**Leishmanias Infecting Humans**

2. *L. braziliensis* (New World cutaneous).
   
   a. Mainly in the new world
   
   2. In woodland areas
   
   b. Also vectored by sand flies (*Lutzomyia*)

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**L. braziliensis**

c. Lesion usually heals up with no problem.

d. But, occasionally metastasizes if it involves mucous membranes.
   
   1. can erode face, resp. structures
   
   2. conditions is known as "uta" or "espundia."

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**Leishmania mexicana**

1. Mainly in central Mexico, Caribbean.
   
   a. Responsible for a condition called "chiclero" after harvesters of gum tree, *chiclé* (Chicklets)

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**Leishmania Medications**

1. Usually with *antimonials* (mercury containing compounds).
   
   a. some plants are useful too (dogbanes, gentians).

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- Kala azar is treated today essentially as it was in 1940. The major drug is Sodium stibogluconate or Pentastam, a derivative of antimony, which was developed in 1930! Severe reactions including death occur in 10% of those treated. It is very expensive, and the recommended one month treatment costs around $150. Drug resistance has also developed. Up to 70% of infected patients in India are resistant to this drug.

- Amphotericin is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone.

- Pentamidine isonionate has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high and it is associated with serious side-effects.

- Recently a new drug was developed, miltefosine. This is a membrane signaling pathway inhibitor. This can be taken orally and is very effective against visceral leishmaniasis. In clinical trials has a 95% cure rate!

- Pentamidine is also used for New World cutaneous leishmaniasis, but it usually heals spontaneously.

- There is no treatment for muco-cutaneous leishmaniasis.
Trypanosomes of Importance to Humans

b. Trypanosoma
1. More recent (DNA based) classification systems have suggested that there may be several genera here, but current classification system is familiar and accepted.

Trypanosomiasis
2. Usually known as "sleeping sickness" or other chronic malaises.
3. Tends to be intercellular - a blood parasite.

c. Both are vectored by insects
a. Probably is the original source of the parasite.

Trypanosome Transmission
Vectored by insects in two ways:
1. Anterior station - bite of insect.
2. Posterior station - feces of insect.

Trypanosome Transmission
This has generated two sections of trypanosomes that probably do reflect evolutionary relationships.
Trypanosome Systematics

1. Section Salivaria - metacyclic (infective) trypomastigotes in salivary glands.
2. Section Stercoraria - metacyclic trypomastigotes in hind gut.

Trypanosome Life Cycles

a. Trypomastigotes ingested by insect with blood meal.
b. Multiplication of trypomastigotes in insect midgut.
c. Multiplication of epimastigotes in salivary glands or hind gut.
1. transformation to metacyclic stage (infective).

d. Transfer of metacyclic trypomastigotes to vertebrate host.
e. Replication of slender trypomastigote in vertebrate.
f. Transforms to stumpy trypomastigote - transferred to insect.
g. These stages seem to be associated with different changes in metabolism of trypanosome - See fig. 5.6 in R&J.

The Life Cycle of T. brucei

a. Involves changes in Krebs cycle
1. Loss of mitochondrial function in vertebrate host.
2. Evidently occurs because glycolysis alone is possible.

Important Species:

1. T. brucei (variants gambiense and rhodiense)
   a. Three species of African trypanosome cause different pathologies in cattle and man.
   b. Vectored by the tsetse fly (Glossina).

Important Species

T. brucei brucei - nagana
1. Resident in native ungulates.
2. Infects introduced animals as well - often fatally.
**Important Species**

T. brucei gambiense - West african sleeping sickness.
1. In humans only, no reservoir host known.
2. Causes chronic form of disease.
   a. Often takes several years to form.

T. brucei rhodiense - East african sleeping sickness
1. Onset is faster than T. b. gambiense.
2. Several reservoir hosts exist.
3. Involves lymph like b.b.g, but death comes sooner.

**T. brucei gambiense**

b. Year one - localized in blood lymph.
c. Year two - associated with nervous system.
1. Causes coma and death - often insanity too.

**T. brucei rhodiense**
a. Winterbottom's sign - swollen lymph nodes.
1. Named after the British officer that noticed it.
2. Was justification for throwing slaves overboard.
Immunological Notes

1. Successive dominance of VATs.
   a. Just as host’s immune system becomes successful at overcoming the parasites variant antigenic type (VAT).

2. The parasite expresses another one - a new VAT.

Production of New VATs

1. Can go on for over 100 types!
   a. A good example of more rapid evolution of parasite than host due to more rapid generation time
   b. Some consider this the context not only for form of vertebrate immunity, but also the evolution of sex.

Production of New VATs

2. Three mechanisms of occurrence (see book for details).
   a. Result in a single dominant type, but with multiple circulating VATs.

History of Control Mechanisms

• 1902 Ford and Dutton, two English physicians working in The Gambia, identified one causative agent of trypanosomiasis, a parasite which they named Trypanosoma brucei gambiense.
• 1903 Castellani working in Uganda observed the parasite in the cerebrospinal fluid of one of his patients. In the same year, the tsetse fly was recognized by David Bruce as being the vector of the parasite.
• 1906 Ayres Kopke introduced an arsenic compound, Atoxyl, for the treatment of the disease.
• 1920 Jamot, a colonel in the French army working on trypanosomiasis control, observed that in the Ubangi river loop more than half of all deaths were due to sleeping sickness. The major epidemics early in the century claimed hundreds of thousands of lives. Entire populations were affected, and indeed Jamot reported that a whole ethnic group had been wiped out in northern Congo.
• 1924 Tryparsamide, a drug still based on arsenic but less toxic than Atoxyl, was used on a wide scale in Belgian Congo and Cameroon.
• 1930 A headline stated: “Our doctors have vanquished the tsetse fly!”
**History of Control Mechanisms**

- 1932: 700 patients became blind after receiving the wrong dose of Atoxyl. In response to this disaster, Professor Friedheim, a Swiss physician and chemist, developed the drug melarsoprol, the bold concept of which was a single product containing a highly toxic arsenic-based molecule and its antidote.
- 1960: Melarsoprol was used systematically in cases where there was involvement of the central nervous system.
- 1984: The World Health Organization (WHO) launched a programme to control trypanosomiasis.
- 1993: WHO developed the central African initiative, a major project for regional approach to Sleeping Sickness in ten countries: Angola, Cameroon, Central African Republic, Congo, Gabon, Equatorial Guinea, Uganda, Sudan, Chad and Zaire.

**Current Control Mechanisms**

1. Certain drugs are effective, but only on early stages of trypanosomes.
   a. Arsenic drugs.
   b. Difluoromethylornithine (DFMO)
2. Elimination of *Glossina* resting sites - high vegetation.
   a. Expensive and needs to be repeated.

**Other Trypanosomes**

1. *T. congolense* - causes disease in cattle similar to nagana.
   a. Recognized by lack of flagellum
   b. Can be transmitted mechanically by cattle flies, *Tabanus*.
2. *T. evansi* - infects camels, horses and other ungulates.
   a. Introduced to Western Hemisphere by Spaniards.
   b. Causes *surra*.
Other Trypanosomes
3. *T. equinum*, related to *T. evansi*
   a. Mechanically transmitted by *Tabanus*.
   b. Also transmitted by vampire bats - causes *murrina*.

Other Trypanosomes
   a. Transmitted by coitus, causes swelling and depigmentation of genitalia
   b. Fatal if untreated.

Section Stercoraria
1. These are trypanosomes transmitted via posterior station.
   a. Transmitted mainly by blood-feeding bugs (Hemiptera).
   b. Metacyclic trypomastigotes develop in hindgut of bug.
   c. Usually from Family Reduviidae.

Reduviid Bugs
1. Many species defecate during feeding, host rubs feces into wound.
   a. Trypanosomes also seem to be transmitted among bugs – horizontal transfer.
   1. Cannibalism seems to occur.
   2. Possible transmission during mating.