In 1841 G. Valentin in Berne, Switzerland, saw a protozoan in the blood of a trout that moved by means of its undulating membrane; it was a trypanosome. Two years later David Gruby in Paris discovered a similar organism in frog blood and called it Trypanosoma sanguinis. *Trypanosoma* is derived from the Greek word “trypano” meaning auger or screw-like and “soma” meaning body, and *sanguinis* comes from the Latin word for blood, “sanguis”. Trypanosomes were considered mere curiosities and of no economic, medical or veterinary importance.

Fig. 20. Trypanosomes of lower vertebrates. (×1600). *Trypanosoma percae* from Perch (After Minchin 1909); b. *T. mega* from Congo toads and frogs (After Dutton et al. 1907); c. *T. mega* from toad (After Brumpt 1928); d, e. *T. rotatorium* from frog (After Laveran & Mesnil 1912); f. *T. isopinatum* from frog (After França 1915); g. *T. karyozoitus* from toad (After Brumpt 1928); h. *T. varani* from Monitor lizard (After Wenyen 1909); i. *T. erythrolampri* from snake (After Wenyen 1909).
African Trypanosomiasis

In 1880 Griffith Evans, an English veterinarian in Punjab, India, found trypanosomes in the blood of horses, mules and camels suffering from a fatal wasting disease called surra. Inoculation of blood containing trypanosomes into healthy animals produced surra. Evans was convinced that the trypanosome (later named *Trypanosoma evansi*) was a parasite but he did not discover how horses, mules or camels became infected. The vector, a biting stable fly, was discovered in 1899.
In the early 1890s the British colonial farmers of Zululand were faced with the decimation of their European breeds of cattle by a wasting disease called nagana, a word meaning in Zulu “in low or depressed spirits.” Native cattle were unaffected.
In 1894, Bruce was sent to investigate Nagana in cattle. When he examined the blood of diseased cattle he described a rapidly vibrating body, lashing about among the red blood corpuscles. Bruce then went on to establish Koch’s postulates for nagana: if he injected blood from cattle suffering with this disease into dogs severe wasting symptoms resulted, and abundant trypanosomes were found in the dog’s blood. He wrote: “the clinical features of nagana are defined by the constant occurrence in the blood of a protozoan parasite”.

Discovery of trypanosomes as cause of Nagana
In 1895 Bruce discovered the vector for nagana: the blood-sucking tse-tse fly (genus: Glossina). Bruce hypothesized, and then proved, that wild game—buffalo, wildebeest, and bushbuck—were the source of infection and that transmission was the result of the bite of the tse-tse flies which infested the area in which these game animals lived.
Fossil tsetse fly

Florissant Fossil Beds National Monument

55.8 ± 0.2 to 33.9 ± 0.1 Ma (million years ago),
Losses in meat production, milk yield and tractive power are estimated to cost approximately $500 million annually and, if lost potential in livestock and crop production are also considered, the disease costs Africa an estimated $5 billion per year (1994 prices). Complete control of tsetse would result in an increase in beef production of 1.5 million tons per annum. However, this would also have a massive impact on the use of land and significantly reduce the possibilities for wildlife in Africa. (From http://www.icp.ucl.ac.be/~opperd/parasites/)
Human Sleeping Sickness

Was observed by Arab doctors as early as 1375. In 1702 an English naval surgeon John Atkins, described a disease (“the sleepy distemper”) in Africans living along the Guinea Coast. In 1803 Thomas Winterbottom, a physician working in the colony of Sierra Leone, published an account of the “African lethargy.” He recognized a telltale clinical characteristic: swelling of the cervical lymph nodes.
In May 1901 a 42-year-old Englishman who worked on the steamships plying the Gambia River came down with a fever. He was admitted to the hospital, and was treated with quinine for malaria without success. When his blood was examined no malaria parasites could be found, however, there were trypanosomes. In 1902 this trypanosome of humans was named by Joseph Everett Dutton of the Liverpool School of Tropical Medicine, *T. gambiense*.
"disease under culture," and those who suffer from it have all the time "out of healthy life. This "world hunger" will then, it is said, in a short time disappear. These doctrines, alien as they are to all universal practice, are not entirely baseless, but it will be curious to see which of the adherents will be found in Manchester. One local daily paper said, "Die or Diet?" accompanying the query by a humorous sketch.

CORRESPONDENCE.

THE PRELIMINARY GENERAL EDUCATION OF MEDICAL STUDENTS.

Sr.-Mr. McCormick's letter on this subject published in the British Medical Journal of November 15th calls for some notice. I shall deal briefly with his points in his own order.

1. The passage quoted has been dislocated from its context. When read as it stands in my paper it does not bear the construction suggested by Mr. McCormick. It is merely part of an argument that in 1892 the United Kingdom was unusually prepared for adoption of medical students, after reasonable notice given, a standard of preliminary general education applicable to candidates of 17 years of age.

2. The reasons referred to were submitted, with others mentioned by Mr. McCormick, to the General Council, and therefore undoubtedly concern us. It is not true to say I have misrepresented them, as any one may satisfy himself from the minutes of the Council.

3. I am sorry if Mr. McCormick fails to understand what seems to me sufficiently clear. Uniformity of standard is most desirable. It is not to be expected that one can be better prepared for the medical profession than in another country.

4. The "expert advisors" were asked to fill in a "minimum standard." A minimum standard was already fixed. They were asked to fill in an "average minimum standard,” and this they did not do.

5. When Mr. McCormick quibbles he must surely fail to realize the seriousness of the question he is dealing with. I should be very sorry indeed to think that the three "experts" represented the real views of the educational profession, and that their unsatisfactory knowledge from the answers to Sir John Tuke's letter of December 27th, 1907, that they did not—I am, etc.

Exeter, Nov. 19th.

W. GORDON.

NOTE ON THE DISCOVERY OF THE HUMAN EHRICHIA.

Sr.—We have recently seen in the medical press several very inaccurate accounts regarding the authorship of the important observation of the human trypanosomes in human blood, which Dr. Nason and Daniels, which, after all, would probably have escaped notice but for the previous work of Dr. Dutton. We may mention also—that this is another point which the Journal of the Royal Society of Tropical Medicine appears to have forgotten—that before his departure for Africa Dr. Dutton gave at this laboratory a detailed demonstration of both the parasite and the clinical features of the case of Drs. Nason and Daniels, and to one of the editors of the periodical referred to. "The omission, then, appears to be due rather to want of memory than to want of knowledge. The journal of the Royal Society of Tropical Medicine also states that while the first case (namely, that of Dutton and Forde) was regarded only as a "curiosity," the discovery of the second case (namely, that of Daniels and Nason) "opens up a new field for investigation and elucidation," and so on. This view of the relative importance of an original discovery and of a mere confirmation of that discovery is somewhat novel. But the facts regarding the discovery of the Ehrlichia are as follows.

The facts regarding the history of the discovery—which was made nearly a year ago—have already been publicly and adequately published both by Dr. Forde and by Dr. Dutton, Colonial Surgeon, British Guiana, tells us that the case in which the parasites were first observed came under his notice in May, 1901; that he found in the blood some worms.

like, extremely active bodies which I prematurely pronounced a species of flijia, a parasite of a peculiar undulant type; Dr. Dutton it was who positively excluded malaria as the cause of the symptoms; it was he who saw that those symptoms roughly resembled those of a very disease and cured it by having a particular undulant type; Dr. Dutton says, who recognized the fever was of malaria without its symptoms. In order to make a discovery it is too difficult for an object; it is necessary also to recognize the nature of the object seen, to publish accurate and adequate descriptions of the discovery. For example, Virchow and others long ago saw the parasites of malaria without recognizing their parasitic nature; but it is to Laveran, who did recognize their parasitic nature, that science gives the credit for the discovery of the new organism and it is to him that science will give the principal credit for the new observation.

It seems to us particularly unfortunate that the Journal of the Royal Society of Tropical Medicine should have so ostentatiously omitted the name of Dr. Dutton at the moment when it was engaged in performing the greatest prominence to a case of Drs. Nason and Daniels, which, after all, would probably have escaped notice but for the previous work of Dr. Dutton. We may mention also, that this is another point which the Journal of the Royal Society of Tropical Medicine appears to have forgotten—that before his departure for Africa Dr. Dutton gave at this laboratory a detailed demonstration of both the parasite and the clinical features of the case of Drs. Nason and Daniels, and to one of the editors of the periodical referred to. "The omission, then, appears to be due rather to want of memory than to want of knowledge.

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THE ABSORPTION OF UTERINE FIBROIDS.

Sr.—It is too late to deny the disappearance of uterine fibroids under a variety of conditions, and to contend that the idea is a "pure superstition." I am able to add to the gradually accumulating evidence and to assert it as an ob-
Gambian Sleeping Sickness Epidemic

In 1901 a severe epidemic of sleeping sickness broke out in Uganda and so the Royal Society of London sponsored a commission headed by Bruce to investigate its cause. By 1902 the commission had discovered that the distribution of persons with Winterbottom’s Sign corresponded with the distribution of sleeping sickness. Further, examination of the cerebrospinal fluid from a case with sleeping sickness by one of the members of the commission, Dr. Aldo Castellani, showed trypanosomes. He found that in the cerebrospinal fluid from 34 cases, 20 had trypanosomes, whereas in 12 control cases none were found.

Bruce suspected that the tse-tse fly was involved in the transmission of Gambian sleeping sickness. Later, when it was found that monkeys were susceptible to the disease, and a tsetse fed on a human case could transmit the disease to monkeys, it was concluded:

Sleeping Sickness is a human tsetse disease.
Rhodesian Sleeping Sickness

In 1910 J. W. Stephens of the Liverpool School of Tropical Medicine discovered a new species of trypanosomes: it was from a patient with sleeping sickness who had acquired the disease in 1909 in Rhodesia, an area where *T. gambiense* and its vector (*Glossina palpalis*) did not occur. The disease was more acute and the parasites had a different morphology. He called them *T. rhodesiense*.

In 1912 Bruce headed another sleeping sickness commission in an area near Lake Nyssa. He found *T. rhodesiense* in the blood of 1/3 of the 180 game animals examined. Bruce compared the morphology of *T. rhodesiense* with *T. brucei* from cases of nagana and found them to be identical. He concluded: “*T. rhodesiense* is neither more nor less than *T. brucei*, and that the human trypanosome disease in Nyasaland is nagana”. The vector was suspected to be the most abundant tsetse, *G. morsitans*. 
Because this mode of transmission is by inoculation during biting, the *brucei* group of trypanosomes are also referred to as saliva-type or “Salivarian”.

*T. cruzi*, on the other hand, is transmitted by fecal contamination and is referred to as a “Stercorarian” or dung-type.
Epidemic in the 1930s

1950-60 years of victory

Since 1980: the scourge is back

Sleeping Sickness in Central Africa
## Annual Morbidity & Mortality of Selected Parasitic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number Infected</th>
<th>Number deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Sleeping Sickness</td>
<td>300 thousand</td>
<td>&gt; 30 thousand (10%)</td>
</tr>
<tr>
<td>Malaria</td>
<td>500 million</td>
<td>2.7 million (0.5%)</td>
</tr>
<tr>
<td>Ascariasis</td>
<td>1.2 billion</td>
<td>60 thousand (0.005%)</td>
</tr>
</tbody>
</table>

WHO (1997)
Localization of *T. gambiense* in West Africa and *T. rhodesiense* in East Africa
Trypanosoma (brucei) gambiense

West Africa
Rivers
*Glosina palpalis* group
Anthroponosis
Death in months to years
Trypanosoma (brucei) rhodesiense

East Africa
Dry Savannah
Glosina morsitans group
Zoonosis (Antelope, Wildebeast)
Death in weeks to months
The savanna vectors *G. morsitans* and *G. palidipes* are responsible for the transmission of *T. rhodesiense* in East Africa, while the principal vectors of West African sleeping sickness are *G. palpalis*, *G. fuscipes* and *G. tachinoides*. The range of African trypanosomiasis is determined by the range of the vector. Interestingly, only newly hatched tsetse flies are competent to transmit the disease. *Glossina* is in fact a poor vector in nature since less than 1% of the flies are infected.
The data set contains a number of data layers: ground-based meteorological records (temperature means, minima, and maxima); elevation; and annual mean, minimum and maximum Normalised Difference Vegetation Indices derived from the Advanced Very High Resolution Radiometer on board the NOAA series of meteorological satellites.
Predicted areas of suitability for savanna tsetse

*Morsitans group*

This map shows the predicted areas of suitability for tsetse flies. It was produced for FAO - Animal Health and Production Division and DFID - Animal Health Programme by Environmental Research Group Oxford (ERGO Ltd) in collaboration with the Trypanosomiasis and Land Use in Africa (TALA) research group at the Department of Zoology, University of Oxford in November 1999. The modelling process relies on logistic regression of fly presence against a wide range of predictors. The predictor variables include remotely sensed (satellite image) surrogates of climate, vegetation, temperature, moisture, Demographic, topographic and agroecological predictors are also used. The prediction was created at 10-kilometer resolution for the whole sub-Saharan Africa.
This map shows the predicted areas of suitability for tsetse flies:

- **Predicted areas of suitability for riverine tsetse**
- **Palpalis group**

It was produced for FAO - Animal Health and Production Division and DFID - Animal Health Programme by Environmental Research Group Oxford (ERGO Ltd) in collaboration with the Trypanosomiasis and Land Use in Africa (TALA) research group at the Department of Zoology, University of Oxford in November 1999. The modelling process relies on logistic regression of fly presence against a wide range of predictors. The predictor variables include remotely sensed (satellite image) surrogates of climate, vegetation, temperature, moisture, Demographic, topographic and agroecological predictors are also used.

The prediction was created at 5-kilometres resolution for the whole sub-Saharan Africa.
Tsetse fly control methods

Slaughter of wild animals

Rhodesia: Tsetse control programme launched in 1919. For the next 40 years the control programme involved exterminating over half a million large game animals in low-lying parts of the country supposedly to eliminate the fly's food source. Cattle grazing and early burning activities following the settlement of these dry, marginal areas led to land degradation.

Land clearing

Another early technique involved the complete removal of any brush or woody vegetation from an area. Tsetse tend to rest on the trunks of trees so the removal of woody vegetation made the area inhospitable to the flies. However, the technique has not been widely used and has been abandoned in more recent times. Preventing the regrowth of woody vegetation requires continuous clearing efforts which is only practicable where large human populations are present. The clearing of woody vegetation has come to be seen as an environmental problem more than a benefit.
Pesticide campaigns

Pesticides have been used to control tsetse starting initially during the early part of the twentieth century in localized efforts using the inorganic metal based pesticides, expanding after the Second World war into massive aerial and ground based campaigns with organochlorine pesticides such as DDT applied as aerosol sprays at Ultra-Low Volume rates. Later, more targeted techniques used *pour-on* formulations in which advanced organic pesticides were applied directly to the backs of cattle.

Trapping

Tsetse populations can be monitored and effectively controlled using simple, inexpensive traps. These often use electric blue cloth, since this colour attracts the flies. Early traps mimicked the form of cattle but this seems unnecessary and recent traps are simple sheets or have a biconical form. The traps can kill by channeling the flies into a collection chamber or by exposing the flies to insecticide sprayed on the cloth.

Releases of irradiated males

The sterile insect technique has been used to reduce tsetse populations. This technique involves the rearing of large numbers of tsetse, separation of the males, irradiation of these flies with large doses of gamma rays to make them sterile and then release into to the wild. Since females only mate a few times in their life, generally only once, any mating with a sterile male will prevent that female from giving birth to any offspring.
Success story in Zanzibar

First brought tsetse levels down > 90% with pesticides. Then in 1994 they began a 4 year Sterile Insect Technique (SIT) – more than 8 million sterile male flies were used. At the end of 1997, an independent expert group confirmed that, since September 1996, not a single wild fly had been captured in the once heavily infested areas of Zanzibar.

Reasons: Flies can not cross the channel and so do not reinfect. Only a single tsetse species.
## Summary

<table>
<thead>
<tr>
<th></th>
<th>T. gambiense</th>
<th>T. rhodesiense</th>
<th>T. brucei</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>W. Africa</td>
<td>E. Africa</td>
<td></td>
</tr>
<tr>
<td><strong>Glossina vector</strong></td>
<td>palpalis group</td>
<td>morsitans group</td>
<td></td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Chronic</td>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>(months-years)</td>
<td>(weeks-months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parasitemia</strong></td>
<td>Low</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>CNS involvement</strong></td>
<td>Late</td>
<td>Early</td>
<td></td>
</tr>
<tr>
<td><strong>Host</strong></td>
<td>Human</td>
<td>Human &amp; Game Animals</td>
<td>Cattle &amp; Game Animals</td>
</tr>
<tr>
<td><strong>HDL sensitivity</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
In the Insect Vector

The ingested form that is infectious for the fly is termed the **short-stumpy bloodstream trypomastigote**, which is a non-dividing form. Following ingestion, the bloodmeal is retained within the midgut, and the parasite differentiates into a **procyclic form** and divides by binary fission. After about two weeks some procyclics migrate from the midgut through the hemocoel eventually reaching the salivary glands. At this point they differentiate through an **epimastigote stage** into a **metacyclic trypomastigote stage**, which is a non-dividing form infectious for the mammalian host. Metacyclic trypomastigotes are found in the salivary glands ~ 20 days after the bloodmeal, and there are ~ 40,000 trypomastigotes/bite, but it takes only 400 to initiate an infection.
Fig. 96. *Trypanosoma (Nannomonas) simiae* in proboscis of Tsetse-fly (× ca. 500): a. Clusters of flagellates in food canal; b. Flagellates (including metatrypanosomes) in hypopharynx. (From Bruce *et al.* 1913.)
Stage 1 – Long-slender trypomastigotes actively divide
Stage 2 – At high cell densities, long-slenders differentiate into short-stumpys (able to differentiate further into procyclics)
Stage 3 – Mostly short-stumpys, immune clearance of long-slenders
Stage 4 – Immune clearance of short-stumpys
Stage 5 – Next proliferation of long-slenders which can evade host immune response (How? Antigenic Variation)
The long slender forms differentiate into non-dividing short stumpy forms.
In the vertebrate the parasite uses the regulatory mechanisms of the host and utilizes the plentiful energy source of the blood, glucose. The segregation of glycolytic enzymes in the glycosome organelle substantially increases the efficiency of glycolysis. Oxygen is consumed via a plant-like alternative oxidase, which does not produce ATP by oxidative phosphorylation. The differentiation from the long slender to the short stumpy form in the bloodstream involves changes in metabolism. The stumpy forms are infective for the fly. In the fly, glucose is limiting and therefore a more efficient utilization of glucose and amino acids occurs via the TCA acid cycle and oxidative phosphorylation. Metacyclics anticipate transfer to the vertebrate host by the mitochondrion by losing cristae and TCA cycle enzymes.

Repression of mitochondrial metabolism in long slender bloodstream trypanosomes
Trypanosomiasis Pathology

PRIMARY STAGE

When metacyclic trypomastigotes are introduced subcutaneously and multiply. In 2-3 days there is itching, swelling, pain and redness, and after 6 days a trypanosomal chancre may develop at the bite site. This is considered by most to be an innocent boil and is disregarded.
The metacyclic trypomastigotes replicate at the site of infection. There may be an immune response causing inflammation (trypanosomal chancre) at the site of the bite. From there the trypomastigotes move via the lymphatics to the lymph nodes and then to the bloodstream. In *T. gambiense* infection, swollen cervical (neck) lymph nodes are referred to as Winterbottom’s sign. Long- slender bloodstream trypomastigotes divide by binary fission in the bloodstream, generating, on occasion, short-stumpy forms to continue the cycle in the tse-tse fly. The long-slender trypomastigotes are not infectious for the fly.
BLOOD STAGE

The earliest sign of a generalized infection is fever; there may also be malaise, headache and pains in the joints. Five to 12 days after infection trypanosomes are found in the bloodstream. They are scarce in *T. gambiense*, and more abundant i.e. $10^5$/ml in *T. rhodesiense*. Trypanosomes also enter the lymphatics and there is lymphadenopathy. The influx of B-cells results in lymph node enlargement and the lysis of trypanosomes release toxic materials that stimulate macrophages to release tumor necrosis factor (TNF, also called cachectin) and this produces cachexia. The release of trypanosome toxic factors and lymphokines gives rise to a cyclic (or relapsing) fever with an approximate cycle of 7-10 days.
In the **Rhodesian** form there is a rapid illness with invasion of the CNS via lymphatics within a few weeks. Patients may die of myocarditis even before the CNS is invaded. In the **Gambian** form the disease progresses in a more insidious fashion with personality changes, insomnia or irritability signaling invasion of the CNS. CNS involvement may not occur until one or more years after infection. Inflammatory changes lead to a demyelinating meningoencephalitis; there is cerebral edema, hemorrhages, pericarditis, and anemia. The encephalopathy leads to apathy, somnolence and coma. Death is usually caused by intercurrent infections such as pneumonia.
Pathogenesis of African Trypanosomiasis

**PRIMARY**
- Metacyclic
  - Subcutaneous
  - Itching 2-3 d
  - Swelling 6 d
- Tsetse bite
  - Trypanosomal chancre
  - Asymptomatic

**BLOOD STAGE**
- Long slender
- Short stumpy
- Fever, malaise, rash
- Alternating asymptomatic
  - Flu-like symptoms
  - Lymphatics

**LATE STAGE**
- Meningoencephalitis
- Cerebral edema
- Hemorrhage
- Pericarditis
- Coma
- Pneumonia
  - CNS
  - Death
COMPARATIVE PATHOGENESIS OF TRYPANOSOMIASIS

AFRICAN

Metacyclic → subQ
multiply
2-3 days itching, swelling
6 days

TSE - TSE (bite)

TRYPANOSOMAL CHANCRE
(trypomastigotes)

ASYMPTOMATIC
(weeks - months)

scanty in T. gambiense
1000,000/ml T. rhodesiense

AMERICAN

REDUVID (feces)

CHAGOMA
(ama
tigotes)

ROMAÑA'S SIGN
(few days)

BLOOD

5-12 days
stumpy & slender
divide

anemia

slender

headache

flulike
symptoms

FEVER, MALAISE, RASH
alternatively ASYMPTOMATIC

REGIONAL LYMPH NODES

older children
adults

young children

doctors

BLOOD

(few trypanosomes) (many trypanosomes)

ENLARGED GLANDS,
HEPATOSPLENOMEGALY

months
transient

CURE

WINTERBOTTOM'S SIGN

enlarged cervical
lymph node

CURE

CNS
(trypomastigotes)

encephalitis
(cachexia
from mo)

DEATH

demyelination may result from

lysis of
 tries → TNF, also
called cachectin
released

auto-antibodies with a proteolipid
epitope of T. brucei

FINAL STAGE

meningoencephalitis

cerebral edema

hemorrhage

pericarditis

coma

pneumonia

is immediate

cause of death

in 50% of cases

DEATH
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pentamidine</th>
<th>Suramin</th>
<th>Metarsoprol</th>
<th>Eflornithine</th>
<th>Nifurtimox†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduced</td>
<td>1937</td>
<td>1922</td>
<td>1949</td>
<td>1990</td>
<td>–</td>
</tr>
<tr>
<td>Chemical status</td>
<td>Diamidine</td>
<td>Sulphated naphthylamine</td>
<td>Arsenical</td>
<td>Difluoromethylornithine</td>
<td>Nitrofuran</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Intramuscular</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Oral</td>
</tr>
<tr>
<td>Effective in relation to disease stage</td>
<td>Early-stage <em>T. b. gambiense</em></td>
<td>Early-stage <em>T. b. gambiense</em> and <em>T. b. rhodesiense</em></td>
<td>Early or late <em>T. b. gambiense</em> and <em>T. b. rhodesiense</em></td>
<td>Early or late <em>T. b. gambiense</em></td>
<td>Arsenical-resistant <em>T. b. gambiense</em></td>
</tr>
<tr>
<td>Dosage regimen</td>
<td>4 mg/kg body weight &gt; 10 daily injections</td>
<td>20 mg/kg body weight 5-7 injections every 5-7 days</td>
<td>3.6 mg/kg body weight 3-4 series of 4 injections separated by 1 week</td>
<td>400 mg/kg body weight 100 mg every 6 hours for 14 days</td>
<td>10 mg/kg body weight daily 60-90 days</td>
</tr>
<tr>
<td>Resistant strains</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>T. b. rhodesiense refractory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Side-effects</td>
<td>Vomiting, hypotension, hypoglycaemia</td>
<td><em>Pyrexia, joint pains, rash, desquamation</em></td>
<td>Encephalopathy, diarrhoea</td>
<td>Diarrhoea, anaemia, thrombocytopenia</td>
<td>Convulsions, psychosis, vomiting, neuralgia, polyarthritis, paraesthesia</td>
</tr>
<tr>
<td>Cost of drug/treatment ($US)</td>
<td>100†</td>
<td>15</td>
<td>47</td>
<td>266</td>
<td>60-100</td>
</tr>
<tr>
<td>Costs of complementary drugs ($US)</td>
<td>–</td>
<td>–</td>
<td>130 if encephalopathy occurs</td>
<td>200, i.v. fluid, perfusion kits, etc.</td>
<td>–</td>
</tr>
<tr>
<td>Hospitalization costs ($US)</td>
<td>60 (12 days)</td>
<td>120 (30 days)</td>
<td>150 (30 days)</td>
<td>70 (14 days)</td>
<td>Not available</td>
</tr>
<tr>
<td>Total costs $US</td>
<td>160</td>
<td>175</td>
<td>197 (or 327)</td>
<td>536</td>
<td>–</td>
</tr>
</tbody>
</table>

*Test dose in onchocerciasis areas.
†Pentamidine is presently being supplied by WHO at a nominal cost through the courtesy of Rhône Poulenc—the manufacturer.
‡Nifurtimox has not been widely used in African trypanosomiasis. Figures are based on best estimates from use in Chagas' disease.
+Resistance to drugs exists.
# Current Treatment of Human African trypanosomiasis

<table>
<thead>
<tr>
<th>Stage</th>
<th><em>T.b. gambiense</em></th>
<th><em>T.b. rhodesiense</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>First stage</td>
<td>Pentamidine&lt;br&gt;4 mg/kg i.m. at 24 hourly intervals for 7 days i.m. (or as i.v. short infusion)</td>
<td>Suramin&lt;br&gt;Test dose of 200 mg i.v.&lt;br&gt;20 mg/kg day 1, 3, 7, 14 and 21 [10]</td>
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<td>Second stage</td>
<td>Eflomithine&lt;br&gt;Intravenous eflomithine (100 mg/kg every 6 h) for 14 days&lt;br&gt;Eflomithine/Nifurtimox combination&lt;br&gt;Intravenous eflomithine (200 mg/kg every 12 h) for 7 days and oral nifurtimox (15 mg/kg per day, every 8 h) for 10 days&lt;br&gt;Melarsoprol&lt;br&gt;2.2 mg/kg i.v 10 daily doses</td>
<td>Melarsoprol&lt;br&gt;2.2 mg/kg i.v 10 daily doses&lt;br&gt;Pre-treatment with suramin&lt;br&gt;Test dose of 4–5 mg kg&lt;sup&gt;−1&lt;/sup&gt; body weight at day 1</td>
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Anencephalopathic syndrome (ES) comprising convulsions, progressive coma, and psychotic reactions, the long duration of treatment, and the increasing rate of treatment failures reaching up to 30%. ES occurs variably with an average frequency of 4.7% for *T.b. gambiense* and 8% for *T.b. rhodesiense* HAT and has a fatality rate of about 50%.

In the absence of controlled trials there are currently no treatment guidelines of ES.
The best treatment now is eflornithine, sometimes called the resurrection drug because it can pull the dying out of comas.

It is almost a miracle that eflornithine is available. It was discovered in 1980 at Pace University in New York. By early 2000, the last 7,500 doses in the world were running out. The patent holder, a precursor of the drug maker Sanofi-Aventis, abandoned it in 1995 because it had not lived up to its anticancer potential. Then, in late 2000, plans to make a topical form emerged. It was the key ingredient in Vaniqa, a cream to prevent facial hair in women.

After critics accused Sanofi-Aventis of catering to vain rich women while letting poor Africans die, the company agreed to make an injectable form of the drug and now gives it free to the World Health Organization and Doctors Without Borders.

But in rural Africa, eflornithine is very hard to use. Patients need intravenous infusions four times a day for two weeks. When a “hospital” is a row of iron beds under a thatched roof, and the “nursing staff” is mostly relatives of the sick who sleep on the floor, round-the-clock treatment is hard. There might be no night nurse to insert an IV line.
Fexinidazole

A 5-nitroimidazole drug – undergoing Phase 1 clinical studies.

**in vitro:**
Showed trypanocidal activity against all *T. brucei* subspecies isolates. The drug metabolizes to sulfoxide and a sulfone metabolites – which are the active forms.

**in vivo:**
Acute mouse model and Chronic mouse model (mimics advanced and fatal stage):

Can be taken orally 4-5 day treatment cures the disease. Works with acute infection or established brain infection. No toxicity at levels tested.

![Chemical structures of Metronidazole, Benznidazole, and Fexinidazole](image)
Fexinidazole, a drug candidate for stage 2 HAT, is the first success of the proactive compound mining efforts DNDi pursued in the Nitroimidazole Project. Fexinidazole was in pre-clinical development as a broad-spectrum antiprotozoal at Hoechst AG in the early 1980s, but was then abandoned. DNDi “rediscovered” it and an extensive profiling has shown that fexinidazole is orally active in animals, crosses to the brain in mice, and has cured in models for both acute and chronic infections with African trypanosomes. Additionally, fexinidazole is not mutagenic (i.e. is not capable of inducing mutation) in a panel of *in vitro* and *in vivo* mammalian genetic toxicology tests, confirming its favourable activity/toxicity profile as a drug candidate.

In 2007, a full pre-clinical programme was established to enable first-in-human studies. This included: process chemistry; GMP (good manufacturing practice) manufacturing of the active pharmaceutical ingredient; pre-clinical formulation; ADME-PK (absorption, distribution, metabolism, excretion, and pharmacokinetics) profiling and confirmatory studies in animal models of HAT; and the regulatory toxicology package. In May 2009, DNDi signed an agreement with sanofi-aventis (now: Sanofi), whereby DNDi is responsible for non-clinical, clinical, and pharmaceutical development, whereas sanofi-aventis is responsible for the industrial development, registration, and production of the drug at its manufacturing sites. Fexinidazole entered into Phase I first-in-human studies in September 2009, which makes it the only new drug candidate currently in clinical development for sleeping sickness. By the end of 2010, the three planned studies (single ascending dose, food effect, multiple ascending dose) had been completed. Additional studies are planned in 2011 in order to find the adequate regimen and treatment duration.
Trypanosoma congolense

Causes Ngana in cattle and is transmitted by the tsetse fly. Wild animals are a reservoir.
Other animal disease-causing trypanosome species

*Trypanosoma lewisi*

Infects rats. Vector is the flea. Stercorarian transmission: An infected flea takes a blood meal from a rat and then defecates, passing metacyclic trypanosomes in the faeces. The rat licks the wound and also ingests the flea faeces. Transform to trypomastigotes in bloodstream.
Historical extinction of endemic rat population on Christmas Island was caused by *Trypanosoma lewisi* infections.
Trypanosoma evansi

Causes “Surra” in camels and also horses. This was the first pathogenic trypanosome discovered. Found throughout mid to Northern Africa and the Middle East. Was introduced by the Spaniards into the New World. Transmitted *mechanically* by tabanid flies (horse flies). In the New World, Vampire bats can also transmit *T. evansi*. Some strains of *T. evansi* lack the kinetoplast DNA and some just maxicircle DNA.
Blood-sucking dipterous flies of the genus *Tabanus*.

Tabanids are very determined feeders, going from host to host, perversing despite disturbances. It takes five seconds of feeding time for a tabanus to become infected and it takes approximately the same amount of time for that infected fly to transmit the organism to a desired host. *T.evansii* does not survive for more than 10-15 minutes in the proboscis of the fly.
**T. equiperdum**

Causes “Dourine” in horses. This is a venereal disease and has no insect vector. Was introduced into Europe, Russia, Siberia, Middle East, Indonesia and even North America. Some strains lack kDNA!
Diagram illustrating the relationships between three subspecies of *Trypanosoma brucei* and *Trypanosoma evansi* based on known genetic differences.