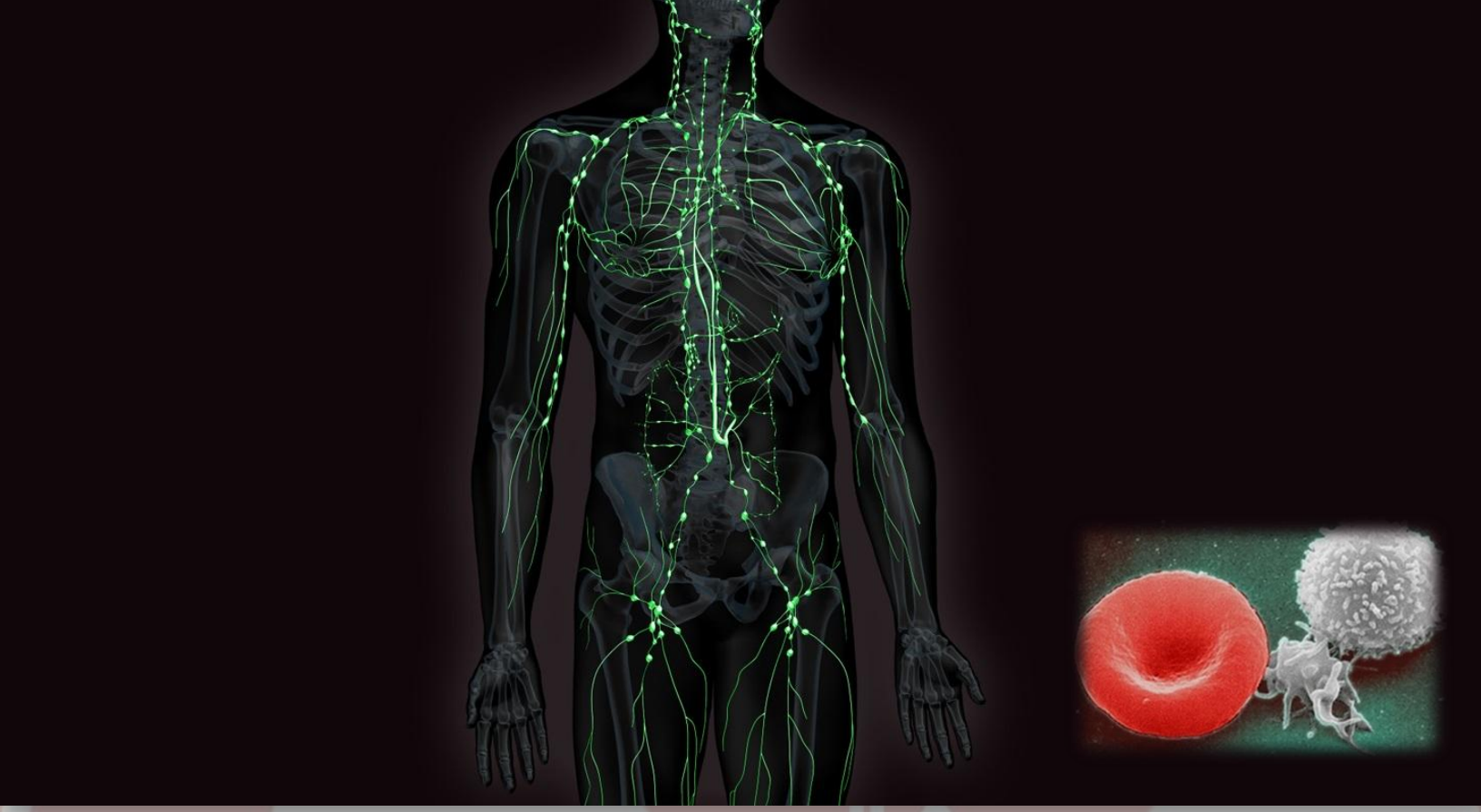


Hemolymphatic system

Microbiology

Lecture 4: Leishmaniasis and Trypanosomiasis

Done By:

Hossam Al-Noaimi

HLS module, microbiology lecture 4 summary

Leishmaniasis and Trypanosomiasis

حكي الدكتور باللون الأحمر، والسلايدات بالأزرق

#Introduction

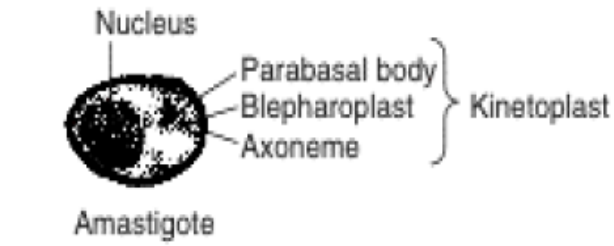
**Two of the many genera of hemoflagellates are pathogenic to humans, Leishmania and Trypanosoma.

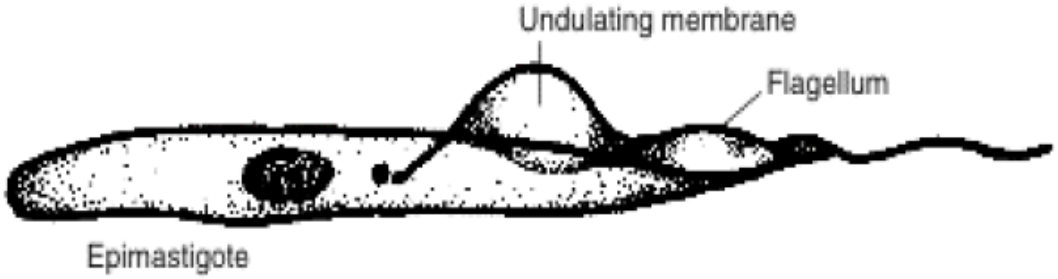
hemoflagellates: hemo >> blood // flagellates >> flagella which allow these parasites to swim in the blood

**They reside and reproduce within the gut of specific insect hosts. The life cycle is completed when a second insect ingests the infected mammalian blood.

**During the course of their passage through insect and vertebrate hosts, flagellates undergo developmental changes.

لازم تمر هاي الطفيليات على حشرة، وممكن تقرص الانسان، فبوخذ الانسان منها هاي الطفيلية، بتتطور جواه، وممكن تيجي حشرة ثانية تقرص هاذ الانسان وبتوخذ منه هاي الطفيلية وبتكمل تطور،، وعملية التطور هاي بتكتمل لما تقرص هاي الحشرة انسان ثاني وتدخل عليه الطفيليات، راح نشرح كلشي بالتفصيل لقدام ☺





المرحلة الأولى (الصورة الأولى) : الي فيها الطفيلية بتشبه شكل الخلية وبنسميها Amastigote

هون بكون في عنا نواة واضحة وكبيرة، وفي اشي عطرف الخلية بنسميه Kinetoplast

المرحلة الثانية (الصورة الثانية) : هون بلشت الطفيلية تصير أطول (elongated)،، وبلش الذيل (flagellum) يظهر، وبنسميها Promastigote

المرحلة الثالثة (الصورة الثالثة) : هون تطور اشي بنسميه (Undulating membrane)،، وهاذ بساعد في حركة الطفيليات،، وبنسمي الطفيل في هذه المرحلة Epimastigote

المرحلة الرابعة (الصورة الرابعة) : هون صار الطفيل مكتمل النمو تماما، وبنسميها Trypomastigote،، وهون صار ال(Undulating membrane) اطول وصار بغطي الطفيلي من اوله لآخره

1. Leishmania (also called *Kala Azar disease*)

#Species:

**The many strains can be more simply placed in four major groups based on their *serologic*, *biochemical*, *cultural*, and *behavioral characteristics:*

Remember:

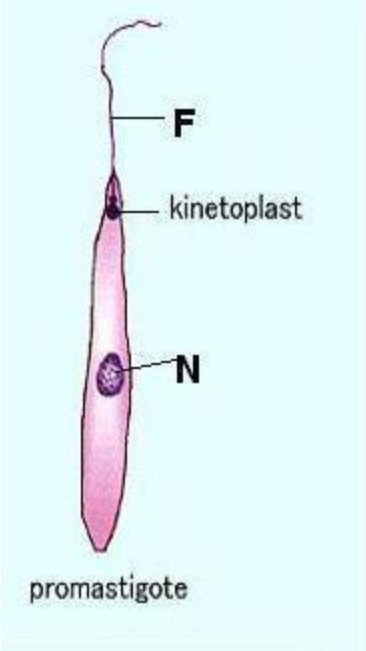
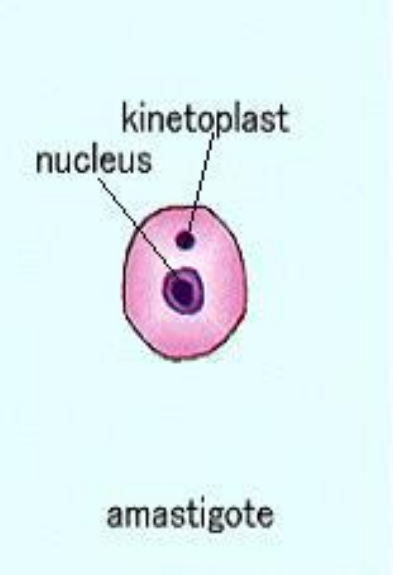
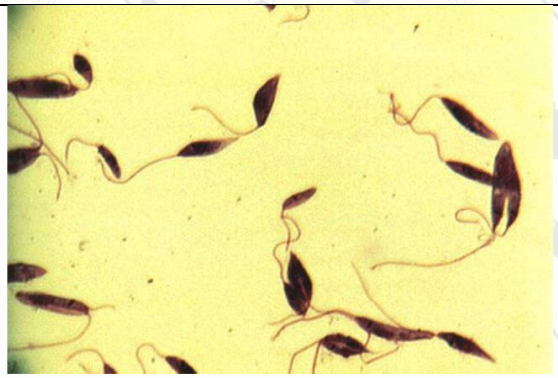
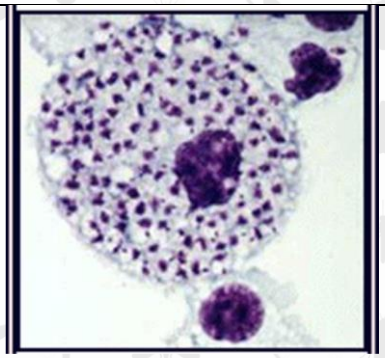
- ➔ serological classification = refers to the diagnostic identification of antibodies in the serum.
- ➔ Biochemical classification= based on chemical properties

- *Leishmania tropica* and *L. mexicana* produce a localized cutaneous (skin) lesion or ulcer, known popularly as ***oriental sore*** راح نوخذه بالتفصيل لقدام

- *L. braziliensis* is the cause of ***American mucocutaneous leishmaniasis***

- *L. donovani* is the etiologic agent of ***kala azar***

#Morphology:

Promastigote	Amastigote
	
	 This image shows a macrophage which has engulfed large amounts of amastigotes

#Epidemiology:

**Endemic in 88 countries.

**It is estimated that over 20 million people worldwide suffer from leishmaniasis and 1 to 2 million additional individuals acquire the infection annually.

**More than 90% of C.L (Cutaneous Leishmaniasis) cases occur in: Iran, Algeria, Afghanistan, Brazil, Peru, Saudi Arabia, and Syria.

**More than 90% of V.L (Visceral Leishmaniasis) (also called systemic leishmaniasis) cases occur in 5 countries; Bangladesh, India, Nepal, Sudan, and Brazil. هون المرض بنتقل للدم وبروح على أعضاء ثانية ما بضله بس عالجلد

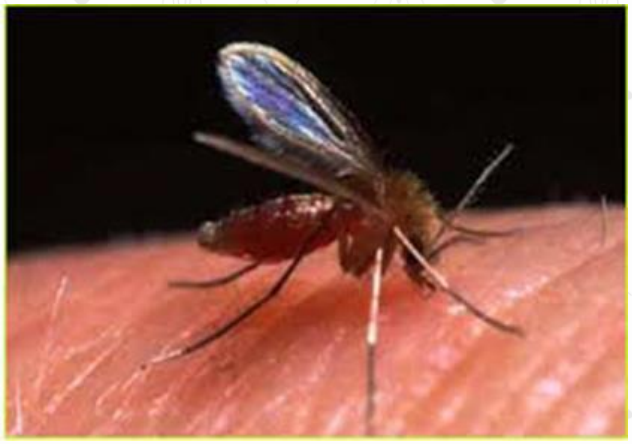
**Annual death due to V.L is 59,000 cases.

N.B: Cutaneous Leishmaniasis isn't lethal, while Visceral Leishmaniasis causes a number of deaths each year.

#Life Cycle:

1- ***Amastigotes*** ingested in the course of a meal assume the flagellated promastigote form, multiply within the gut, and eventually migrate to the buccal cavity of phlebotomine sandfly (ذبابة الرمل)

بتيجي هاي البعوضة بتلسع الشخص،، اذا كان عند هاذ الشخص هاي الطفيليات بتوخذها البعوضة في اللسعة،، وفورا لما تدخل على بطن البعوضة بتتحول الى promastigote form،، بتضلل تتكاثر في بطن البعوضة وبعدين بتروح للbuccal cavity
***ولازم هاذ النوع بالتحديد من البعوض يكون موجود عشان ينتقل المرض.



2- When the fly next feeds on a human or animal host, the buccal promastigotes are injected into the skin of the new host together with salivary peptides capable of inactivating host macrophages.

هاي الذبانة نفسها راح تقرص شخص ثاني،، وبتنقل الطفيليات الي فيها بالإضافة الى شوي من لعابها الي بحتوي على مواد بتمنع تجلط الدم، ومواد بتعمل زي التخدير عشان ما نحس بألم القرصة، ومواد بتبطل عمل الmacrophages تبعت هاذ الشخص الي قرصته.

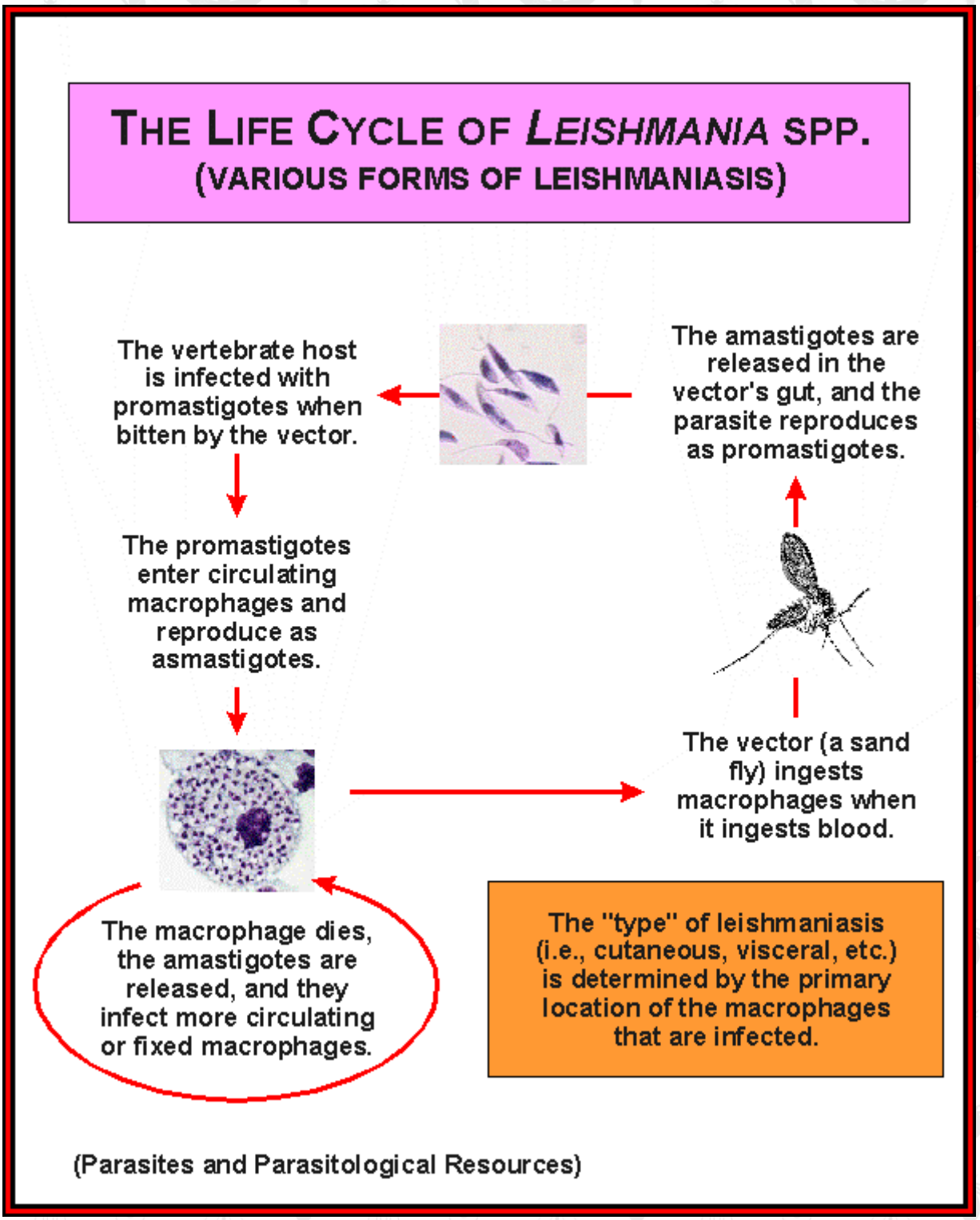
3- Amastigotes invade macrophages and divide until the infected cell ruptures.

لما تدخل هاي الطفيليات على دم الشخص المصاب ببتحول من promastigote إلى Amastigotes، وبتروح على الmacrophages وببتكاثر جواتها لحتى ما نفجر الخلية.

4- The sandfly acquires the organisms during the blood meal.

هون ممكن تيجي ذبانة ثانية مش مصابة ممكن تقرص هاذ الشخص المصاب وتوخذ هاي الطفيليات وتعمل دورة جديدة بكل الي حكيناه فوق.

هاي الصورة بتوضح الي حكيناه



#Pathogenesis:

**After the host is bitten by an infected sandfly, the parasites disseminate in the bloodstream and are taken up by the macrophages of the spleen, liver, bone marrow, lymph nodes, skin, and small intestine

الmacrophages المصابة ممكن تنقل هاي الطفيليات الي جواتها الى الأعضاء السابقة

**Histiocytic proliferation in these organs produces enlargement with atrophy or replacement of the normal tissue

نتيجة انتقال هاي الطفيليات الى هاي الأعضاء بصير عنا Histiocytic proliferation فيها

N.B: **Histiocyte**: A type of white blood cell, also called a macrophage, that **is** created by the bone marrow. They usually stay in place, but when **histiocytes** are stimulated by infection or inflammation they become active, attacking bacteria and other foreign matter in the body.
(من العم جوجل الله يخليلنا اياه)

#Disseminated Intravascular Leishmeniasis (Kala azar):

Kala azar, which is caused by *L. donovani*, occurs in the tropical and subtropical areas of every continent except **Australia.

In Africa, *rodents* serve as the primary reservoir. Human cases occur **sporadically, and the disease is often acute and highly lethal (if the fly bites a human). In Eurasia and Latin America, the **domestic dog** is the most common reservoir.

بما ان هاي الطفيليات موجودة عند القوارض،، فمعناته اذا انتقل للإنسان ما راح يكون عنده مناعة تجاهه وبالتالي راح يكون المرض مميت.

**Human disease is endemic, primarily involves children, and runs a subacute to chronic course.

في المناطق الي بكون فيها الاصابات كثيرة للبشر زي الهند،، بكون عندهم مناعة منيحة تجاهه، وهاذ بفسر ليش معظم المصابين عندهم بكونو أطفال لأنهم لسا ما تعرضوا لهاي الطفيليات بحياتهم عشان يبنو ضدها مناعة، واذا هذول الأطفال رجعو انصابوا بالمستقبل بكون المرض عندهم أخف

واذا صابهم مرة ثالثة بكون أخف أكثر لحتى ما يبطل يصيبهم بالمرة أو يصير مرض مزمن (chronic).

**In India, the human is the only known reservoir, and transmission is carried out by sandflies. The disease recurs in epidemic form at 20 year intervals, when a new nonimmune children and young adults appears in the community.

الوضع بالهند لسا أسوء،، لأنه أصلا الطفيليات موجودة عند البشر مش القوارض،، يعني بتنتقل مباشرة من إنسان لأنسان،، وبالتالي المرض بكون منتشر أكثر بكثير،، فالأطفال هم الأكثر عرضة للإصابة وبتكون عليهم الأعراض كثير شديدة، اذا نجو من المرض ببنو مناعة جزئية تجاهه، واذا انصابو كمان مرة بكون المرض أخف زي ما حكينا فوق، وبعد عشرين سنة لما يكبرو هذول الأطفال بصير عندهم مناعة منيحة تجاه المرض،، ولما ييجي جيل جديد من الاطفال الغير مصابين بتبلش دورة جديدة للمرض وهكذا.

**There appears to be a high incidence of visceral leishmaniasis in patients with HIV infection (immune-compromised patients in general).

#Manifestations:

The majority of infections are asymptomatic

Symptomatic disease most commonly manifests itself **3 to 12 months after acquisition of the parasite. It is often mild and self-limited

**A minority of infected individuals develop the classic manifestations of kala azar:

1- Fever, which is usually present, may be abrupt or gradual in onset. It persists for 2 to 8 weeks and then disappears, only to reappear at irregular intervals during the course of the disease. A double-quotidian pattern (two fever spikes in a single day) is a characteristic but uncommon finding

2- Diarrhea and malabsorption are frequent in Indian cases, resulting in progressive weight loss and weakness
3- Physical findings include enlarged lymph nodes and liver, massively enlarged spleen, and edema.
4- In light-skinned individuals, a grayish pigmentation of the face and hands is commonly seen, which gives the disease its name (kala azar, black disease).

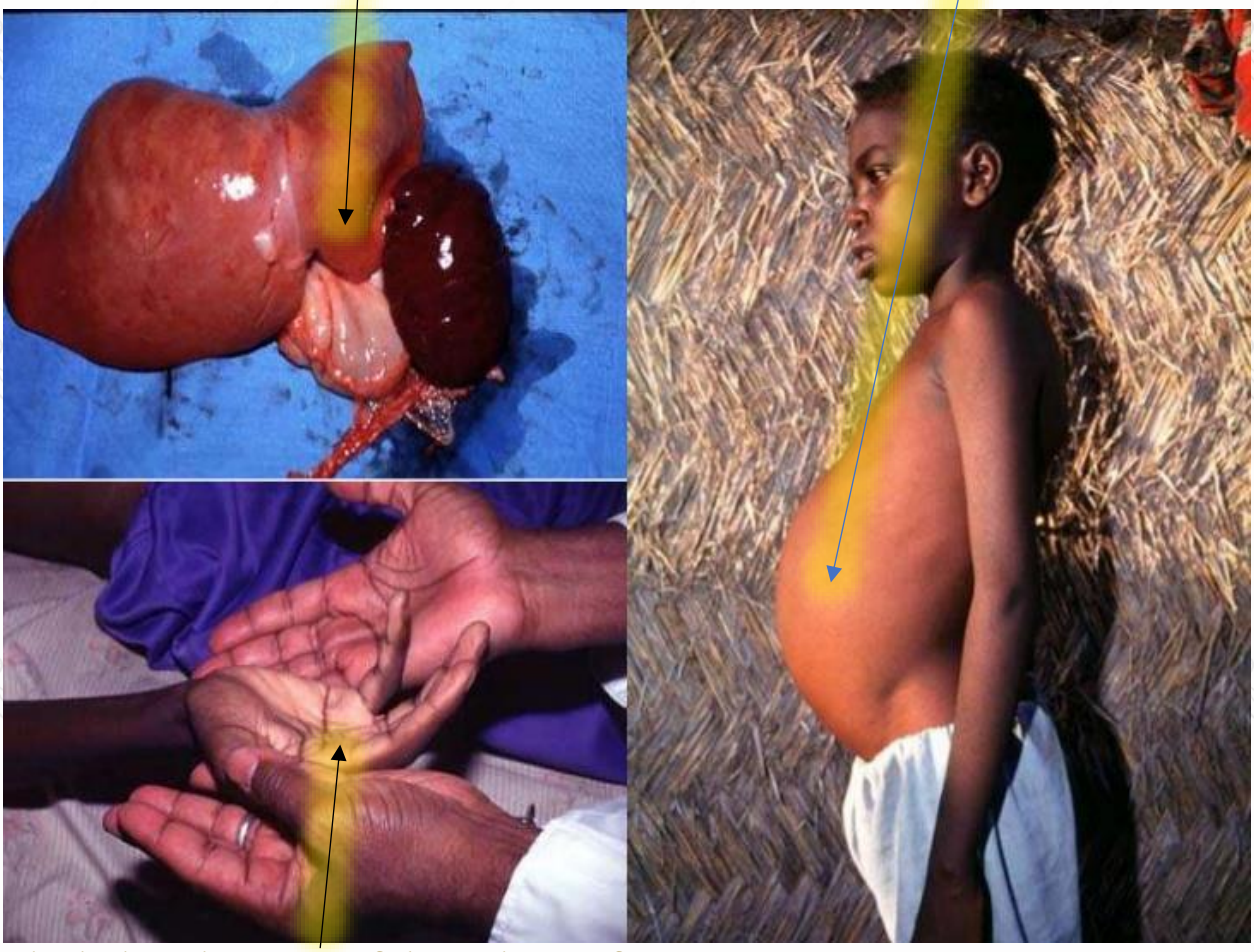
kala azar معناتها تحول للون الأسود

5- Anemia are typical in advanced cases. Thrombocytopenia induces petechial formation and mucosal bleeding. The peripheral leukocyte count is usually low; agranulocytosis with secondary bacterial infections contributes to lethality.
6- Serum **immunoglobulin G** levels are enormously elevated but play no protective role. Circulating antigen-antibody complexes are present and are probably responsible for the glomerulonephritis seen so often in this disease.

Enlargement in liver and spleen

Ascites due to

Enlargement in liver and spleen (advanced stage)



Black discoloration of the palms & face

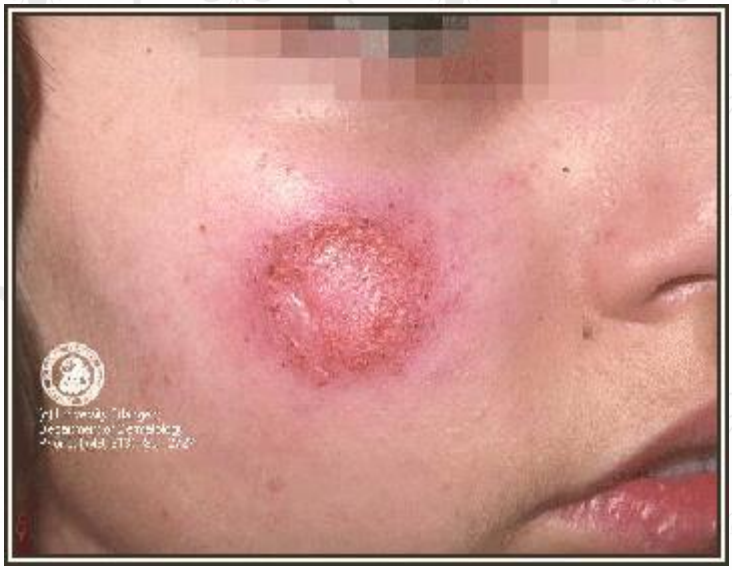
#Cutaneous Leishmaniasis:

Leishmania tropica: Anthroponotic cutaneous leishmaniasis: Dry lesions with minimal ulceration

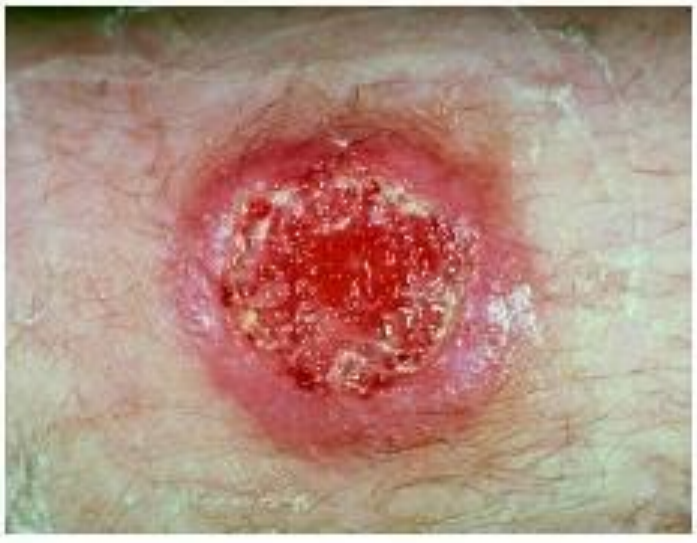
Leishmania major: Zoonotic cutaneous leishmaniasis: wet lesions with severe reaction

Oriental sore (most common) classical self-limited ulcer

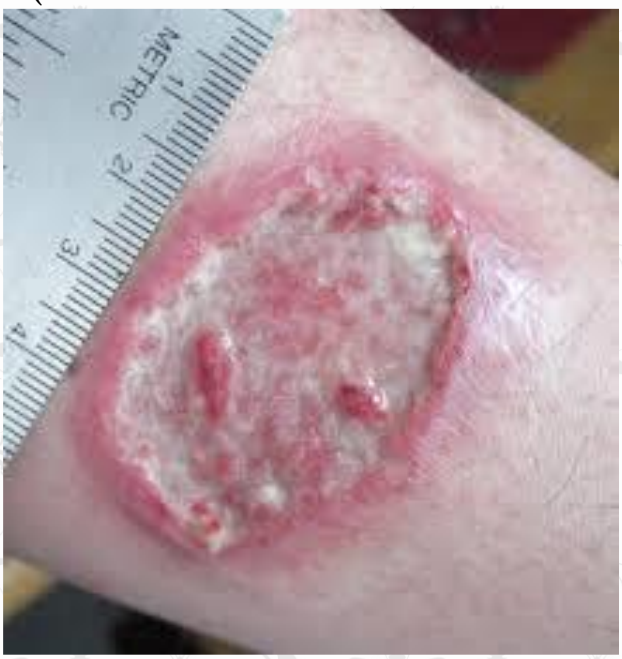
Leishmania tropica (mild damage to the skin, no acute alcur)



Leishmania major (more destruction, acute ulceration)



Oriental sore (severe destruction and ulceration, final stage)



#Diagnosis:

**The diagnosis is made by demonstrating the presence of the organism in aspirates taken from the bone marrow, liver, spleen, or lymph nodes.

**The specimens may be smeared, stained, and examined for the typical Leishman-Donovan bodies (amastigotes in mononuclear phagocytes) or cultured in artificial media and/ or experimental animals.

**A rapid, direct, species-specific diagnosis by PCR and probes to kinetoplast DNA is used. دقيق وسريع بس غالي

**Results of the leishmanin skin test are negative during active disease but become positive after successful therapy.

في أول المرض، بنحط كمية من الantigens تبعت الLeishmania تحت الجلد، في المرحلة الأولى بما ان المريض لسا ما عنده مناعة بكون سلبي،، عند نهاية المرض او بعد العلاج لما يصير عند المريض مناعة كويسة بصير ايجابي،، فهاذ الفحص ما بنفعنا بالتشخيص بالacute stage وأنما بحكيلنا اذا المريض عنده مناعة للمرض ولا لا أو قديش صارت مناعته لما يصير نتيجة الفحص ايجابي

#Treatment and Prevention:

**The mortality in untreated cases of kala azar is 75 to 90%.

**Treatment with pentavalent antimonial drugs lower this rate dramatically. Initial therapy, however, fails in up to 30% of African cases, and 15% of those that do respond eventually relapse.

من غير علاج،، 75-90% من المرضى بموتوا،، مع العلاج الوضع أحسن، بس للأسف في 30% من الحالات العلاج ما بقتل الطفيليات فما بستفيدو،، و15% بتحسنوا بالبداية بس برجعلهم المرض لأن الطفيليات بتكون أقوى من العلاج

**Control measures are directed at the Phlebotomus vector, with the use of residual insecticides, and at the elimination of mammalian reservoirs by treating human cases and destroying infective dogs.

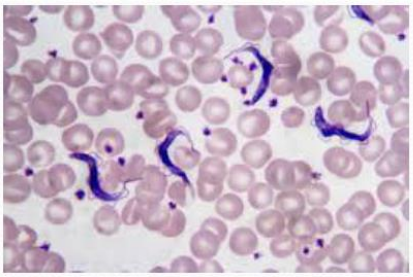
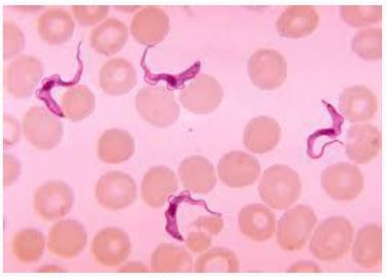
في كثير من الدول حاولو يقضو على ذبابة الرمل نفسها، لكن في المناطق الحارة والاستوائية الي الطفيليات منتشرة فيها بكثرة صعب ان نقضي عليها، وفي الدول الي فيها الكلاب والقوارض هي الحامل الرئيسي للمرض حاولو يقضو عليها كمان.

2. African Trypanosoma (also called Sleeping sickness)

#Introduction:

The trypanosomes that produce these diseases are morphologically and serologically identical. Accordingly, they are considered varieties of a single species, *Trypanosoma brucei*

The three subspecies are: *T. brucei gambiense, T. brucei rhodesiense,* and *T. brucei brucei.*


#Life Cycle:

1- On ingestion by the ***tsetse fly***, and after a period of multiplication in the midgut, they migrate to the insect's salivary glands and assume the epimastigote form

2- After a period of weeks, they are transformed into trypomastigotes, rendering them infectious to mammals.
3- When the fly again takes a meal, the parasites are inoculated with the fly's saliva.

نفس دورة حياة الLeishmania ، بس الي بفرق هو اسم الحشرة الي بتنقل الطفيليات والي هي ال***tsetse fly***

#The disease:

African trypanosomiasis is a highly lethal ***meningoencephalitis* (the hole mark of the disease).

**It occurs in two distinct clinical and epidemiologic forms:

1- West African or Gambian sleeping sickness 98%, found in 24 countries in west and central Africa.

2- East African or Rhodesian sleeping sickness 2%, found in 13 countries eastern and southern Africa.

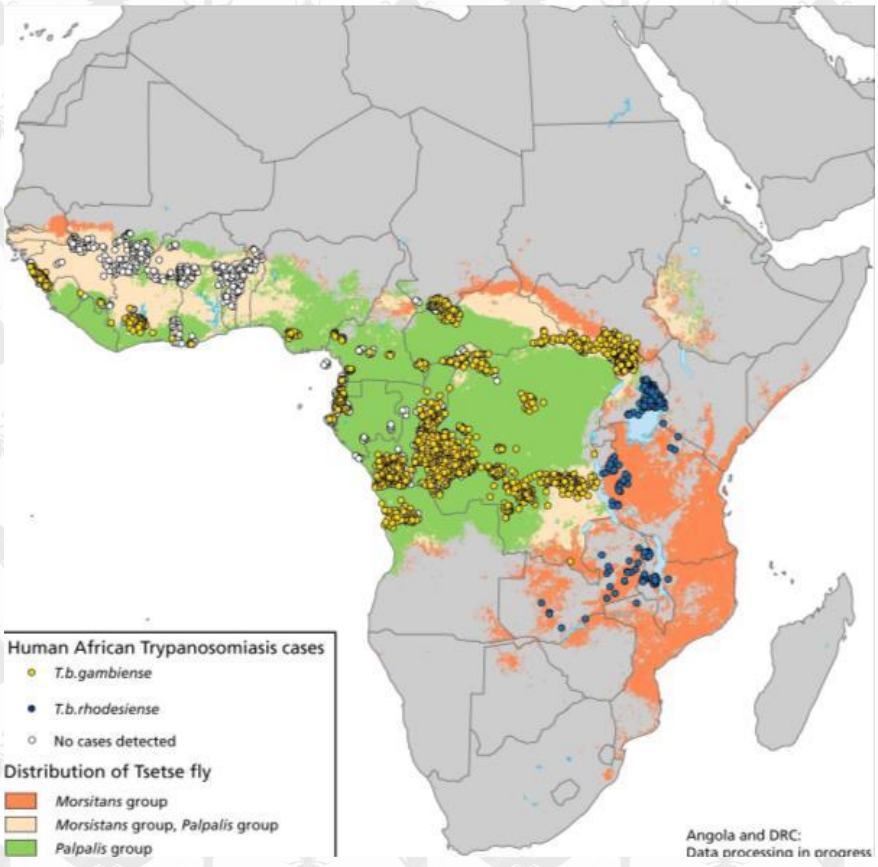
#Epidemiology:

**Sleeping sickness is confined to the central area of Africa by that continent's two great deserts, the Sahara in the north and the Kalahari in the south.

**Sleeping sickness threatens millions of people in 36 countries in sub-Saharan Africa.

**In 1998, almost 40 000 cases were reported, but estimates were that 300 000 cases were undiagnosed.

**The infection rate is affected by proximity to water but seldom exceeds 2 to 3% in nonepidemic situations.



#Pathogenesis:

1- Multiplication of the ingested ***trypomastigotes*** at the inoculation site (bite site) produces a localized inflammatory lesion (chancre).
2- Organisms spread through lymphatic channels to the bloodstream, inducing a proliferative enlargement of the lymph nodes.
3- The subsequent parasitemia (parasite growth in blood) is typically low grade and recurrent.
4- As host antibodies (predominantly ***IgM***) are produced to the surface antigen they bind to the organism, leading to its destruction by lysis and opsonization.

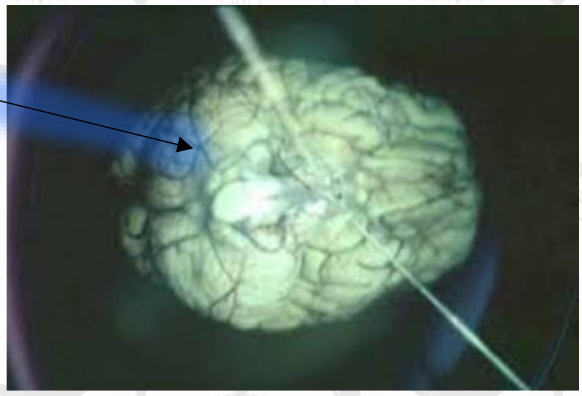
اذا ما في أعراض،، ولكن اذا كانت الطفيليات أقوى من الIgM أو كان عددهم كثير كبير (مثلا ممكن تقرصه بعوضة ثانية أو أكثر بفترة قصيرة) فبصير غزو للدم بهاي الطفيليات.

5- During the course of the parasitemia, trypanosomes localize in the small blood vessels of the *heart and central nervous system.*

Most common site is the CNS, then the heart.

6- This localization results in endothelial proliferation and a perivascular infiltration of plasma cells and lymphocytes. In the brain, hemorrhage and a demyelinating panencephalitis may follow.

In this image we can see the inflamed vessels of the brain.



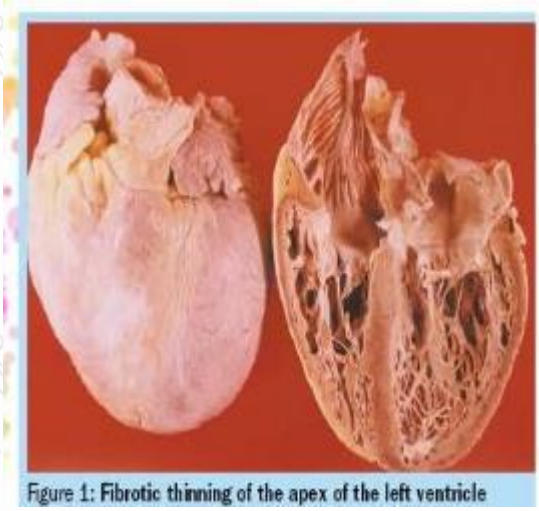
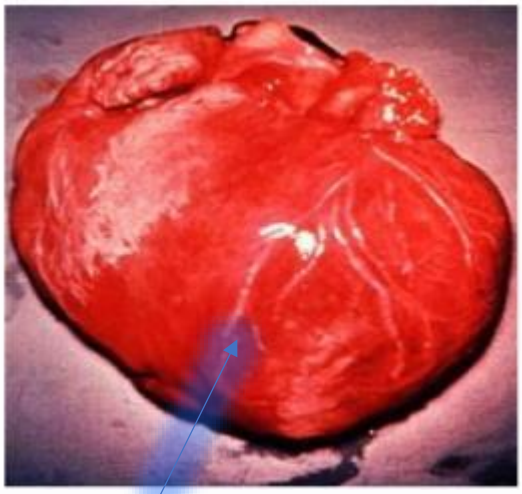


Figure 1: Fibrotic thinning of the apex of the left ventricle



here we can see the inflamed vessels of the heart.

#Manifestations:

**The trypanosomal chancre appears 2 to 3 days after the bite of the tsetse fly as a raised, reddened nodule on one of the exposed surfaces of the body.

**With the onset of parasitemia 2 to 3 weeks later, the patient develops recurrent bouts of fever, tender lymphadenopathy, skin rash, headache, and impaired mentation.

**In the Rhodesian form of disease, myocarditis and CNS involvement begin within 3 to 6 weeks. Heart failure, convulsions, coma, and death follow in 6 to 9 months.

**Gambian sleeping sickness progresses more slowly. Bouts of fever often persist for years before CNS manifestations gradually appear.

**Spontaneous activity progressively diminishes, attention wavers, and the patient must be prodded to eat or talk.

**Speech grows indistinct, tremors develop, sphincter control is lost, and seizures with transient bouts of paralysis occur.

**In the terminal stage, the patient develops a lethal intercurrent infection or lapses into a final coma.

#Diagnosis:

**A definitive diagnosis is made by microscopically examining lymph node aspirates, blood, or cerebrospinal fluid for the presence of trypomastigotes.
**Early in the disease, actively motile organisms can often be seen in a simple wet mount preparation smear.
**If these tests prove negative, the blood can be centrifuged, and the stained buffy coat examined.
**Inoculation of rats or mice can also prove helpful in diagnosing the Rhodesian disease.
**The patient may also be screened for elevated levels of IgM in the blood and spinal fluid or specific trypanosomal antibodies.

#Treatment and Prevention:

Lumbar puncture must always be performed before initiation of therapy. If the specimen reveals evidence of CNS involvement, agents that penetrate the blood-brain barrier must be included. Unfortunately, the most effective agent of this type is a highly toxic arsenical, **melarsoprol (Mel B).

**If the CNS is not yet involved, less toxic agents, such as suramin, pentamidine, or eflornithine, can be used. In such cases, the cure rate is high and recovery complete.

**Tsetse fly control measures, eradication of disease reservoirs, and attempts to develop effective vaccines have been tried with poor effect.

**A degree of personal protection can be achieved with insect repellents and protective clothing.

الدكتور ما شرح American Trypanosoma(Chagase disease) وحكا ان مش مطلوب.

“In the middle of every difficulty lies opportunity.” – ..