About 70 million people in sub-Saharan Africa are at risk of developing sleeping sickness, also called human African trypanosomiasis (HAT), and current treatments for the late, central nervous system (CNS) stage of the disease are fraught with difficulties – leading to death in almost 10% of cases treated with intravenous melarsoprol. However, untreated, or inadequately treated, sleeping sickness is almost always fatal. But work being done in Glasgow has the potential to transform outcomes for people with this neglected tropical disease, as Professor Kennedy explained.

African trypanosomiasis has been around for centuries as a disease in cattle and also in people; in fact, it’s believed that an emperor of Mali contracted the disease many centuries ago. It’s an extremely serious condition, occurring throughout 36 countries in sub-Saharan Africa, and transmitted by the bite of the tsetse fly. Left untreated, it’s invariably fatal, and current treatment with intravenous melarsoprol for late-stage brain disease is so off-puttingly painful and hazardous that some patients in the African field will actually choose to die rather than be treated with it. In any case, the ten-day intravenous melarsoprol treatment actually kills almost 10% of those who receive it.

Scotland has played an important part in the history of HAT. In the late 19th Century, the Scots microbiologist David Bruce (who discovered brucellosis) started work on the fatal wasting disease known as nagana, in cattle. He discovered protozoan parasites called trypanosomes in the blood of infected cattle, and established that healthy wild animals were the host reservoirs of the disease. This was then transmitted to domestic animals by the bite of the tsetse fly. In 1899, Bruce identified the causative parasite, which bears his name (Trypanosoma brucei). Discoveries followed thick and fast after that. In 1902, Everett Dutton identified (in a European patient) a subspecies called Trypanosoma brucei gambiense, which became known as the West African form of the disease. Eight years later, the East African form (Trypanosoma brucei rhodesiense) was first described (by J W W Stephens and H B Fanthorpe).

Other important names in the history of HAT are the Italian microbiologist Aldo Castellani, who first identified trypanosomes in the spinal fluid of affected humans, and also Scotland’s famed explorer, doctor and missionary David Livingstone, who was the first person to give arsenic for trypanosomiasis, using it in a sick mare. The horse got better, but didn’t like the treatment and refused to take a further dose when it relapsed with the disease, said Professor Kennedy, adding that things hadn’t changed that much in terms of treatment today.

“Sleeping sickness prevalence goes up and down”, he said. “Just when it seems as though it’s subsiding, various factors conspire to ensure a re-emergence”. For example, socio-economic instability disrupts disease surveillance and public health
systems (war in Angola and the DRC is a case in point). Money is another issue – if there are not enough resources allocated to the disease, even in peacetime, then that’s a real risk.

Other factors are increasing parasite drug resistance, changes in climate and vegetation, unpredicted population movements of animal reservoirs and changes in host disease susceptibility. Cattle markets, for example, can bring in different types of the disease, leading to an upsurge in cases in specific locations. Unfortunately, circumstances in sub-Saharan African countries can be unpredictable (e.g., through war), which can create the perfect melting pot for new epidemics. Although, for example, NGOs, some governments and the WHO work very hard, adverse circumstances can hinder efforts to control and prevent spread of the disease.

The two types of sleeping sickness are actually very different in terms of the way they act and the outcomes for those affected. *T.b. gambiense*, which accounts for around 95% of infections, is a chronic infection which lasts for months, or even years. *T.b. rhodesiense*, on the other hand, is an acute disease in which, if untreated, death will come in a matter of weeks. Although this accounts for only 5% of infections, it is the cause of about 72% of cases in Europeans and people from the United States, and is responsible for 18% of the total risk from sleeping sickness in Africa.

From the latest figures, it actually looks on the face of it as though HAT could be on its way out. The 300,000 cases reported in 1998 fell to 50–70,000 in 2006 and to less than 10,000 in 2009. However, both continued vigilance and caution must always be exercised because of the problems of under-reporting and under-diagnosis of the disease.

There is a band of sub-Saharan Africa that is infested by the tsetse fly, known as the Tsetse Belt. This is around 10 million square kilometres – just over a third of the area of Africa, but still slightly bigger than the area of the USA. There are about 31 different types of tsetse fly and at least six can transmit HAT; if bitten, there’s probably about a one in 20 chance of getting the disease.

So why is it so serious and what does it involve? The trypanosome genome has around 10,000 genes, and the genetic make-up means that the parasite can change its surface glycoproteins continually, so that it can evade the host’s immune response. Unfortunately, this means that a vaccine is not possible – because the changing parasite with its antigenic variation would always win.

Professor Kennedy said he had been in the field 25 times and had never been bitten by a tsetse fly – for which he is very thankful. He described how the disease progresses, from stage one (early or haemolymphatic stage) where the parasites are in the blood, lymphatics and peripheral organs, through to stage two (late, central nervous system (CNS) or encephalitic stage) where parasites cross the blood–brain barrier and invade the CNS.

Symptoms of stage one include intermittent fever, headache and malaise; while stage two features include personality changes, motor and sensory deficits, development of seizures, altered sleep patterns, and coma. It can take years to reach stage two in *gambiense* disease, but weeks or just a few months for *rhodesiense* disease. It’s hard to stage the disease, because the two stages can merge into each other, but being able to stage disease is crucial if treatment is to be effective. Untreated, it will kill you. “Not many things do, but this will,” said Professor Kennedy. The name sleeping sickness is appropriate, as the disease is characterised by sleep disturbances, including day-time somnolence and night-time insomnia. In the final stages, there’s a continuous urge to sleep.

There is evidence for changes in the sleep structure in stage two of the disease, which might open up an avenue for diagnosis and potentially monitoring the
response to therapy. A number of diagnostic tools can be used, including observation of symptoms, MRI, and laboratory tests, but it can be hard to get a definitive diagnosis, especially at an early stage. That makes it very hard to decide on a treatment protocol. “If you get it wrong either way, you’ve got the risk of killing patients,” explained Professor Kennedy. It’s possible, too, that there’s an intermediate stage, which adds to the complexity. Some people also become asymptomatic, so could be considered resistant or tolerant.

None of the drugs that are used today would likely be approved under the rigorous processes of current regulatory authorities such as the FDA, he said. “These are old drugs, because there’s no money in it,” he added simply. “Big Pharma wouldn’t get its money back [if it invested in trying to find new treatments].” The early-stage drugs “aren’t too bad”, he said, but intravenous melarosprol for late stage is not pleasant and carries an almost 10% risk of death.

There are some new drugs in the pipeline, he added. A phase III trial of one (oral DB 289) was stopped because it was found to be toxic to the liver and kidneys, but a new combination therapy (NECT), which uses two older drugs (eflornithine and nifurtimox), has now been established as first-line therapy for the gambiense form, although it is not effective in rhodesiense disease. Around 10% of patients treated with melarsoprol will get a condition called reactive arsenical encephalopathy, and over half of them will die. There is, therefore, a pressing need for new, effective and safer treatments, particularly for stage 2 of the disease. And that’s precisely what researchers are aiming for in Glasgow – and the prospect of a new treatment is very real.

Professor Kennedy discussed the work being done in his lab using an innovative and highly reproducible mouse model, in which a condition mirroring sleeping sickness is induced. In Glasgow, Professor Kennedy and colleagues have been using sophisticated imaging and other diagnostic techniques to determine what’s going on with the parasite load in the brain before CNS disease is established, when the neuro-inflammatory reaction sets in, and what happens to the blood–brain barrier function. Getting a really good idea of what’s going on, particularly in the brain, at each stage of the disease is crucial for knowing where and when to target treatments.

Quoting Sir James Black, he said that “The most fruitful basis for the discovery of a new drug is to start with an old drug”. So that’s what he and his team have been doing. Currently, melarsoprol is a cumbersome and painful treatment, but it’s the only drug that is effective in the late stage of the more aggressive form – the rhodesiense disease. Giving it means multiple injections, each one extremely painful, given over ten consecutive days, with side effects including cellulitis and tissue necrosis. But combining it with cyclodextrins (naturally-occurring oligosaccharides that are non toxic and widely used by the pharmaceutical industry) has the real potential to transform the treatment. Research has shown that giving melarsoprol cyclodextrin inclusion complexes as an oral fusion drug in the mouse model, over seven days, is highly effective, rapidly clearing parasites from the CNS and reducing CNS inflammation. The blood–brain barrier function is also rapidly restored after infection.

There are pluses on a practical and financial level too. Using an oral formulation of melarsoprol means there’s no need for hospitalisation, reduced treatment costs and, of course, reduced pain of administration increases patient compliance. Essentially, it has great promise to be effective at clearing the disease, and to be cheaper, pain-free and much easier to administer (particularly for the unfortunate patient).

It’s hoped that a pharmaceutical company will be willing and able to manufacture the drug prior to testing in the field. Excitement about the treatment is such that the researchers have been given permission go straight to phase II trials, and, if this is
successful, it could be used in Africa almost straightaway (although phase III trials would be required if it is to be used in the EU, except under certain very controlled circumstances).

After many years, then, a new treatment that could revolutionise care of the more aggressive form of sleeping sickness is coming very close – and it’s all happening in Glasgow.

Questions

Asked why *T.b.rhodesiense* is more aggressive to the host than the other type (*T.b.gambiense*), Professor Kennedy said that it seems to be due mainly to *Tb.rhodesiense* possessing the SRA gene, which codes for a protein which inactivates the trypanosome lytic factor present in normal human serum. The other form does not possess this gene.

Asked why wild animals in Africa don’t get ill from sleeping sickness (while domestic ones do), Professor Kennedy said that no-one really knows. It might be that some have become ‘trypanotolerant’ over time.

One member of the audience asked who might fund the new drug combination. Professor Kennedy said that it is difficult because there is no profit in it, and the WHO isn’t “cash rich”. He said it would probably come down to pharmaceutical companies and governments to pay for it.

Asked whether climate change would mean that sleeping sickness would travel up to the Mediterranean and Europe, Professor Kennedy said it is a very interesting question, but said that it did seem to be confined to that one band of Africa. If we get “unbelievably warm”, however, it could potentially happen but he didn’t think there is much risk.

The Vote of Thanks was offered by Professor Peter Holmes OBE FRSE, who thanked Professor Kennedy, saying that the lecture showed that although there are a lot of problems, we can be optimistic about the future.