9

African Trypanosomiasis

Hayden T. White

Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa

INTRODUCTION

African trypanosomiasis (sleeping sickness) results from infection due to organisms of the genus *trypanosoma* (order kinetoplastidae and family trypanosomatidae)(1). These organisms are digenetic parasites whose life cycle involves 2 hosts: a definitive mammalian host and an intermediate arthropod host (which is responsible for dissemination of the organism). They are classified into 2 groups; stercoraria and salivaria. **Stercoraria** comprises species that develop in the arthropod's hind gut (reduviid bug) and are therefore found in the bug's feces. This includes the causative agent of Chaga's disease or American trypanosomiasis, *Trypanosoma cruzi.* **Salivaria** include species that are found in the salivary glands of the tsetse fly *(Glossina* species) and are transmitted via inoculation into mammalian skin. The species infecting humans is known as *Trypanosoma brucei.* The brucei complex consists of the subspecies *gambiense* (west African trypanosomiasis, WAT) and *rhodesiense* (east African trypanosomiasis, EAT). Another subspecies, *T. brucei brucei* infects cattle, goats and sheep but not humans. While it has become useful to classify African sleeping sickness in terms of the 2 subspecies, it should be recognized that many different strains exist which are capable of infecting man (2).

MORPHOLOGY

The trypanosomiasis parasite is characterized by the presence of a free flagellum arising from the kinetoplast (an organelle containing DNA) and an undulating membrane that gives the organism motility (3,4). The organism exists in different stages in the various hosts. The epimastigote stage occurs in the insect vector (5,6). This stage is not infective to humans but transforms into the infective metacyclic trypanosome, which is considered the young form of trypomastigote. The trypomastigote is the mature form and is found in the blood of mammalian hosts. Polymorphic forms may be present and represent the brucei complex. If the species is monomorphic, then *T. cruzi* is diagnosed.

EPIDEMIOLOGY

The distribution of human trypanosomiasis follows that of the vector, the tsetse fly. Thirty-six countries in sub-Saharan Africa are considered to be endemic with some 50 million people at risk. Approximately 10 million km^2 are infested with tsetse, severely limiting the agricultural potential of these areas. Sleeping sickness has reached epidemic proportions in Angola, Uganda and the Sudan. Although 25000 new cases are reported annually, it is estimated that the true figure is closer to 300000 (7). During the 1960's the prevalence of sleeping sickness in most African countries had been reduced to < 0.1%. However, civil unrest over the past few decades and the subsequent decline in control programs has resulted in a marked increase in the prevalence of disease. Some areas have reported figures as high as 18%. Nowhere is this more evident then in the Democratic Republic of the Congo. The recent war has led to estimates that over 100000 people will die annually from trypanosomiasis. Another example is Angola, where 60% of the population in the north of the country has evidence of past or present infection. Civil wars and the breakdown of health services are the primary reasons for the resurgence of sleeping sickness in much of Africa.

VECTOR

The trypanosomes are transmitted by blood sucking flies of the genus *Glossina.* The fly may live for several weeks and is capable of transmitting the disease with each bite. The reproductive cycle of the parasite takes place in the midgut of the fly (6). The resulting metacyclic epimastigote enters the bite wound via the hypopharynx. They enter the blood stream where they begin to multiply by asexual binary fission, once every 6-8 hours. Later, some trypanosomes will enter the cerebrospinal fluid (CSF).

Flies are infected 18 to 35 days after feeding from an infected host. The vector for **WAT** is the riverine tsetse fly of the *palpalis* group. The fly is endemic throughout West and Central Africa. Its habitat is dense vegetation along rivers and forests. Humans are the preferred host but several species of animal may also be infected. Humans however, are the only known reservoir. The flies feed during the daylight hours and are attracted to dark skin. The incubation period tends to be long and asymptomatic carriers of the disease are common, increasing the risk of spread. **EAT** is transmitted by tsetse of the *morsitans* group. It is distributed from Uganda and Kenya in the north to Botswana in the south. The flies live in woodlands and thickets of the savanna. They are more inclined to bite animals then humans, who are incidental hosts. Bushbuck, hartebeest and cattle are the main reservoir. Man is usually infected while venturing into areas that the animals inhabit.

PATHOGENESIS

The pathogenesis is ultimately linked to the inability of the immune system to rid itself of the parasite. The African trypanosome is found in the extracellular compartment and survives in the mammalian host by periodically altering its surface antigenic coat, thereby aborting the developing immune response. The surface of the parasite is dominated by 2 glyoproteins, namely the variant surface glycoprotein (Vsg) of the blood stream stage and procyclin of the procyclic stage. The main function of the Vsg is to provide a protective coat that covers the entire surface of the parasite. The intention however, is not to avoid the immune system

completely but to exploit it for the parasites benefit. The benefit of this system is that it leads to persistent infection due to the presence of a relatively constant and tolerable number of parasites rather then rapid killing of the host as would occur in the case of uncontrolled growth. Each parasite has the ability to display literally hundreds of different Vsg proteins and can evade the immune system indefinitely (8).

IMMUNOLOGY

Acquired immunity is antigen specific. Therefore, sleeping sickness is characterized by recurring parasitemias, with each new wave of parasites representing the selection of an immunologically distinct antigenic variant. During an infection, trypanosome variant surface glycoprotein (VSG) (9), determinants stimulate B cells through T cell dependent and T cell independent mechanisms. Polyclonal hypergammaglobulinemia, particularly increased immunoglobulin M is striking and a constant feature. However, little of the IgM produced is specific antitrypanosome antibody.

CNS DISEASE

Complex neuropathological changes are commonly found. Neurological complications occur more frequently with *T.b.gambiense.* The levels of several neurotransmitters may become significantly altered, especially in areas involved in sleep control. There can be marked increase in the levels of prostaglandin D_2, one of the ultimate sleep regulating substances (10). This may be responsible for several of the neurological manifestations including headache and somnolence. Pathologically, CNS involvement results in meningoencephalitis. Morular or Mott cells may be seen. These cells are plasmacytes with vacuolated cytoplasm and pyknotic nuclei that are thought to play a role in the production of immunoglobulin M (IgM).

CLINICAL PRESENTATION

Clinical manifestations of sleeping sickness are not pathognomonic and may vary. Broadly speaking, the disease progresses from local inoculation of the skin, to the hemolymphatic system, organ infiltration (heart and CNS) and ultimately death. *T.b. rhodesiense* tends to cause a fulminate disease with early CNS involvement, cardiac involvement and death within a few weeks. In contrast, *T.b. gambiense* infiltrates the lymph glands and the CNS later, and leads a chronic progressive course that may last months to years before death ensues.

A chancre may develop within the first 2 weeks at the site of the tsetse bite. Classically, it is painful, indurated and appears as a red papule, 2-5cm in diameter (11). It is not always present and tends to be found more often in non-Africans. Within 1-3 weeks of the bite, the parasite enters the blood stream. The invasion is accompanied by high fever, malaise, headaches, joint pains, tachycardia and hypoglycemia (glycolysis being the sole source of energy for the parasite). The fever may last for 1-7 days and then follows an intermittent course during which the patient feels well. An irregular circinate rash may appear. Further dermatological features include pruritus, hyperaesthesia (Kerandel's Sign) and edema of the face, hands and feet. Involvement of the eyes leads to interstitial keratitis and conjunctivitis. General lymphadenopathy follows as the disease progresses. Involvement of the spleen and liver leads to hepatosplenomegaly.

Death in patients with *T.b. rhodesiense* may occur before CNS involvement. Cardiac disease presents early with arrhythmia or cardiac insufficiency as a result of a pancarditis. Not surprisingly, the ECG tracing shows marked abnormalities. Pericardial effusions have also been documented.

The progression of disease is different for WAT and follows a more indolent course. Months to years may pass before the onset of clinical symptoms. Lymphadenopathy is a prominent feature of the disease. Characteristically, the supraclavicular and posterior cervical lymph nodes are enlarged (Winterbottom's Sign). This sign has also been associated with CNS involvement. Patients may present with irritability, insomnia,

personality changes and lack of concentration long before the parasite is detectable in the CSF. Daytime somnolence and nocturnal insomnia is a prominent feature (12). Psychiatric disorders such as mania and delirium may intervene and patients with sleeping sickness have been found in psychiatric institutions. Patients may present with Parkinsonian like features with rigidity, shuffling gait and slurred speech. Eventually epilepsy intervenes and patients become severely disabled. The final stages of the disease include progressive dysfunction with patients being unrousable and subsequently are unable to eat or drink. This leads to progressive malnutrition, intercurrent infections and death.

Laboratory abnormalities that may be found include hemolytic anemia (Coomb's positive), abnormal liver function tests, thrombocytopenia, hypocomplementemia, crypglobulinemia, and abnormal clotting profiles indicative of disseminated intravascular coagulation. None of these are pathognomonic. Spurious hypoglycemia is sometimes observed due to the metabolism of glucose by the parasite. Recent studies have shown abnormalities with the hypothalamic-pituitary axis with resultant adrenal insufficiency, hypothyroidism and hypogonadism. The IgM in the serum and CSF is usually raised. CSF shows a mononuclear cell infiltrate and morular/Mott cells may be present.

DIAGNOSIS

It is important to make a definitive diagnosis of sleeping sickness. This is because the treatment varies depending on the strain of the offending parasite and organ system involved (i.e. CSF). Furthermore, the drugs used to treat the infection are extremely toxic (with an estimated mortality of 5-10% on treatment). The parasite can be isolated from blood, CSF, lymphnode and chancre aspirates. Serology is helpful but not diagnostic. The disease progression is nonspecific and may be confused with many others including, malaria, TB, brucellosis, syphilis, and viral encephalitis.

The parasite may be detected in peripheral blood. Both thick and thin smears, stained with either Giemsa or Wright's stains are required to confirm the diagnosis. *T.b. rhodesiense* is more easily diagnosed then *T.b. gambiense* as the later is less likely to be seen in peripheral blood. Blood is more commonly positive in the early stages of disease and should be

examined on several occasions, as the parasitemia tends to occur intermittently. The two species cannot be differentiated by microscopy alone. Numerous techniques have been developed to increase the yield of specimens e.g. the use of an anion-exchanger DEAE-52 cellulose membrane and buffy coat examination (13). Both the haematocrit centrifugation and the quantitative buffy coat techniques have been evaluated in Uganda with varying degrees of success. For *T. b. gambiense,* the most dependable sites for recovering trypanosomes are aspiration of the chancre or a lymph node. Multiple specimens are usually required. Other, more laborious techniques include animal inoculation, which is the most sensitive test for *T.b. rhodesiense* and culture of the organism.

As the involvement of the CSF alters management and worsens prognosis, every patient with sleeping sickness should have a lumbar puncture. Demonstration of an increased white cell count (WCC) or elevate protein suggests CNS invasion. IgM is raised and morular cells may be seen. Parasites are not always detected, but the presence of WCC and protein abnormalities in the face of peripheral invasion is indicative of CNS disease. CSF IgM levels may remain elevated for long periods after effective treatment.

Serological testing has been used extensively. Patients with sleeping sickness produce a range of antibodies directed against variant surface glycoproteins as well as other antigens. Serological tests have the drawback of being unable to differentiate infected from exposed individuals. They are therefore important for population studies but are of limited use in diagnosing infected individuals. Newer tests are under investigation that may improve the diagnostic capabilities. The card agglutination test for trypanosomiasis (CATT) detects variant antigen types (VAT) of *T.b. gambiense.* The presence of VAT in the CSF correlates directly with the trypanosome infection of CSF. Unfortunately for *T.b rhodesiense,* the serodiagnosis relies on the detection of relatively small amounts of antibody against the invariant surface antigens, for which tests lack both sensitivity and specificity. A newer antigen detection system for *T.b. rhodesiense* uses a monoclonal antibody against a procyclic invariant antigen to detect the parasite in the peripheral blood (14). Field tests are underway in order to establish whether these serological techniques would be sufficient for parasite detection (15).

TREATMENT (table 1)

It is imperative that the diagnosis of HAT is accurate and the treatment is monitored for side effects and efficacy. Currently no distinction is made between infection and asymptomatic carriers; therefore if the parasite is found, the patient should be treated. The use of serology is less clear as one can be serologically positive in the absence of infection (16). These "serological suspects" are usually followed with sequential parasitological assays. Distinguishing between the two organisms is similarly important as this may alter management. Although it is impossible to distinguish them morphologically, DNA probes are available at a few research labs (17). Alternatively, the recommendations are to treat the patient according to the clinical presentation.

Early

Suramin. Suramin is a sulfonated naphthylamine polyanionic molecule. It was originally introduced in 1922 and is still the drug of choice for both *T.b. gambiense* and *T.b. rhodesiense.* A full course will cure virtually 100% of cases (18). It does not however cross the blood brain barrier so is of little use for treating CSF invasion (19). The mechanism of action is not known but suramin has been shown to inhibit various dehydrogenases and kinases including RNA polymerase and L-α-glycerophosphate. This drug is relatively slowly cidal, trypanosomes only disappearing from blood 12-36 hrs after injection.

Suramin is administered by slow intravenous injection in a 10% aqueous solution. The drug must be used within 30 minutes of reconstitution as it deteriorates in air. Suramin is a potentially toxic drug. Approximately 1 in 20000 people will have an idiosyncratic reaction that may include nausea, vomiting, seizures and shock. Other less significant and transient side effects include joint pain, fever, pruritus, urticaria, photophobia, conjunctivitis and paresthesias. Lab abnormalities include a transaminitis, raised urea and creatinine, and thrombocytopenia. Suramin is deposited in the renal tubules and may lead to albuminuria and renal failure. Albuminuria usually clears within a few weeks and therefore treatment should not be stopped. If however, the proteinuria worsens or casts appear, then an alternate treatment should be sought. Severe reactions

including agranulocytosis, adrenal insufficiency, hepatitis and death have been reported. Most advocate the use of an initial test dose of 200 mg. Some would even consider giving a dose of steroids pre-treatment.

Pentamidine. Pentamidine is an aromatic diamidine, which was originally introduced in 1937. It is available in two preparations; the isothionate (1.74mg salt equivalent to 1 mg base) and the dimethane sulfonate (1.56mg salt containing 1mg base). While it is a potent inhibitor of nucleic acid synthesis by inhibiting S-adenosyl-1-methionine decarboxylase, the mechanism of action remains unclear. (20). Trials suggest that it has a prolonged action and slow rate of excretion. Following a single dose, volunteers were protected for as long as 295 days. Although small amounts can be detected in the CSF, it is not recommended for the treatment of late stage disease.

Pentamidine is recommended for the treatment of both EAT and WAT. While it is very effective in treating WAT the rates of cure are less than suramin for EAT. At one stage pentamidine was advocated for prophylaxis of persons at high risk and was given as an intramuscular injection every 3-6 months. The high cost and toxicity has led to the abandoning of this practice.

Minor side effects including hypotension, nausea, hypoglycemia, vomiting and tachycardia are temporary and should not interfere with treatment. The hypotension occurs secondary to histamine release but anaphylaxis is rare. The route of administration is usually via intramuscular injection although intravenous preparations are available. Injection sites tend to become very tender and sterile abscesses are not uncommon.

Diminazene aceturate. Like pentamidine, diminazene is an aromatic diamidine. Originally a veterinary compound, it has shown activity against EAT. There are no pharmacokinetic studies in humans although the half-life in sheep is 11-14 hours. Although not registered for human use it has been used extensively in endemic areas, as it is cheap and effective. The relapse rate is reported to be around 2-3% (21).

Late: CNS Invasion

Melarsoprol. Melarsoprol or Mel B was synthesized over half a century ago by Dr Freidheim. It was first made available in Africa in 1949. This drug will cure all stages of sleeping sickness. However, because of its toxicity, it is reserved for late disease. Melarsoprol contains 18.8% arsenic and is supplied in a 3.6% propylene solution. The mechanism of action is complex. It has been shown to irreversibly bind to trypanothione resulting in a compound called Mel T. Trypanothione represents over 80% of glutathione in trypanosomes and is essential for maintaining cellular resistance to oxidant stress. It may also interrupt glycolysis through the inhibition of the parasitic pyruvate kinase.

Despite being the drug of choice for late stage disease, the CSF penetration is poor with some authors reporting levels of near zero. Nevertheless, trypanosomes in the CSF are slower moving and fewer in number only 5-8 hours after the first injection. The dosing regimen is controversial. Numerous studies have reported various strategies from single dose therapy for early stage WAT to multiple dosing for late stage EAT. Certain generalizations are possible. For early stage WAT, a single dose of Mel B may be sufficient. In late stage disease, a cumulative dose of 30 - 50 mg will cure most patients.

In an attempt to simplify treatment with melarsoprol, a team of researchers in Angola studied the effects of a modified treatment protocol on side effects and outcomes in 767 patients with late stage WAT (22). The treatment schedule comprised 10 daily injections of 2.2 mg/kg of melarsoprol. Parasitological cure 24 h after treatment was 100% in both groups; there were six deaths (all due to encephalopathy) 30 days after treatment in each group. The number of patients with encephalopathic syndromes was also the same in each group. Skin reactions were more common with the new treatment, but all could be resolved by additional medication or withdrawal of treatment.

Side effects are common. They include, abdominal pain, nausea, albuminuria, hepatic dysfunction and exfoliative dermatitis. A Jarisch-Herxheimer type reaction may also occur following the lyses of trypanosomes. This can be prevented by the administration of a single

dose of either suramin or pentamidine before initiating melarsoprol therapy. Extravisation during intravenous injection may lead to an intense local reaction. Polyneuropathy occurs in 10% patients. This does not respond to steroids and may progress to severe weakness. Although no formal evidence is available, some authors treat the neuropathy with regular thiamine injections.

Like all arsenicals, melarsoprol may cause severe CNS side effects. Reactive encephalopathy occurs in up to 18% of patients and in 1% leads to death. 2 types have been described i.e. a hemorrhagic encephalitis which is almost invariably fatal, and a reactive encephalopathy from which the large majority eventually recover. The onset is unpredictable. It is characterized by headache, tremor, and difficulty in speech, convulsions and coma (23). Encephalopathy will usually occur at the end of the first series of injections, during the interval between the first and second series or during the second series.

Treatment is controversial. The drug should be stopped and reinstituted slowly a few days later. Dimercaprol (a heavy metal chelator) and corticosteroids have been used to treat the encephalopathy. The impression of most clinicians is that dimercaprol is ineffective, which is not surprising given the hypothesis that the encephalopathy is immune mediated.

The treatment of the encephalopathy depends on the presentation (23);

1. On the first sign of CNS symptoms, the patient should be dripped with a 5% glucose solution. Mannitol 250 g/l can be administered and repeated if symptoms persist. The patient should receive 25 IU of ACTH or 50 mg prednisone immediately.
2. Convulsions should be treated with diazepam and epanutin. If persistent, repeat doses of mannitol may be given.
3. Subcutaneous injections of adrenalin may be given, provided there are no contraindications
4. General patient management strategies including fluid administration, airway management, level of consciousness etc. should be continued until patient improves.

If the patient survives, no sequelae are seen. There is some evidence that the prior administration of prednisone (with or without azathioprine) may decrease the incidence of encephalopathy. A large randomised trial comparing the concomitant use of prednisolone in patients with late stage Gambian trypanosomiasis demonstrated an overall reduction in the frequency of encephalopathy related deaths from 6.2 - 2.8% (24).

A-Difluoromethylornithine (DFMO)(Eflornithine). For the 6% of Gambian trypanosomiasis patients who relapse following melarsoprol therapy, eflornithine is remarkably effective. It is an irreversible inhibitor of ornithine decarboxylase, which is the key enzyme in the pathway leading to biosynthesis of polyamines, essential for proliferation of prokaryotic and eukaryotic cells (25). It is a suicide inhibitor, being a substrate of its target enzyme. The pharmokinectics have been well studied in humans. CSF penetration is excellent and contributes to the efficacy of eflornothine. In a large series from West Africa, gambiense disease refractory to arsenicals was treated with DFMO. The relapse rate was only 9% and is more common in patients with high CSF WBC and those treated with oral medication.

Although more convenient to administer, oral therapy should only be used in patients with poor venous access. It is safe but has a low efficacy and its duration of action is so short that frequent dosing is required. Although some advocate adding oral eflornithine for 3 weeks after the initial intravenous phase, this is probably of no added benefit. The minimum duration of treatment necessary for cure is unknown. Currently a 14-day course of intravenous therapy is recommended but trials are underway to evaluate the efficacy of a 7-day course. Documented side effects include, diarrhoea and anemia and more rarely, rash, seizures and thrombocytopenia (26).

Nifurtimox. Nifurtimox is a 5-nitrofuran that has been used since the mid 1970's to treat Chaga's disease. It inhibits the production of trypanothione reductase, leading to the production of superoxide. It has a short half-life and requires multiple daily dosing to maintain adequate levels.

Trials in WAT have been limited. Several small trials in the Sudan and Zaire on patients with CNS involvement have yielded mixed results.

Although the CSF appears to become sterile fairly rapidly, biochemical abnormalities continue to exist. Cure rates are said to range from 36% to 80%. Given the drugs questionable efficacy and substantial toxicity, it is currently only used in the treatment of melarsoprol resistant *T.b.gambiense* (27).

Nifurtimox is toxic at therapeutic doses. Along with the potential for inducing hemolytic anemia in patients with G6PD deficiency, there are numerous reports of severe CNS abnormalities. These range from a mild polyneuropathy to marked CNS symptoms of cerebellar disease, movement disorders and seizures. Most will resolve upon cessation of treatment but the long-term side effects are not known.

Future Therapies

Part of the difficulty with developing new agents is to identify targets in the parasitic metabolism that are not evident in the host. Trypanothione, a polyamine-containing analogue of glutathione, is unique to trypanosomatids. Inhibitors kill the organism by subverting the normal antioxidant role of trypanothione. Current drugs that are known to interfere with the synthesis include DFMO, nitrofurazone and some trivalent arsenicals.

A drug similar to DFMO, MDL73811 that is an inhibitor of S-adenosylmethionine decarboxylase has undergone animal experiments and was shown to be effective in eradicating *T.b. rhodesiense* infection in mice. Anticancer agents such as alkylphophocholines have had limited success in animal models of sleeping sickness. A recently developed diaminotriazine derivative (SIPI 1029) was found to be effective against resistant strains of *T.b. rhodesiense* in mice (28).

Table 1. Dosing regimens of the drugs used to treat African trypanosomiasis

Drug	Dosage	Therapy
Suramin	- 20 mg/kg ivi to max. 1 g - 200 mg test dose initially - dose given on day 1,3,7,14 and 21 to total of 5 grams	- slow ivi injection in 10% aqueous solution. - must be used within 30 min. of reconstitution
Pentamidine	- 3-4 mg/kg imi daily for 10 doses	- prepare in 3ml distilled water
Melarsoprol *	- 3.6 mg/kg ivi - 3-4 series of 4 injections separated by 1 week	- preparation includes deworming, short course antimalarial and single dose suramin/pentamidine - thiamine supplement - premedication with oral steroids - prednisolone (1mg/kg/d max. 40mg/d)
Eflornithine	- 100 mg/kg ivi 6hly for 14 days	- optional oral therapy for a further 2 weeks - main drawback is cost
Nifurtimox	- 10-15 mg/kg po for 60-90 days	- used mainly for relapse
Diminazine	- 5 mg/kg po every 2 days x 3 doses	- also available in im formulation

* An alternative regimen involves a 10-day non-interrupted course using 2.2 mg/kg/d of melarsoprol.

Intravenous injections of melarsoprol often lead to a severe phlebitis. This and the fact that cross infections with needles are common have led to the development of alternate routes of drug administration. Experimental work in the mouse model demonstrated good results with the topical melarsoprol gel therapy, alone or in combination with the nitrofuranes and the nitroimidazoles (29). Further studies are required, including the development of a transdermal delivery system, and pharmacokinetic and pharmacodynamic investigations before any clinical trials.

Combination therapy is becoming popular. Suramin was combined with various 5-nitroimidazole compounds and found to cure 100% of early stage sleeping sickness in mice. DFMO has been combined with suramin, bleomycin and melarsoprol and been shown to have improved activity against both early and late stage disease. Another promising combination is that of nitroimidazole and melarsoprol (30). Not only were there substantial cure rates for late stage, but the treatment course was shortened and lower levels of arsenicals were required, potentially reducing the incidence of encephalopathy.

VECTOR CONTROL AND SOCIAL PROGRAMS

During the early and mid 20^{th} century, programs to limit the spread of the disease through vector control and population screening were relatively successful. Subsequently, the social and political unrest that has ravaged much of sub-Saharan Africa, has led to a marked resurgence of sleeping sickness (31). Early identification of infected individuals leads to better cure rates and lower costs and decreases the chance of transmitting the disease to others. It is therefore important to screen at risk populations in order to diagnose these cases early. As the treatment and prevention of trypanosomiasis is complicated and costly, efforts to control spread of the disease have centered on controlling the vector. The object is to reduce man/fly contact rather then to completely eradicate the fly. Various techniques have been employed with varying degrees of success including;

- Aerial and ground spraying with insecticides including DDT and more recently pyrethrins (deltamethrin).
- Targets and impregnated traps have reduced the spread of disease in several epidemics (Uganda, Congo, Cote d'Ivoire). The traps are inexpensive and nonpolluting. In a recent outbreak in the Busoga region of Uganda, 8000 pyramidal traps were distributed over an area of 2850 km^2. Within 3 months the fly density was reduced by 98% and the incidence of sleeping sickness by 80%.
- Live bait using insecticide sprays and dips or pour-ons for cattle in tsetse fly infested areas increase the chances of contact between fly and insecticide.

CONCLUSION

As the interaction between the vector and human populations is complex, it is imperative that sufficient social planning occurs before a plan of action is put into place. Much of the control mechanisms in the past involved the relocation of millions of inhabitants in an attempt to decrease fly/man interaction. This led to major disruptions to local economies and much suffering for the indigenous populations. Future plans will require consultation with the local inhabitants to improve participation. Combinations of the various prevention techniques are most likely to have the greatest impact on the spread of disease. These will have to be tailored to the needs of the community and local conditions. The WHO is already heavily involved in prevention strategies throughout Africa. Major funding from western governments is necessary for these projects to advance.

REFERENCES

1. Hoare CA. *The trypanosomes of mammals. A Zoological Monograph.* Oxford: Blackwell, 1972.
2. Molyneux DH, Pentreath V, Doua F. African Trypanosomiasis in Man. In *Manson's Tropical Diseases.* (20th edition), Cook GC, ed. London: WB Saunders Co, 1996.
3. Smith DH, Pepin J, Stich A. Human African trypanosomiasis, an emerging public health crisis. Brit Med Bull 1998; 54: 341-355.
4. Richards FF. The surface of the African trypanosome. J Protozool 1984; 31: 60-64.
5. Wery M, Mulumba PM, Lambert PH, Kazumba L. Hematologic manifestations, diagnosis and immunopathology of African trypanosomiasis. Semin Hematol 1982; 19: 83-92.
6. Vickerman K, Tetley L, Hendry KA, Turner CM. Biology of African trypanosomiasis in the tsetse fly. Biol Cell 1988; 64: 109-119.
7. World Health Organisation. Planning overview of tropical disease control. Division of Control of Tropical Disease. Geneva: WHO, 1995.
8. Barry JD, Graham SV, Fotheringham M, et al. VSG gene control and infectivity strategy of metacyclic stage *Trypanosoma brucei.* Mol Biochem Parasitol 1998; 91: 93-105.
9. Donelson JE, Hill KL, El-Sayed NM. Multiple mechanisms of immune evasion in African trypanosomiasis. Mol Biochem Parasitol 1998; 91: 51-66.
10. Pentreath UW, Rees K, Owolabi OA, Philip KA, Doua F. The somnogenic T lymphocyte suppression prostaglandin D2 is selectively elevated in

cerebrospinal fluid of advanced sleeping sickness patients. Trans R Soc Trop Med Hyg 1990; 84: 795-799.

11. McGovern TW, Williams W, Fitzpatrick JE, Cetron MS, Hepburn BC, Gentry RH. Cutaneous manifestations of African trypanosomiasis. Arch Dermatol 1995; 131: 1178-1182.
12. Murray HW, Pepin J, Nutman TB, et al. Recent advances. Tropical medicine. BMJ. 2000; 320: 490-494.
13. Cattand P, de Raadt P Laboratory diagnosis of trypanosomiasis. Clin Lab Med 1991; 11: 899-908.
14. Rebeski DE, Winger EM, Rogovic B, et al. Improved methods for the diagnosis of African trypanosomiasis. Mem Inst Oswaldo Cruz 1999; 94:249-253.
15. Asonganyi T, Doua F, Kibona SN, et al. A multi-centre evaluation of the card indirect agglutination test for trypanosomiasis (Tryp Tect CIATT). Ann Trop Med Parasitol 1998; 92: 837-844.
16. Atouguia J, Costa J. Therapy of human trypanosomiasis: Current situation. Mem Inst Oswaldo Cruz 1999; 94: 221-224.
17. Truk P, Jammoneau V, Cuny G, Frezil J. Use of polymerase chain reaction in human African trypanosomiasis stage determination and follow-up. Bull WHO 1999; 77: 745-748.
18. Wang CC. Molecular mechanisms and therapeutic approaches to the treatment of African trypanosomiasis. Annu Rev Pharmacol Toxicol 1995; 35: 93-127.
19. Van Voorhis WC. Therapy and prophylaxis of systemic protozoan infections. Drugs 1990; 40: 176-202.
20. Sands M, Kron MA, Brown RB. Pentamidine: a review. Rev Infect Dis 1985; 7: 625-634.
21. Peregrin A, Mammen M. Pharmacology of diminazene. Acta Trop 1993; 54: 301-308.
22. Burri C, Nkunku S, Merolle A, Smith T, Blum J, Brun R. Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense:* a randomized trial. Lancet 2000; 355: 1419-1425.
23. Pepin J, Milford F. African trypanosomiasis and drug induced encephalopathy: risk factors and pathogenesis. Trans R Soc Trop Med Hyg 1991; 85: 222-224.
24. Pepin J, Milord F, Guern Z, Mpia B, Ethier L, Mansinsa D. Trial of prednisone for prevention of melarsoprol induced encephalopathy in gambiense sleeping sickness. Lancet 1989; i: 1246-1250.
25. Milord F, Pepin J, Loko L, Ethier L, Mpia B. Efficacy and toxicity of eflornithine for the treatment of *Trypanosoma brucei gambiense* sleeping sickness. Lancet 1992; 340: 652-655.
26. Denise H, Barrett MP. Uptake and mode of action of drugs used against sleeping sickness. Biochem Pharmacol 2001; 61:1-5.
27. Pepin J, Milford F, Meurice F, Ethier L, Loko L, Mpia B. High –dose nifurtimox for arseno-resistant *Trypanosoma brucei gambiense* sleeping sickness: an open trial in central Zaire. Trans R Soc Trop Med Hyg 1992; 86: 254-256.
28. Bacchi CJ, Vargas M, Rattendi D, Goldberg B, Zhou W. Antitrypanosomal activity of a new triazine derivative, SIPI 1029, *in vitro* and in model infections. Antimicrob Agents Chemother 1998; 42: 2718-2721.
29. Atouguia J, Jennings F, Murray M. Successful treatment of experimental murine *Trypanosoma brucei* infection with topical melarsoprol gel. Trans R Soc Trop Med Hyg. 1995; 89: 531-533.

30. Jennings FW. Combination chemotherapy of CNS trypanosomiasis. Acta Trop 1993; 54: 205-213.
31. Molyneux DH. Patterns of change in vector-borne diseases. Am Trop Med Parasitol 1997; 91: 827-839.