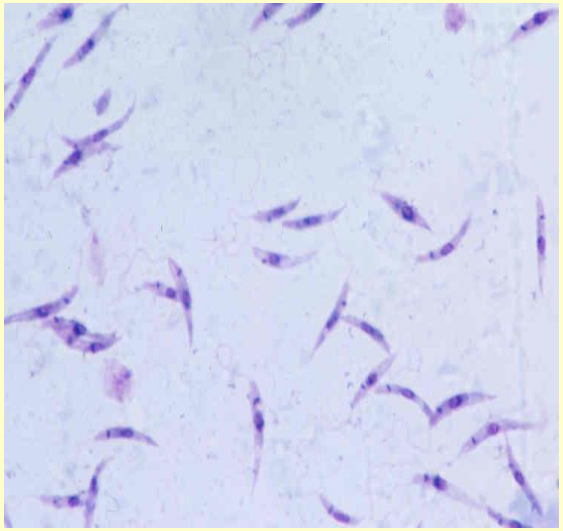
**Biomolecular methods:** PCR



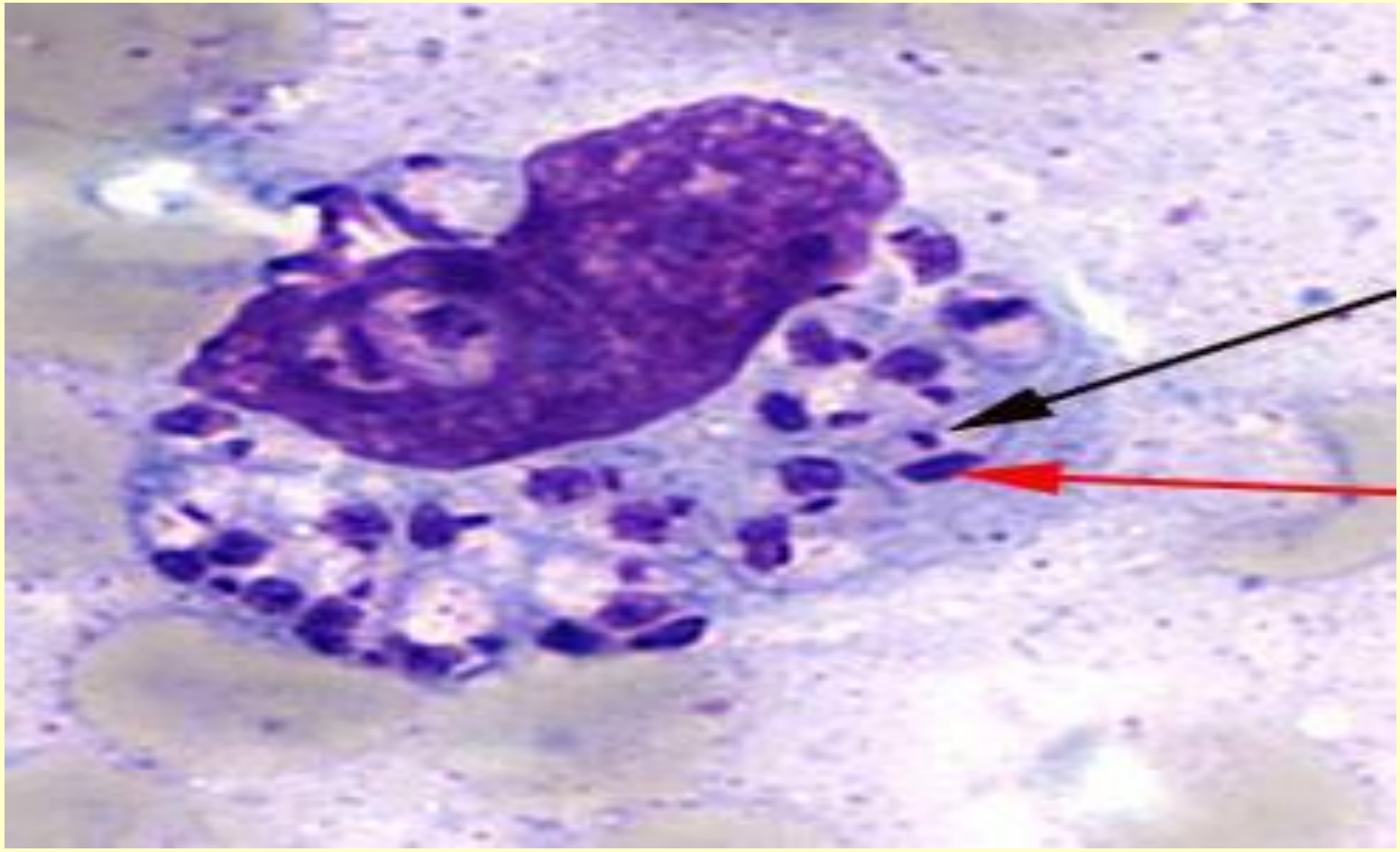
staining after Romanowsky-Giemsa



RIF



culture on artificial media (NNN)



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.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis implies ruling out:

- malaria,
- influenza,
- typhoid fever and paratyphus,
- sepsis,
- lymphogranulomatosis,
- anemia of a different origin,
- bacterial endocarditis,
- trypanosomiasis,
- chronic brucellosis,
- tropical splenomegaly, etc.

# Visceral leishmaniasis treatment
## (current WHO-recommended drugs)

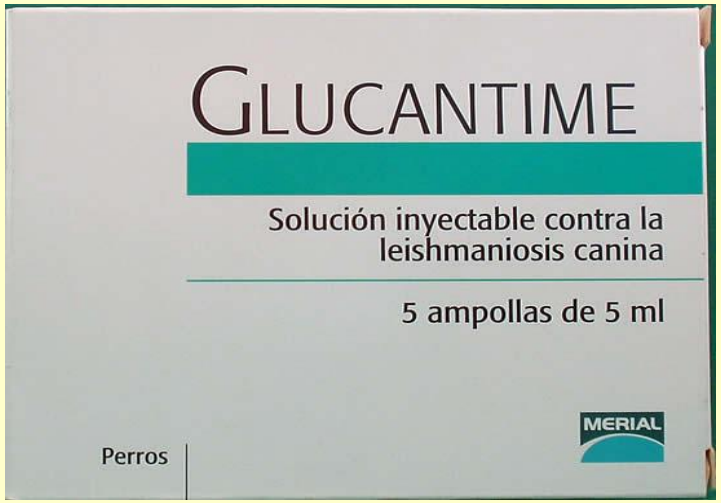
**This is carried with:**

- **5-valent antimoniate preparations:**

***Meglumine antimoniate (Glucantim)* - amp. 5 ml (405 mg)**

***Sodium Stibogluconate (Pentostam)* - flac. 100 ml (100 mg/ml)**

**They are dosed to 20 mg/kg b.w./d, i.m. for 21-60 days**

- **Diamidine derivatives**

*Pentamidine (Pentam)* - flac. 300 mg

*Lomidin* - amp. 3 ml


**Prescribed dose is:**

**4 mg/kg b.w./d, i.m., three times a week**

**for 5 to 25 weeks.**

- **Conventional amphotericin B (Amphotericin B)**

  **Fungizone flac. 50 mg**

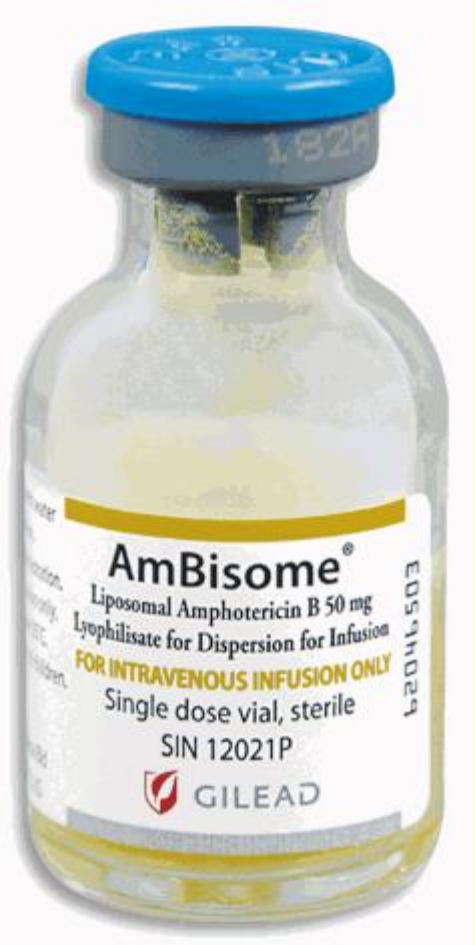
  They are dosed to **0.5-1 mg/kg/d i.v.**

  every other day for 28 days

- **Liposomial Amphotericin B**

  **AmBisome flac. 50 mg**

  **2-10 mg/kg/d i.v. for 2-10 days**



# EPIDEMIOLOGY

**Source of infection**

Depending on the geographical distribution and the type of causative agent, several types of leishmaniasis are distinguished:

1. Mediterranean-Middle Asian type (L. infantum). The main source and reservoair are dogs, jackals, foxes and rats. Infected humans are rarely infectious.
2. Indian type (L.donovani). The only source of infection known so far is an infected human individual.
3. American type (L. chagasi). The source and reservoair are dogs and foxes.

The main **mechanism of transmission** is transmissible. Vectors of transmission are various types of genus *Phlebotomus*. Other mechanisms of transmission are ***transplacental*** and through ***hemotransfusion***.

**Susceptibility and immunity.** Susceptibility is high, though infectivity index is quite low. After illness, strong immunity is built, that precludes reinfection.

There is no vaccine against this parasitosis.

## PREVENTION

Efforts are put:

1. Early diagnosing the disease.
2. Etiological therapy.
3. Registration of cases and follow-up of diseased individuals.
4. Epidemiological studies when leishmaniasis cases are registered.
5. Slaughtering of wild and domestic animals that are reservoir for the infection.
6. Application of insecticides against the vector.
7. Prevention of phlebotomus bites (repellents, bed nets, window nets, etc.).
8. Health education for the population of endemic regions or people traveling to tropical and subtropical countries.

Specific prophylaxis against visceral leismaniasis is not carried out.

# *Cutaneous leishmaniosis of the Old World*

Cutaneous leishmaniasis is a transmissive protozoosis with endemic distribution in tropical and subtropical regions, characterized by limited damage of the skin. There are several types of the disease.

## *ETIOLOGY*

Cutaneous leishmaniosis of the Old World is caused by three causative agents of the ***L. tropica complex*** :

***L. tropica (causes urban type of the disease)***

***L. major (causes rural type of the disease)***

***L. aethiopica (causes lepromatous leishmaniasis)***

* Their morphology and life cycle are similar to those of the representatives of the *L. donovani* complex.

# PATHOGENESIS AND PATHOLOGY

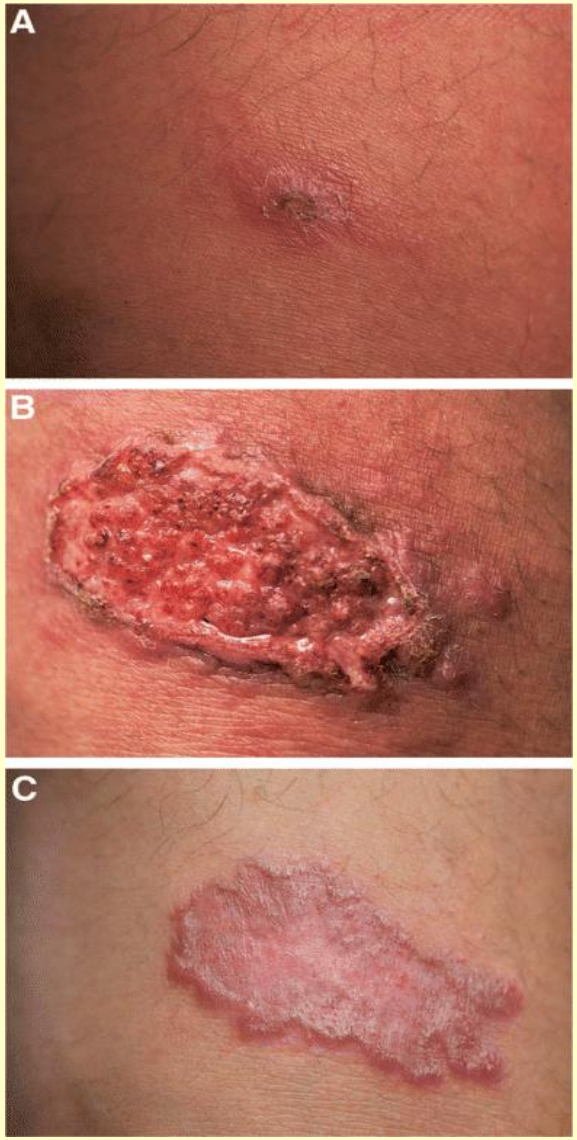
On the site of inoculation of *leishmania*, a specific granuloma of the skin appears. The parasites, localized in the histiocytes, are surrounded by lymphocytes, plasma cells and mononuclear cells.

After cell proliferation, the following stages occur:

1. **Necrosis in the center of the infiltrate with ulceration;**
2. **Fibrosis;**
3. **Scar formation.**

* In infections due to *L.tropica*, dissemination of the leishmania by route of lymphatics is possible, resulting in lymphadenites, and lymphangitides with multiple granulomatous nodules.

## All stages of pathological process during the *cutaneous leishmaniosis*




*A*, Initial superficial lesion of cutaneous leishmaniasis.

*B*, Ulcerated and enlarged lesion - 90 days after initiation of treatment with *Glucantime*.

*C*, Atrophic scar with infiltration in the borders - 60 days after initiation of a second course of *Glucantime*.

# CLINICAL PRESENTATION. CLINICAL FORMS.

## *1. Cutaneous leishmaniasis, caused by L.tropica (urban type, dry bouton d'Orient)*

The disease tends to present with isolated sores, and slower progress and longer duration (a year or more).

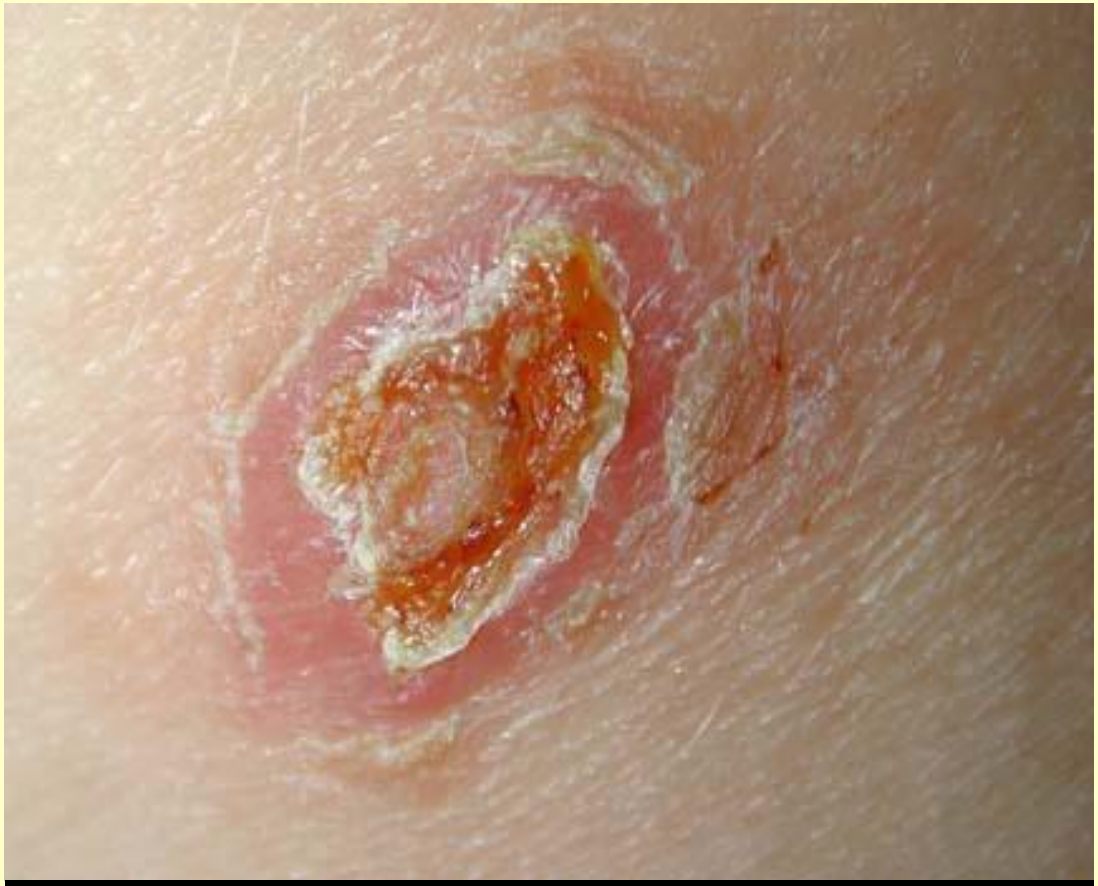
The incubation period varies from 2 to 8 months to 1 to 5 years or longer;

On the site of the phlebotomus bite a smooth pink primary papule forms, 2-3 mm in diameter, which grows to 1-2 cm in 3 to 6 months;

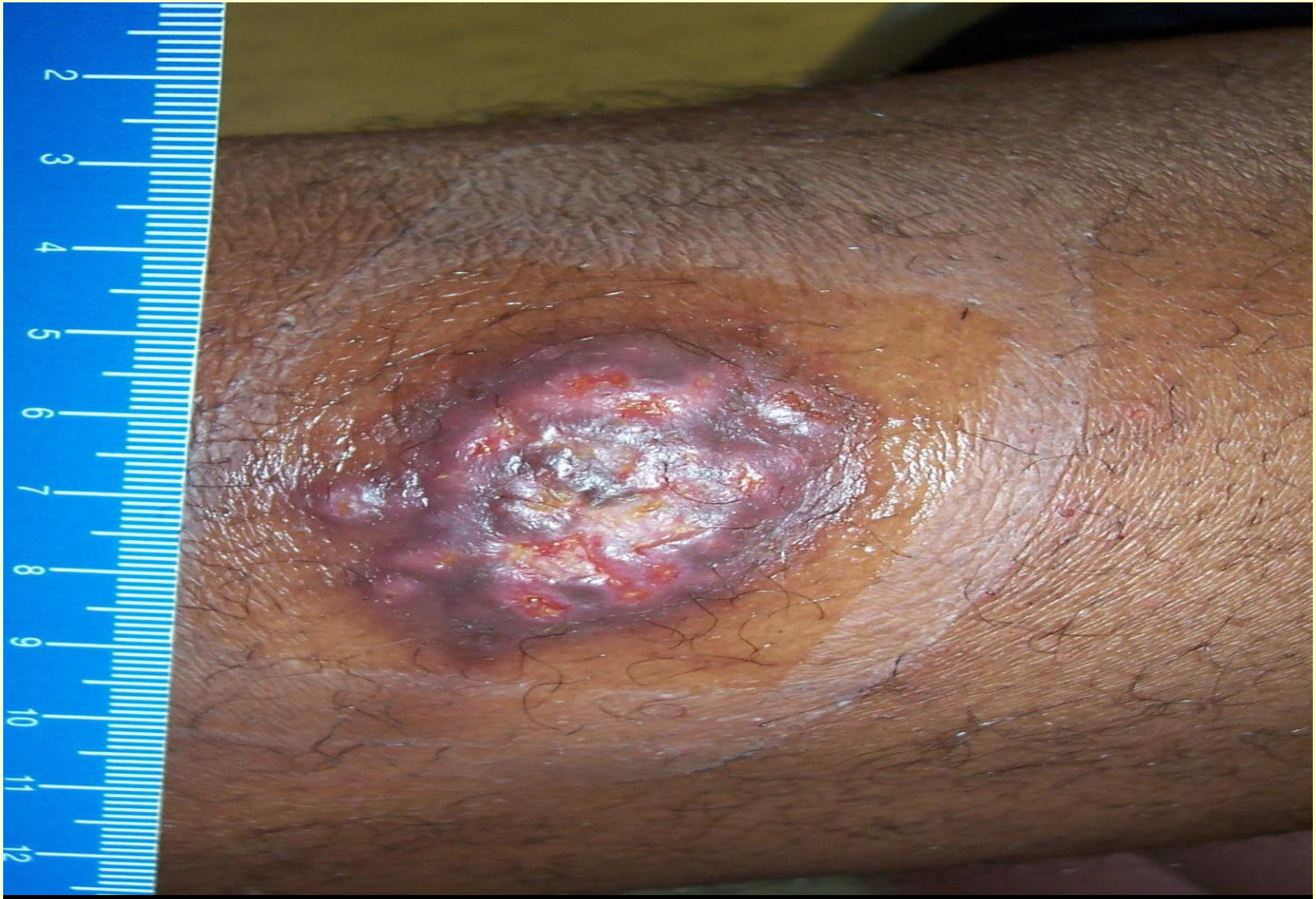
A crust appears at the center, and when it peels off, a sore is seen with a granulated bottom and a pussy coating. The sore is round or oval in shape, irregular contours and elevated peripheral edges, surrounded by infiltrate (after 6 to 10 months); The diameter may grow as large as 4 to 6 cm in 8-12 months;

The sores are located mainly on the face and extremities and are not painful. Secreted material is scarce, serous or pussy and serous. The general health of the patient remains good. Several months later a scar begins to form. Usually, cicatrix formation stops 6 to 7 months after the appearance of the papules.

Child with cutaneous leishmaniasis awaiting treatment in Kabul, Afghanistan.



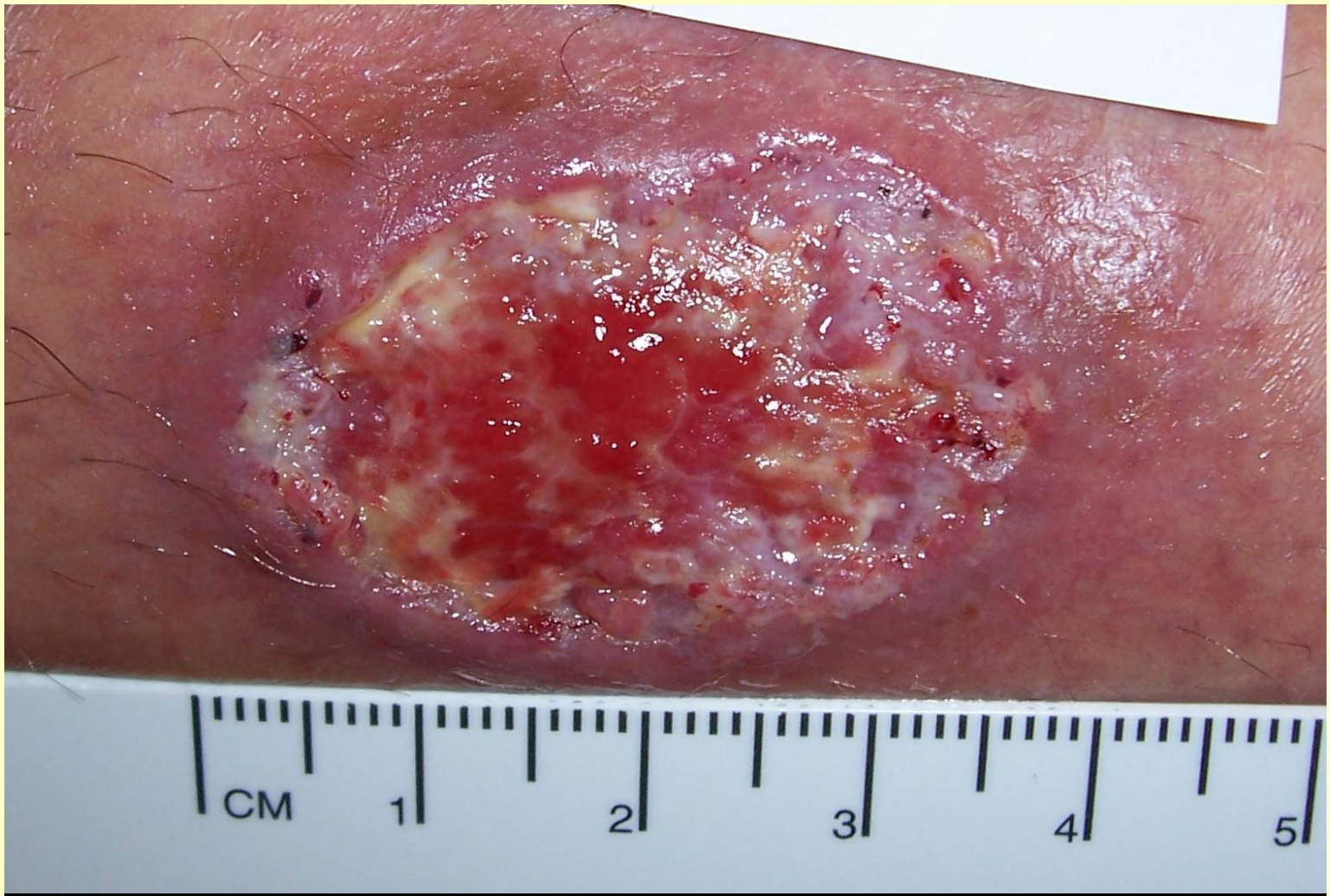
Old World localized cutaneous leishmaniasis located on the trunk of a soldier stationed in Kuwait. This lesion was a 3 cm by 4 cm nontender ulceration that developed over the course of 6 months at the site of a sand fly bite.



Cutaneous leishmaniasis with keloid formation in a black soldier.


Patient with cutaneous leishmaniasis being treated in Dar Al Aman, Kabul, Afghanistan. Kabul harbours the largest number of cutaneous leishmaniasis patients in the world.

The presence of a secondary bacterial flora causes complications and protracts the clinical course.



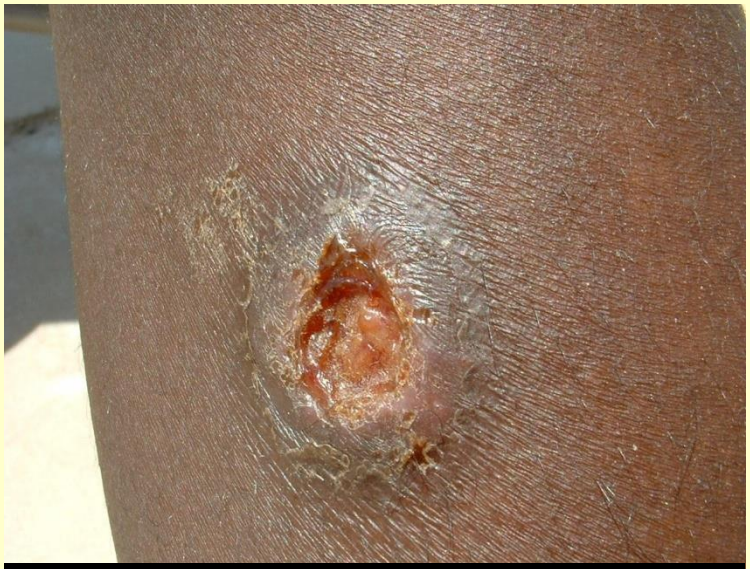

Active cutaneous leishmaniasis lesion with likely secondary infection

## 2. Cutaneous leishmaniasis, caused by L.major (rural type, wet ulcer).

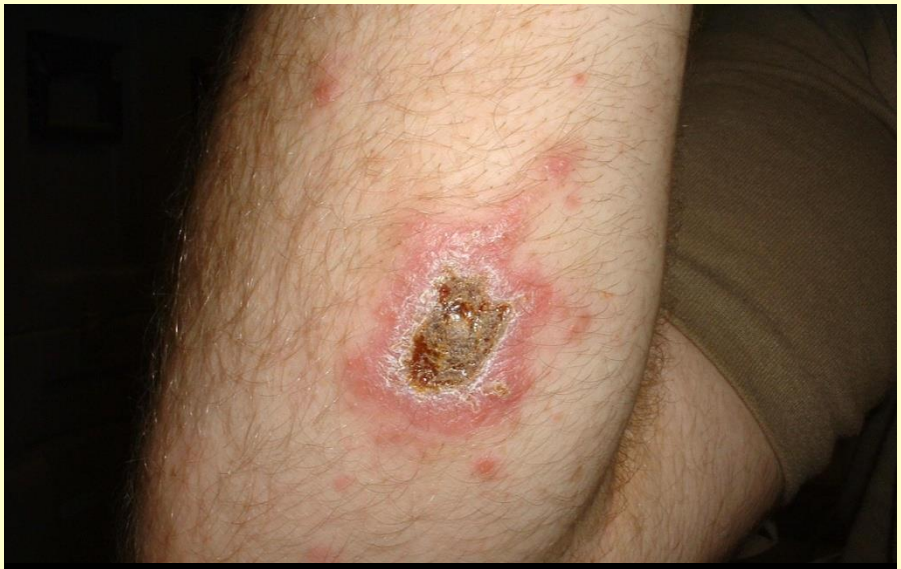
It is characterized by multiple ulcers, a short incubation period, quick progress and cicatrix formation. The stages of the disease, as well as the clinical forms are similar to those of the urban type of cutaneous leishmaniasis.

The incubation period varies from 1 week to 1-1.5 months (most commonly 10-20 days);

The necrosis in the center of primary papules begins 1-2 weeks after inoculation of leishmania, and ulcers 10-15 cm in size with abundant serous pussy exudates are formed, painful to touch.

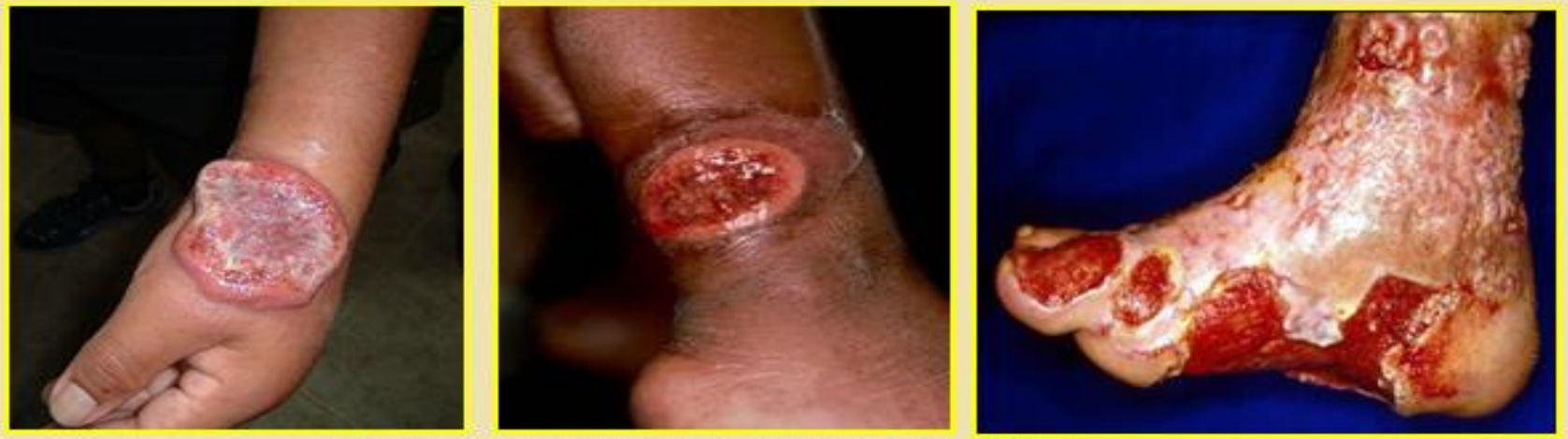


*Classic Leishmania major lesion from a case in Iraq shows a volcanic appearance with rolled edges.*



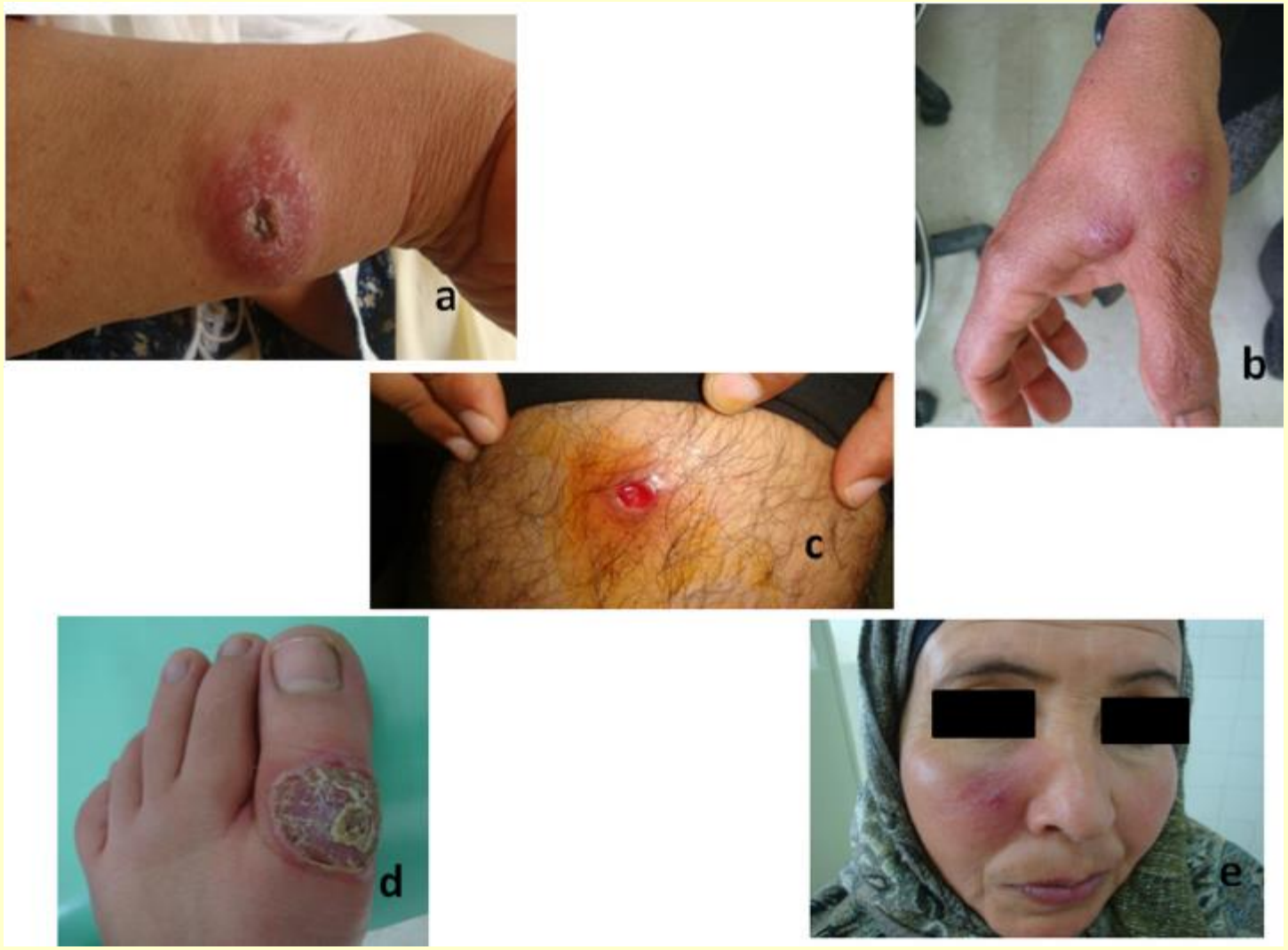
*Atypical appearance of Leishmania major lesion with local spread beyond the borders of the primary lesion.*

The number of the ulcers is several times greater;
The rural type is characterized by formation of multiple small tubercula around the primary papule. Later, these tubercula ulcerate and join together, thus causing extensive lesions;
The presence of a secondary bacterial flore causes complications and protracts the clinical course;
Usually, cicatrix formation stops 6 to 7 months after the appearance of the papules.



*Picture courtesy: CDC (Centre for Disease Cure & Prevention)*

**Fig: Severity of lesions caused by cutaneous leishmaniasis**



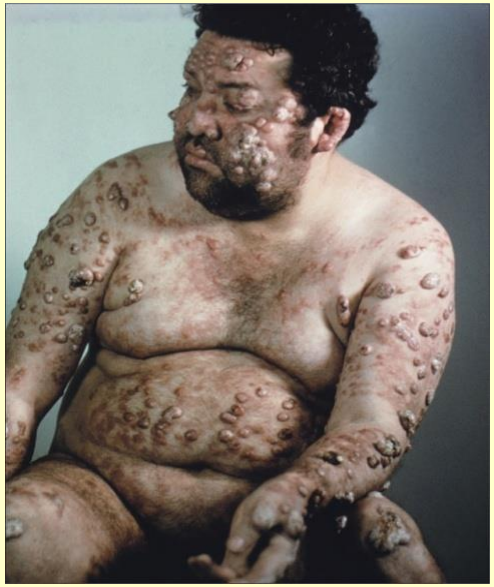

*Clinical polymorphism of cutaneous lesions caused by L. major : (a) Ulcero-crusted (b) nodular, (c) ulcerous, (d) erythemato-squamous and (e) nodulo-papulous.*

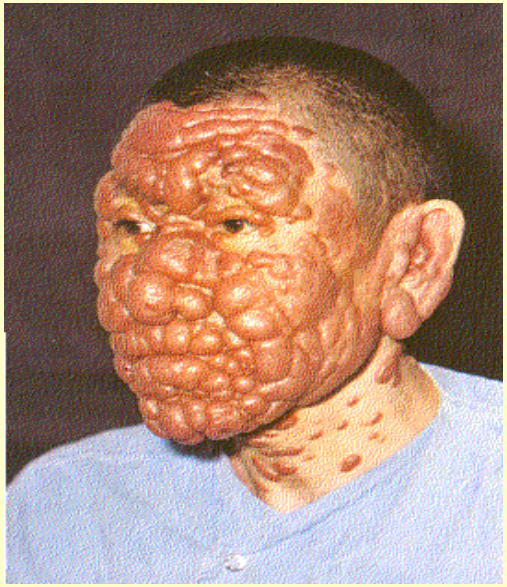
### *3. Cutaneous leishmaniasis, caused by L.aethiopica.*

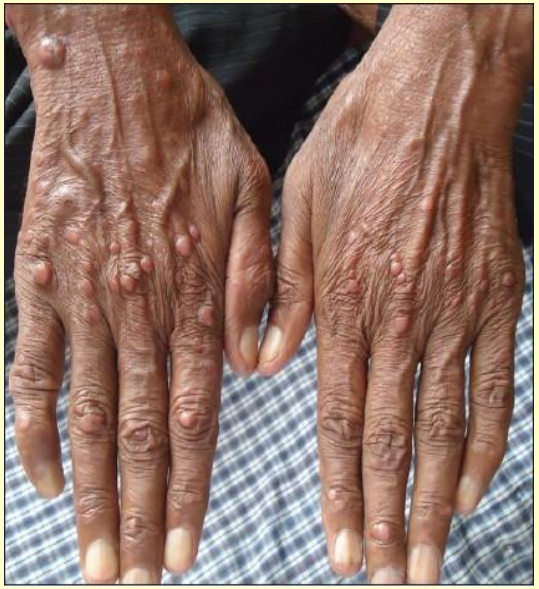
The lesions are similar to those caused by *L. tropica*.

The incubation period varies from 2 to 8 months to 1 year or longer;

This form of the disease is known as diffuse cutaneous leishmaniasis (lepromatous leishmaniasis). Nodules form, similar to those in leprosy, without ulcerations. The process spreads to gradually affect the whole body, mainly the face and the extremities;







*Diffuse cutaneous leishmaniasis (lepromatous leishmaniasis)*

# *Cutaneous leishmaniosis of the New World (Leishmaniasis americana)*

# *ETIOLOGY*

Cutaneous leishmaniosis of the New World is caused mainly by representatives of two complexes:

***L. mexicana complex:***
*L. mexicana;*
*L. amazonensis;*

***L. brasiliensis complex:***
*L. guyanensis;*
***L. braziliensis;***
*L. peruviana;*
*L. panamensis;*

* The morphological and biological features of the parasites are similar to those of the other leishmania.

## PATHOGENESIS AND PATHOLOGY

These are similar to those of cutaneous leshmaniasis of the Old World - necrosis in the center of the infiltrate with ulceration, fibrosis and scar formation, but they inflict more severe skin lesions. Frequently, the mucosa of the nose, mouth, pharynx, larynx, organs of the reproductive system is involved.

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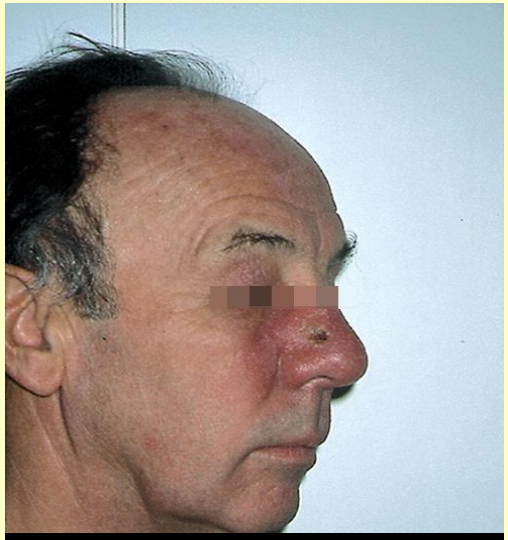
# CLINICAL PRESENTATION. CLINICAL FORMS.

## *1. Mucocutaneous leishmaniasis, caused by L. braziliensis*

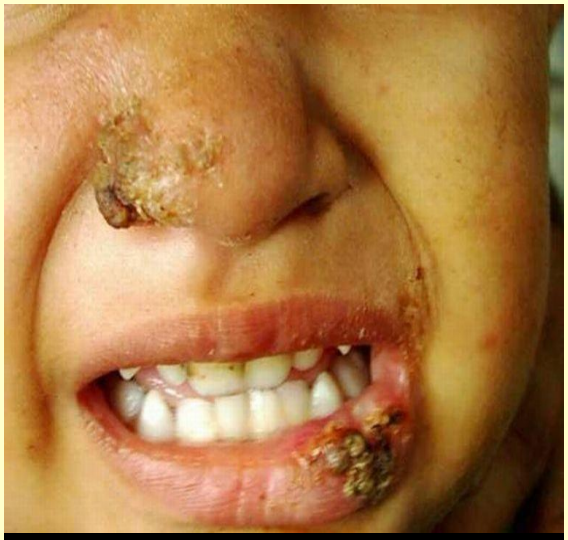
L.(v.) braziliensis causes the most severe form of mucocutaneous leismaniasis ***(forma espundia)***.

The incubation period varies between 2-3 weeks to 1-3 months;

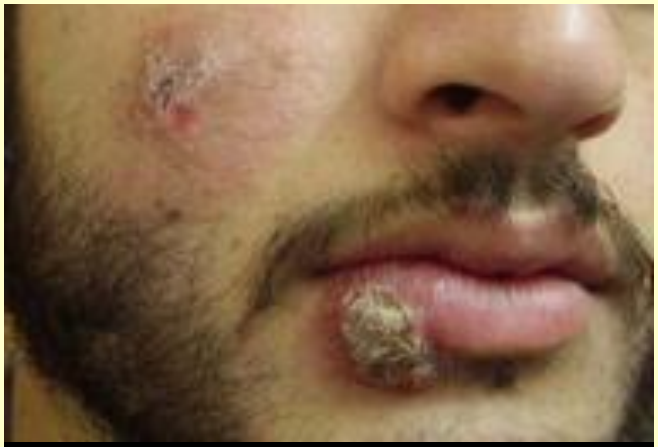
The primary lesion is like that in the rest of leismaniases. It is painless, Sometimes itchy and undergoes regressive development for about 6 months.



*Early Leishmania braziliensis infection, with lesions on the nose. This differs from espundia.*



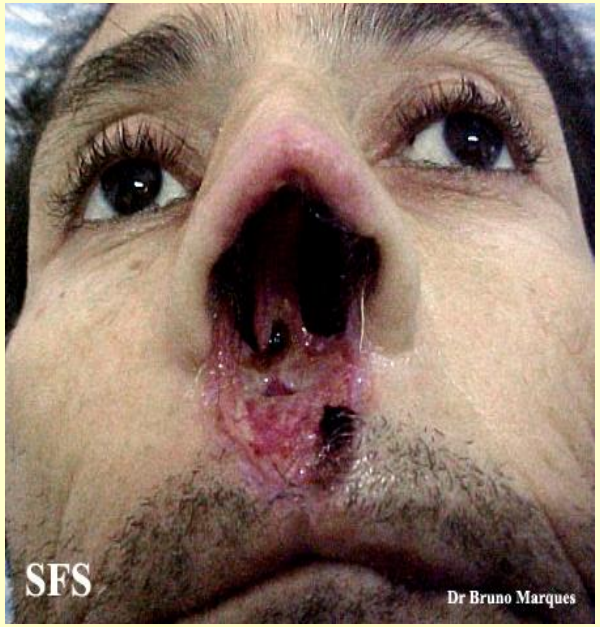
*Involvement of cutaneous as well as mucosal surfaces of lip and nose in a child*

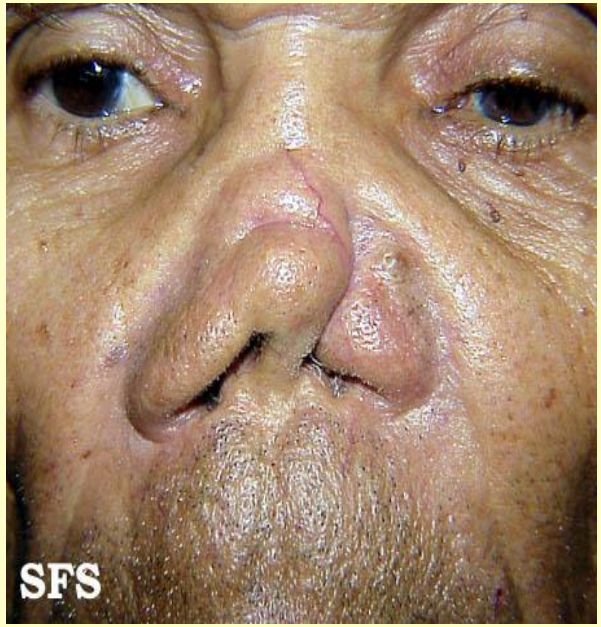


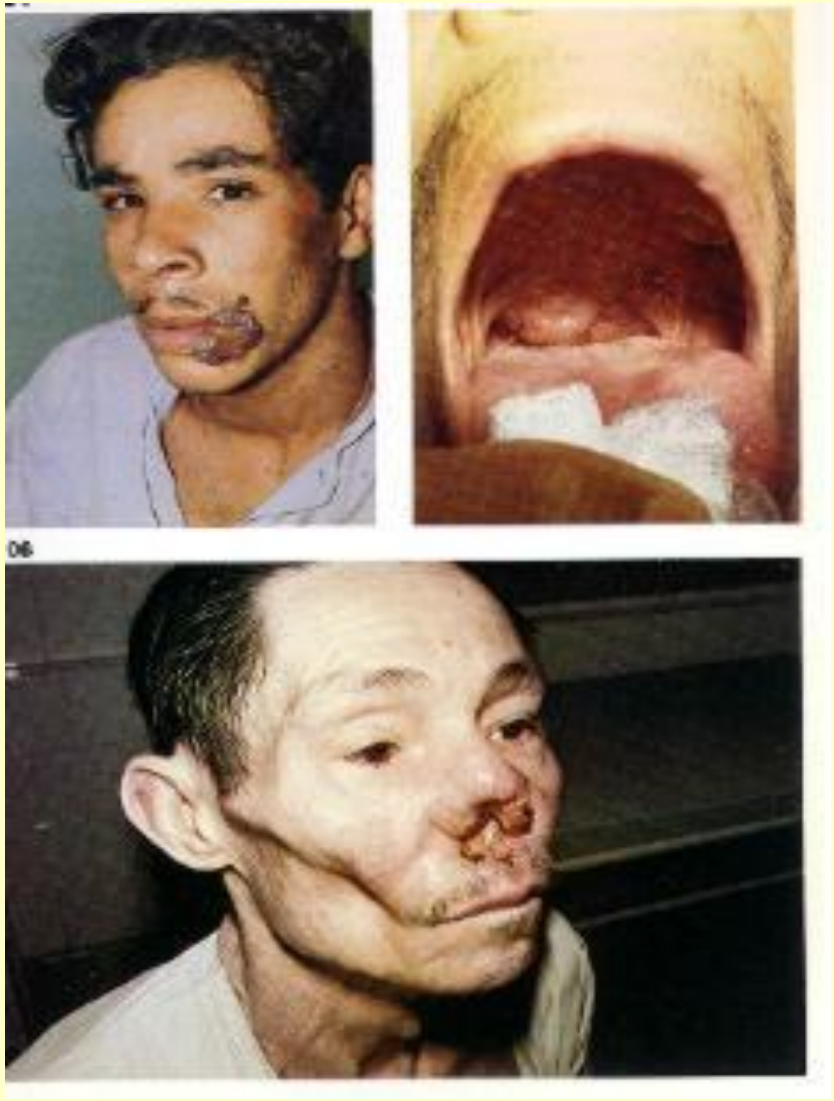
*Early stage of mucocutaneous leishmaniasis*

## *Mucocutaneous leishmaniasis, caused by L. braziliensis*

The mucocutaneous damages become obvious in about 2 years (sometimes as late as 20 years).
The mucocutaneous leishmaniasis are characterized by ulcerations, polyp formation, perforations leading to progressive destructive alterations of soft tissues and cartilage, nose deformities, involvement of the nasoparynx and the larynx.
Fatal outcome is possible due to aspiration pneumonia in case the pharynx is destroyed and as a result of a concurrent secondary bacterial infection.

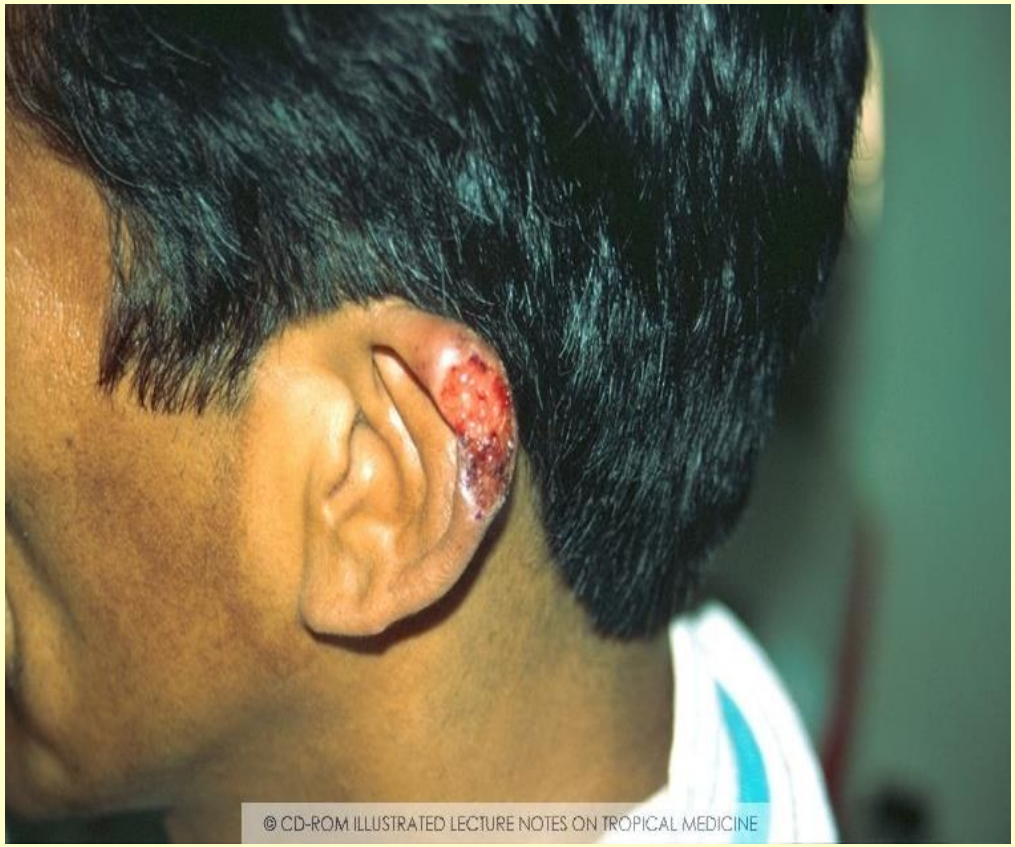


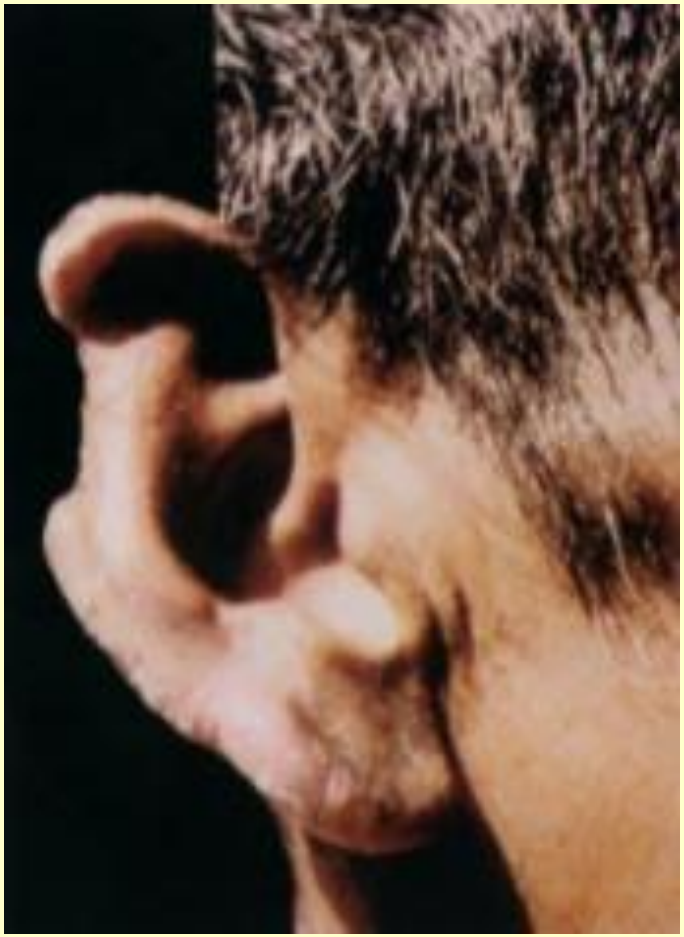





## *2. Cutaneous leishmaniasis, caused by L.(v.) guyanensis, L.(v.) panamensis, L.(v.) peruviana and Leishmania mexicana complex*

- *L.(v.) guyanensis* The course of the disease is characterized by skin lesions in various parts of the body, frequently with dissemination through the lymph vessels. There is no involvement of the nasopharynx.
- *L.(v.) panamensis* Single skin lesions are seen, and the nasopharynx is rarely involved and limited in scope.
- L.(v.) peruviana. The disease is usually benign, with single skin lesions.
- Infections with *Leishmania mexicana* complex also take a benign course and are self-limited to a period of about 6 months. Lesions are single and do not metastasize.


© CD-ROM ILLUSTRATED LECTURE NOTES ON TROPICAL MEDICINE



# DIAGNOSIS OF CUTANEOUS LEISHMANIASIS

The diagnosis is based on clinical, parasitological and epidemiological (travel to tropical and subtropical countries) data.

Samples for investigation are collected from the papule, the infiltrate around the lesion. Skin biopsy specimens are also collected.

Methods of investigation:

Microscopy:

- staining after Romanovski- Giemsa in fixed smears;
- culture on artificial media (NNN or others);

Serological methods:

- blood serum is investigated using immunofluorescence reaction (RIF) and ELISA;

Biomolecular methods: PCR

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis implies ruling out:

- Leprosy;
- Syphilis;
- Tropical ulcers;
- Tuberculosis;
- Skin cancer;
- Lupus erythematosus.

# Cutaneous leishmaniasis treatment: current WHO-recommended drugs

**For treatment are prescribed:**

**Meglumine antimoniate (Glucantim)**

**Sodium stibogluconate (Pentostam)**

**In uncomplicated forms:**

Intralesional infiltrations (1-3 ml), 1-3 times/week for 2-3 weeks

**In complicated forms:**

Systemic administration at the dose of 20 mg/kg/d i.m. for 14-21 days

World Health Organization

# Mucocutaneous leishmaniasis treatment: current WHO-recommended drugs

1. Pentamidine (Pentam, Lomidine) - flac.300 mg, amp.3 ml

   4 mg/kg b.w./d, i.m., three times a week for 5 to 25 weeks.

2. Amphotericin B (Fungizone) flac.50 mg

   1 mg/kg/d i.v. every other day for 28 days

World Health Organization

# EPIDEMIOLOGY

## SOURCE OF INFECTION

1. ***Urban type cutaneous leishmaniasis.*** Sources for the infection caused by *L.tropica* are infected humans and dogs.
2. ***Rural type cutaneous leishmaniasis. -*** the main source of infection are desert rodents and other wild animals.
3. The sources of infection for ***Leishmaniases of the New World*** are wild rodents and some other wild mammals.

## MECHANISMS, FACTORS AND ROUTES OF TRANSMISION

Transmission occurs through vectors flies of the genus ***Phlebotomus:***
*P. papatasi, P. mongolensis, P. alexandri, P. anasarii, P. sergenti,*
*P. duboscqi* in the cases of Leishmaniaseis of the Old World, as for Leishmaniaseis of the New World - flies of the genus ***Lutzomyia:***
*Lu. olmeca, Lu. pessoai, Lu.intermedia, Lu. trapidoi, Lu.cruciata.*

## SUCSEPTIBILITY AND IMMUNITY

**Susceptibility** to all forms of cutaneous leishmaniasis is high.

After illness, strong immunity is built, that protects against reinfection with a homologous type of the disease.

There is no vaccine against this parasitosis.