

Chagas Disease



What is Chagas disease?

Chagas disease, named after the Brazilian physician Carlos Justiniano Ribeiro Chagas who first described it in 1909 while working at the Oswaldo Cruz Institute in Rio de Janeiro, exists only on the American Continent. Chagas' work is unique in the history of medicine, because he was the only researcher so far to describe completely a new infectious disease: its pathogen, vector, host, clinical manifestations and epidemiology.

The disease, also called American trypanosomiasis, is caused by a protozoan parasite, *Trypanosoma cruzi*, transmitted to humans by insects. The blood-sucking bugs have differ-

ent common names, e.g. in Brazil, the bug is popularly known as "barbeiro" or "kissing" bug, so-called because it sucks the blood at night by biting the faces of its victims.

There are two stages of the disease: the acute stage which appears shortly after the infection and the chronic stage which manifests after a latent period that may last many years. The lesions of the chronic phase irreversibly affect internal organs namely the heart, oesophagus and colon and the peripheral nervous system. The acute stage of the disease is generally seen in children, and is characterised by fever, swelling of lymph nodes, enlargement of the liver and spleen, or local inflammation at the site of infection. Swelling around one eye (Romana's sign, see above picture) may occur if insect faeces are rubbed into it.

But, commonly, there are no acute clinical manifestations, and those infected may remain without symptoms. After several years of an asymptomatic period, even after decades of persistent infection, some 25 per cent of patients develop cardiac symptoms which may lead to sudden death, five per cent develop digestive damage, and three per cent will present peripheral nerve damage. Chagas Disease is the leading cause of heart failure in Latin America.

Who does Chagas disease affect?

The geographical distribution of Chagas disease extends from Mexico to Argentina. It is estimated that it affects 16 to 18 million people, in Central and South America, killing about 50,000 every year. Another 100 million people or about 25 per cent, of the population in Latin America is at risk of acquiring the disease. Some six million people are affected in Brazil.

The risk of infection is directly related to poverty: the blood-sucking bug which transmits the parasite finds a favourable habitat in the cracks and crevices in walls and roofs of poor houses in rural areas and in the peripheral urban slums. The rural/urban migration movements that occurred in Latin America in the 1970s and 1980s



Geographical distribution of Chagas disease

changed the traditional epidemiological pattern of Chagas disease and transformed it into an urban infection. Chagas disease can also be transmitted by blood transfusion. The figures of contamination of blood in blood banks in some selected cities amount up to 50 per cent, thus showing that the prevalence of *T.cruzi*-infected blood is high.

Present treatments

There are currently no medicines to cure Chagas disease. Available medicines were developed some time ago and can only be used to treat the early, acute phase. An antifungal compound belonging to the azole group and a sulfoxime anti-protozoal molecule are used to remove parasites circulating in the blood, but are only relatively effective in young people; however, they do not rid the patient of the disease.

In the past, their cost has prevented their wide usage. But now pharmaceutical manufacturers have donated the patent rights to their systemic anti-protozoals to governments in the region and the World Health Organisation (WHO) together with the technology to manufacture the medicines. There is nothing available to treat the chronic phase of the disease which eventually leads to heart failure. In the late stages of infection, treatment focuses on managing the symptoms associated with the disease.

Prevention and control

- **Treatment of homes** with residual insecticides
- **Blood screening** to prevent transmission through transfusion
- **Medicinal treatment** for acute early intermediate and congenital cases
- **House improvement** (substituting plastered walls and a metal roof for adobe-wall, thatch-roofed dwellings)

The control strategy of the WHO for the elimination of Chagas disease over the period 1996 to 2010 is based on interruption of transmission by the vector, and the systematic screening of blood donors.

At present, control of the insect vector has been the most successful method of keeping the incidence of the disease to a minimum. Insecticide sprays, insecticidal paints, fumigant canisters, housing improvement, health education and constant surveillance of the infection of isolated populations has reduced the incidence of the disease in many South American countries and some have been certified transmission-free due to the efforts of control programmes such as the Southern Cone Programme. For the control of blood-transmitted infections, the aim is to screen all blood donors from endemic countries for *T. cruzi* antibodies.

What's in the development pipeline?

The search for new treatment possibilities has been revived due to evidence suggesting azole compounds may prevent heart disease in up to two-thirds of young children in the early stages of the chronic phase. Since 2003, a novel class of azole compounds has been studied to treat Chagas disease in the developing world. Azole compounds which are also used to treat fungal infections inhibit the production of a substance necessary for the survival of *T.cruzi* that does not affect human cells.

Furthermore, researchers are testing a new anti-parasitic compound which works as a protease inhibitor and targets an enzyme that *T.cruzi* needs to survive. Since 2002, the therapeutic principle has been investigated in animal studies and phase 1/2 clinical trials.

The longer-term future

Molecular biology provides the opportunity to search more specifically for new vaccine targets. Vaccine targets currently under investigation are the para-flagella rod (PFR) proteins, proteins specific to *Trypanosoma* and necessary for flagella formation allowing the pathogen to travel to the preferred tissues. The *T.cruzi* trans-salidase genes,

Chagas disease is an infection caused by a parasite that is transmitted by insect bites. After years it can affect the heart. Promising new research should lead to more specific treatments.



ASP-1, ASP-2 and TSA-1 are another possibility as target antigens. These proteins are abundant on the surface of the parasite and appear to have important enzymatic roles in *T.cruzi* survival.

DNA vaccines may be an option to protect against Chagas disease as they are relatively easy to make and can be produced inexpensively, allowing poorer countries to access the vaccination. Testing is still in its infancy and the duration of protection of those vaccines so far tried have been variable. Technology has also provided the opportunity to investigate vaccines made from plant

extracts that may be capable of blocking *T.cruzi* enzymes and providing another avenue for vaccine research.

In July 2005, scientists reported having sequenced and compared the genomes of three of the parasites responsible for sleeping sickness, Chagas disease and leishmaniasis. Each parasite is considered to have some 8,000 to 10,000 genes. Researchers identified about 6,200 core genes that are present in all three parasites in a similar order within each genome. Some of the proteins encoded could serve as targets for medicines and vaccines; a worthy goal, given the fact that there are currently no vaccines for the diseases, and only a few medicines.

The researchers found many genes coding for enzymes not known in humans. The genome project turned up core genes shared by the parasites that were probably acquired from bacteria through a process of "horizontal gene transfer." Medicines that hit these acquired enzymes could be fruitful treatment targets because they are less likely to affect the host.

The researchers found that *T.cruzi* goes through four life-cycle stages during its development in insects and humans. The scientists also complemented the sequencing of three kinetoplastid genomes and performed a proteomic analysis of the life-cycle stages of the parasite. They could show that *T.cruzi* appears to use histidine as an energy source during its development in insect vectors, but uses fatty acids when it resides in mammalian cells. Knowledge of stage-specific pathways may aid in future selection of targets for medicine intervention.

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