

CHAGAS DISEASE – AMERICAN TRYPANOSOMIASIS

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ABSTRACT

Introduction. Despite the fact that more than 100 years have passed since the discovery of Chagas disease, research carried out to date with respect to this condition and especially treatment methods concerning it, are still deemed insufficient. The World Health Organization (WHO) recognizes it as one of the Neglected Tropical Diseases (NTD), occurring primarily in the most destitute regions.

Aim. This work aimed at drawing the attention to the relationship between the levels of interest presented by medical and pharmaceutical circles in American trypanosomiasis and the types of social groups that this disease affects.

Materials and Methods. Available literature concerning this subject, as well as estimates indicating the scale of this problem have been analyzed.

Discussion. American trypanosomiasis is a tropical parasitic disease affecting predominantly the residents of both Americas. Chagas disease is associated mostly with the marginalized social strata, due to a special predilection of *Triatominae* vectors for residing in poor households. All insects belonging to the subfamily *Triatominae* feed on vertebrate blood and thereby transmit the parasite called *Trypanosoma cruzi*. In the disease's course, three key phases may be differentiated: acute, latent and chronic. In the majority of cases, the first two phases are asymptomatic, significantly inhibiting detection of the disease. Despite advances with respect to curtailing vector transmission, research concerning effective treatment of Chagas disease remains insufficient. There are only two types of obsolete medications to treat it. Their availability is limited and production continues unstable, whereas their administration is associated with serious side effects and their effectiveness is quite limited.

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Received 7.01.2011, accepted 7.02.2011

Conclusions. Although vector transmission has been to a significant degree controlled, lack of effective medication which could serve to treat this disease indicates a failure with respect to health policies adopted by endemic countries. American trypanosomiasis, tropical in nature, should become an object of interest for highly developed countries in the near future, because of the increasing migrations concerning infected groups of people.

Key words: Chagas, *Trypanosoma cruzi*, endemic countries, Neglected Tropical Diseases (NTD)

INTRODUCTION

Research carried out to date with respect to Chagas disease and its possible treatment methods are still insufficient, despite the fact that more than 100 years have passed since the discovery of this disease by a physician from Brazil. The World Health Organization (WHO) recognizes it as one of 17 Neglected Tropical Diseases (NTD), which have survived only in the poorest and the most marginalized societies. The majority of them could be easily eliminated. However, due to the political insignificance of those social groups affected by them, NTD are not viewed as priority threats to public health. The majority of diseases from the WHO list are found in regions stricken with extreme poverty, such as remote rural areas, urban slums, or armed conflicts zones. Thus residents of such regions frequently die before they can be diagnosed.

AIM

This work aimed at drawing the attention to the relationship between the levels of interest presented by medical and pharmaceutical circles in American trypanosomiasis and those excluded social groups inhabiting endemic countries that this disease, until recently, has singularly affected.

MATERIALS AND METHODS

Available literature concerning the subject has been analyzed. Official estimates provided by the WHO and Pan American Health Organization (PAHO) have been quoted, which only point to some general tendencies, since they cannot serve to describe specific situations in those endemic countries precisely.

DISCUSSION

American trypanosomiasis is a tropical parasitic disease affecting predominately the poorest residents of both Americas. Although it has been discovered and described relatively recently, its existence is estimated for at least 4000 years. Tests performed on mummified tissues of the representatives of the pre-Columbian Chinchorro culture

revealed fragments of the parasite's DNA, which led to the conclusion that already then the disease had been endemic [14]. It is believed that Charles Darwin's death, he being the author of the famous treatise *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*, was a result of Chagas disease. Both its symptoms as well as its course in time correlate with the characteristics of American trypanosomiasis [2, 32]. Moreover, in his notes devoted to the expedition to South America, Darwin provided a description of the insect's bite, which years later was discovered to be the main vector of the disease [12].

At the beginning of the 20th century, a disastrous sanitary situation occurring in many countries of Latin America prevented the implementation of various infrastructure projects within the policy designed to colonize the interior of the continent. In Brazil, both private entities and governmental agencies involved in such investments were forced to undertake proper measures to eliminate epidemic diseases such as yellow fever, true smallpox and plague, which decimated workers employed in the construction of railways, roads and other public facilities [18]. In 1908, Brazilian physician Carlos Ribeiro Justiniano das Chagas was asked to undertake an antimalaria campaign in the village of Lassance, province of Minas Gerais. Chagas assumed a correlation between the health conditions of the workers and the hemipteran *Triatoma infestans* belonging to the subfamily *Triatominae*, which infested rural huts of this region [8].

Chagas dissected the insect and found in its digestive tract large numbers of single-celled parasites of the genus *Trypanosoma*. Consequently, it was important to confirm whether this insect's bite resulted in a pathogenic reaction in vertebrates. To this end, Chagas carried out an experimental inoculation of various animal species, which shortly afterwards developed disease symptoms and some of them died within a few weeks. Assuming that the final host of this microorganism, which Chagas named *Trypanosoma cruzi*, should be human, he then searched for the parasite in the blood of the people inhabiting huts colonized by the hemipterans. In one of them he found a 2-year old girl, with the symptoms of fever, hepatomegaly, splenomegaly, lymphadenopathy and a swollen face. Animals infected with the blood of this first patient died within a few days. In 1909, Carlos Chagas published a paper in which he described the clinical symptoms of American trypanosomiasis, *T. cruzi* and its life cycle as well as the main vector of the disease [22]. It is particularly remarkable that "he started, so to speak, at the wrong end: with a (possible) vector of a (possible) pathogen, causing a disease yet to be discovered and described" [18]. His discovery was immediately successful. In 1912, Chagas was presented with the Fritz Schaudinn Award, and in 1913 and 1921 he was nominated for the Nobel Prize. There appeared scientists, however, who not only questioned the significance of his discovery, but also challenged the existence of American trypanosomiasis itself. Although numerous polemical papers show that Chagas was most frequently successful in defending

his discovery, for years a false opinion predominated that the disease did not pose a serious threat to the public health in Latin America [22].

Chagas disease is mostly associated with the poorest social strata, due to a special predilection of hemipterans of the subfamily *Triatominae* (belonging to the family *Reduviidae*, order *Hemiptera*) for residing in huts with walls made of clay and palm, bamboo or thatched roofs. Crevices in such surfaces serve them as protection during the day, which they will leave after dusk to prey [6]. Some species live only in selva – tropical forest. Others, most probably because human activity has disturbed the balance of their natural environment, have adapted themselves completely to human households or their whereabouts. These species are exceptionally important in the context of epidemiology (*Triatoma infestans* in Argentina, Bolivia, Brazil, Paraguay, Uruguay, Peru and Chile; *Rhodonius prolixus* in Columbia, Mexico, Venezuela and some countries of Central America; *Triatoma dimidiata* in Ecuador, Mexico, Central America and *Rhodonius pallescens* in Panama) [10, 17, 25]. There exist many popular regional names for the vector of Chagas disease: bedbug, “kissing bug”, *chinche*, *chipo*, *pito*, *bananom*, *chirimacha*, *chichâ*, *chupão*, *chupança*, *bicudo*, *fincão*, *protocó*, *chinche besucona* and *chinche gaucha*. The most common term seems to be *vinchuca*, a word which means “plots while flying” in the quechua language [6].

All insects from the subfamily *Triatominae* feed on vertebrate blood. A bite is not painful, but causes itching. Thus, through a microdamage to the skin, the host contributes to introducing *T. cruzi*, excreted by the insect, into blood vessels [28]. *T. cruzi* is haemoflagellate, which indicates this protozoan’s place of inhabitation in the human host. This is within the blood and closely related tissues such as spleen and liver. Haemoflagellates may assume all four different morphologic forms during their life cycle: amastigote, promastigote, epimastigote, and trypomastigote. “While these forms appear to be successive stages, there is no specific sequential pattern of progression from one form to the next. Each form gives the parasite certain advantages and any of these forms is capable of developing into any other” [4].



Fig. 1. Development forms of *Trypanosoma cruzi*: amastigote, promastigote, epimastigote and trypomastigote (Kingdom: *Animalia*, Subkingdom: *Protozoa*, Phylum: *Sarcomastigophorea*, Subphylum: *Mastigophorea*, Class: *Zoomastigophorea*, Order: *Kinetoplastida*, Family: *Trypanosomatidae*, Section: *Stercoraria*, Genus: *Trypanosoma*, Species: *cruzi*).

Amastigote is an intracellular form of the *T. cruzi* parasite. It is ovoid in shape with a diameter of 1.5–5 μm , a large nucleus, and prominent kinetoplast. Promastigote occurs only in the insect vector. It is elongated with the kinetoplast at the extreme anterior end and the nucleus in the centre of the organism. Its long flagellum is free

anteriorly and serves a function of both locomotion and attachment to the insect gut wall. In epimastigote form the kinetoplast is anterior to the nucleus and the flagellum is attached to the pellicle, producing an undulating membrane. Trypomastigote is characterized by a lengthening of the body (10–20 μm long, 1–3 μm wide), elongation of the undulating membrane and flagellum, and migration of the kinetoplast to a site posterior to the nucleus. The parasite moves in the direction of the free end. The pellicle of the trypomastigote is supported by minute tubular structures which help in maintaining its shape and flexibility during movement. The flagellar membrane is closely attached to the body surface, and when the flagellum beats, this area of the pellicle is pulled up into a fold. The fold and the flagellum constitute the undulating membrane [3, 4].

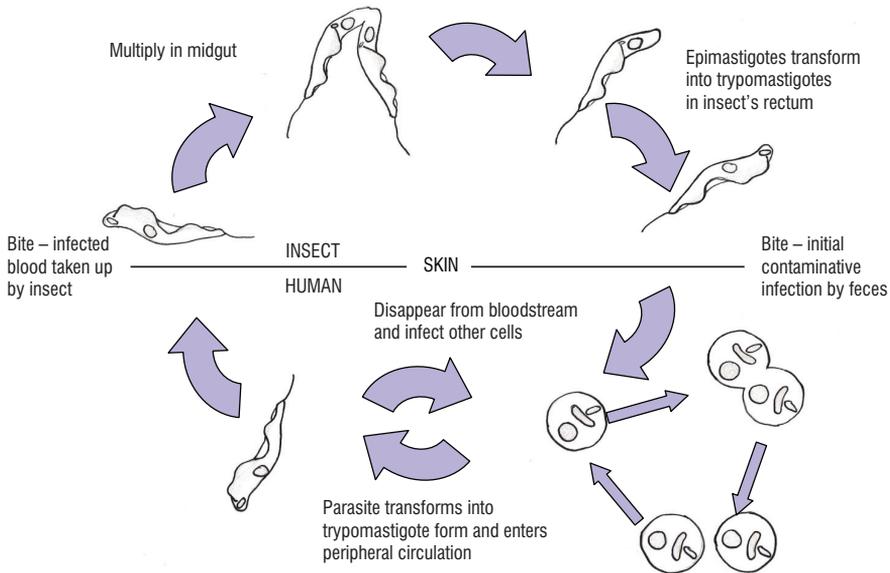


Fig. 2. *Trypanosoma cruzi* life cycle

The stage of *T. cruzi* infective to humans, the trypomastigote, develops in the hindgut of the *Triatominae* insect. The trypomastigote forms are passed out with the feces of the bug, usually as it is taking a blood meal from a vertebrate host. Infection occurs when infected fecal material is rubbed into the bite wound, eyes, or mucous membranes. Upon introduction into a human host, the parasites invade macrophages of the subcutaneous tissue at the site of infection, causing a local, edematous swelling called chagoma. There, the parasites rapidly transform into the amastigote (intracellular) form. The amastigotes evade the lysosome system by escaping into the cytosol of the infected cell. Following repeated longitudinal binary fissions by the

amastigotes, the infected cell ruptures and the released amastigotes enter other cells. Some of the released amastigotes revert to the trypomastigote form and enter the circulatory system. Insects become infected by ingesting blood that contains anteriorly trypomastigotes, which then undergo repeated longitudinal fission during passage through the digestive tract of the insect. By the time they reach the midgut, they have metamorphosed to the epimastigote stage. Still replicating, the epimastigotes pass into the insect hindgut where they attach themselves by their flagella to the epithelium of the rectal gland. As transformation to the trypomastigote forms occurs, the flagellar-epithelial attachment is lost. By the 10th day after ingestion, the infective trypomastigotes appear free in the lumen of the rectum [4].

Apart from the described mode of transmission, others are also possible. Infections during blood transfusions are becoming significant, especially in those regions, where vector elimination programs are being implemented, where a large percentage of the population is infected with *T. cruzi*, and blood donors are not screened for Chagas disease [9, 13]. Vertical transmission occurs when *T. cruzi* manages to penetrate into the placenta of a seropositive mother and infects the embryo or the fetus during birth as a result of the contact between a mother's blood and the child's mucous membranes. The risk of such an infection ranges from 1% in Brazil to 12% in Argentina, Bolivia, Chile and Paraguay [24]. It is estimated that this type of transmission will remain a serious problem for at least 30 years, until a significant reduction in the number of infected women at the reproductive age occurs [9]. Infections caused by laboratory incidents, organ transplants [13, 19] or through the digestive system, when food contaminated with vectors' feces is consumed [5, 9, 26] are relatively rare.

In the course of the disease, three key phases may be differentiated. In the first, acute phase, symptoms associated with the mode in which *T. cruzi* have penetrated into an organism occur. An inflammatory condition develops in the place of inoculation. In many cases a characteristic swelling of the eyelid, called Romaña's sign, occurs. It appears when the parasites have managed to penetrate through the membrane covering the eyeball. In this phase other symptoms, including lymphadenopathy, low grade fever, hepatomegaly, splenomegaly, diarrhea, muscular spasms, respiratory dysfunction, coma, bluish coloration of the mucous membranes, muscle and joint aches, appear after 4–10 days from inoculation indicating the incubation process. All the enumerated symptoms remain for several months and manifest that *T. cruzi* have spread within the organism via the circulatory system. It is estimated, however, that in 70–95% of cases, the acute phase of Chagas disease is asymptomatic. This significantly inhibits its detection during the first phase which is critical with respect to possible treatment [24]. In approximately 1% of such cases, if parasites violently attack cardiac tissues or the central nervous system tissues, the infection may cause sudden death (especially in children less than 1 year of age) [29].



Fig. 3. Romaña's sign [34]

After the acute phase, an immune response of the organism appears and leads to reducing parasitemia, limiting it to some foci. This phase, called latent is characterized by a slow multiplication of parasites and lack of evident symptoms, despite serious changes within the infected tissues [27]. After about 10–35 years, 30–50% of patients enter the third phase – the chronic phase [24, 30]. A large majority of patients develop cardiomyopathy, associated with ventricular hypertrophy, caused by the activity of the parasite within the cardiac tissues. Death of the patients with chronic Chagas cardiomyopathy is provoked by *mors subita cardialis* (55–63%), progressive cardiac insufficiency (20–25%) and thromboembolic complications (10–15%) [15]. When the digestive tract tissues are affected by *T. cruzi*, a pathological dilation of the colonic lumen and enlarged esophagus (megacolon and megaesophagus) ensue [23].

The efficacy of laboratory diagnostic methods in detecting *T. cruzi* depends on the phase of the disease advancement. The applied method should be adequate to the phase in the parasite developmental stage. In the acute phase of Chagas disease, direct microscopic observation of trypomastigote forms in the host blood is possible. This allows for detecting the disease in 85% of cases. This number increases to 95% when concentration methods are employed [20]. In the latent and chronic phases, serological tests are usually performed, most frequently enzyme-linked immunosorbent assay (ELISA) and direct immunofluorescence (IF), with 95–98% sensitivity [24].

Despite advances in curtailing vector transmission, research concerning treatment methods for Chagas disease is deemed insufficient. There exist only two obsolete medications, Nifurtimox® developed in 1965 and Beznidazol® in 1969. Their production is unstable and availability limited [21]. Slight interest in new and more effective medication is most frequently justified by a lack of adequate financial stimuli for the pharmaceutical industry. An average cost of producing a new drug is estimated at US \$800 mln. Thus, it is not surprising that only 1% of newly registered medication is targeted toward controlling tropical diseases, occurring mostly in regions inhabited by

the poorest societies, whereas about 90% of the investment in research and development of this industry has been allocated for pharmaceutical products designed for 10% of the world's population with the highest incomes [33].

The administration of the aforementioned medication does not raise any doubts concerning the acute phase of the disease, as it inhibits intracellular multiplication and spreading of *T. cruzi* in various tissues. In 80% of cases, Chagas disease at this phase can be completely cured. If the medication is administered to the patient within 30 days from the appearance of the first symptoms, pharmacological therapy should last for 3–5 years. Later on, the application of both available medications is advised only for children in the early stage of the chronic phase (parasitic elimination is possible in 60% of cases within 5–10 years of continuous pharmacological therapy). In adults in the chronic phase of Chagas disease, the parasite can be eliminated only in about 20% of cases, as a result of long-term treatment lasting 20–30 years [20].

The advocates of administering available medications argue that “although they cannot eliminate parasitemia in the majority of patients, [treatment] leads to a significant reduction in pathological changes [...] and less frequent exacerbations in the clinical manifestation” [33]. The opponents of prescribing Nifurtimox® and Benznidazol® prove that there is only a slender chance of being cured and it is associated with severe side effects. Complications resulting from taking available medications may last long after the completion of the therapy [21]. In 30% of cases undesirable secondary effects appear, such as: anorexia, nausea, vomiting, stomach aches, diarrhea, skin infections, insomnia, hallucinations and psychosis. Because of doubtful long-term clinical outcomes and a detrimental relation between risks and advantages stemming from the use of such medication, in the majority of cases palliative treatment is ordered [1].

DISCUSSION

In order to assess the extent of Chagas disease, reliable data concerning the number of cases of this disease are indispensable. According to one complete statistical study carried out between 1980–1985 (before the implementation of the regional programs to eliminate the main vector) in Latin America 17.4 mln people were infected with *T. cruzi*, and about 100 mln (i.e., 25% of the inhabitants of the entire region) were directly at risk of being infected. The incidence was estimated at 300 thousand of new cases annually, and mortality at 21 thousand (especially among children) [7]. In 2005, the Pan American Health Organization evaluated the number of people infected with *T. cruzi* to be 7 694 500 [11, 31], and the number of people directly at risk of being infected to be 108 595 000 [11] (Tab. 1).

Tab. 1. Estimated data on Chagas disease in particular Latin American states [7, 11]

	1980–1985			1998–1999	2005			
	Prevalence index [%]	Number of people at risk of infection	People at risk of infection [%]	Sero-prevalence among blood donors [%]	Number of infected people	Prevalence index [%]	Incidence (via vector) [%]	Sero-prevalence among blood donors [%]
Argentina	10.0	—	23	4.10	1 600 000	4.129	0.003	2.47
Belize	—	—	—	1.00	2 000	0.741	0.009	0.40
Bolivia	24.0	1 800 000	32	—	620 000	6.752	0.112	8.00
Brazil	4.2	41 054 000	32	0.73	1 900 000	1.019	0.000	0.21
Chile	16.9	11 600 000	63	0.5–2.60	160 200	0.656	0.000	0.47
Ecuador	10.7	3 823 000	41	1.00	230 000	1.739	0.018	0.36
Guatemala	16.6	4 022 000	54	8.00	250 000	1.984	0.017	0.01
Honduras	15.2	1 824 000	47	1.65	58 600	3.053	0.039	1.40
Columbia	30.0	3 000 000	11	—	436 000	0.956	0.012	0.80
Costa Rica	11.7	1 112 000	45	2.10	23 000	0.532	0.001	0.14
Mexico	—	—	—	—	1 100 000	1.028	0.007	0.60
Nicaragua	—	—	—	—	58 600	1.140	0.015	0.90
Panama	17.7	989 000	47	—	21 000	0.006	0.007	0.90
Paraguay	21.4	1 475 000	31	5.00	150 000	2.543	0.015	3.20
Peru	9.8	6 766 000	39	—	192 000	0.686	0.011	0.57
Salvador	20.0	2 146 000	45	7.00	232 000	3.372	0.036	2.42
Uruguay	3.4	975 000	33	0.06	21 700	0.656	0.000	0.47
Venezuela	3.0	12 500 000	72	0.78	310 000	1.159	0.005	0.78

Although, thanks to the efforts of the states and non-governmental organizations, the problem of vector transmission has been controlled to a large degree, the number of health programs targeted towards people from endemic zones is still insufficient. Though the majority of infected people live in Latin America, in recent decades cases of this disease have been reported also in other parts of the world, in such countries as: Canada, United States, Australia, Japan, Belgium, France, Italy, Spain, Switzerland, the United Kingdom, Austria, Croatia, Denmark, Germany, Luxemburg, Netherlands, Norway, Portugal, Romania and Sweden. The spread of American trypanosomiasis is mostly connected with the increasing tendency of people to migrate to the rich countries of the North. These destination states have not developed any preventive measures, such as screening for Chagas disease in blood banks [31].

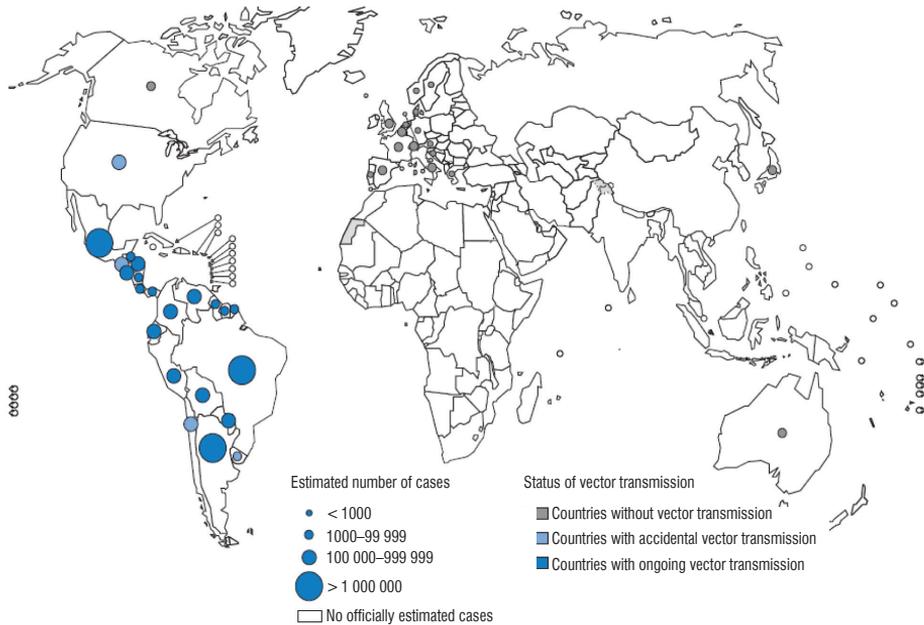


Fig. 4. *Trypanosoma cruzi* infections mapping in the 2006–2009 period [31]

CONCLUSIONS

1. Although vector transmission has been to a large degree controlled, non-existence of effective medication to treat Chagas disease indicates a failure with respect to health policies currently adopted by endemic countries.
2. American trypanosomiasis, tropical in nature, should become an object of interest of highly developed countries in the near future due to the increasing migrations of infected groups of people.

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