

# DOCTOR THOMAS AND TROPICAL MEDICINE IN AMAZONIA IN THE BEGINNING OF THE XX<sup>th</sup> CENTURY

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Rio de Janeiro, RJ, Brasil*Doctor Thomas e a medicina tropical na Amazônia no início do século XX***ABSTRACT**

Harold Howard Shearme Wolferstan Thomas was a researcher from the Liverpool School of Tropical Diseases who enjoyed brief prominence in British medicine at the time he was transferred to Amazonia (1905). Five years earlier, an overseas expedition from this school had been in the region to investigate yellow fever. When Thomas and his colleague Anton Breinl set sail for Manaus, their mission was still to investigate this disease. In the interval between the two expeditions, dynamic processes were underway in the realm of tropical medicine, especially with regard to trypanosomiasis. Thomas gained recognition when he showed that atoxyl was an effective treatment for humans and animals infected with trypanosomes. In this article, Thomas guides us through a web of actors and diseases in the Americas, Europe and Africa. Their synergies reveal the outlines of tropical medicine and the place occupied by the Amazon region within this field at the beginning of the twentieth century, with special emphasis on trypanosomiasis. Until his death in Manaus in 1931, Thomas involved himself with other local health problems and with physicians who were on the forefront of Amazonian public health and experimental medicine, an unusual course for most European researchers sent on missions to colonies and areas influenced by imperial metropolises. Thomas was 'rediscovered' two decades after his death when he was named one of the recipients of a prize from the Belgian government granted to the scientists who discovered the treatment for sleeping sickness. As we shall see, his memory was revived on other occasions in the academic sphere.

**Keywords:** Harold Howard Shearme Wolferstan Thomas, atoxyl, Sleeping Sickness, Chagas Disease, yellow fever.

**RESUMO**

Harold Howard Shearme Wolferstan Thomas foi um pesquisador da Escola de Medicina Tropical de Liverpool que teve fugaz destaque na medicina britânica na época em que foi deslocado para a Amazônia (1905). Cinco anos antes, uma expedição da mesma Escola estivera na região para investigar a febre amarela. Thomas e Anton Breinl viajaram para Manaus ainda com o objetivo de estudar essa doença. Naquele intervalo, transcorreram processos muito dinâmicos na medicina tropical, em particular no tocante às tripanossomioses. Thomas ganhou projeção ao demonstrar que o atoxyl era eficaz no tratamento de animais e humanos infectados por tripanossomos. No presente artigo, Thomas é o fio que conduz a uma trama formada por diferentes atores e doenças na América, Europa e África, cujas sinergias revelam contornos da medicina tropical e o lugar nela ocupado pela região amazônica no começo do século XX. Enfatizaremos especialmente as tripanossomioses. Até sua morte em Manaus, em 1931, Thomas envolveu-se com outros problemas de saúde locais e com médicos que lideravam a saúde pública e a medicina experimental no Amazonas – curso discrepante daquele tomado pela maioria dos médicos europeus que participaram de missões em colônias e áreas de influência das metrópoles imperiais. Nos anos 1950, Thomas foi 'redescoberto' ao receber (postumamente) parte de um prêmio conferido aos descobridores da cura da doença do sono. Sua memória teve outros revivals em ambientes acadêmicos.

**Palavras-chave:** Harold Howard Shearme Wolferstan Thomas, atoxyl, doença do sono, doença de Chagas, febre amarela.

**B**ritish and Italian work on malaria transmission was essential to the institutionalization of tropical medicine at the end of the nineteenth century; this area of medicine gained particular relevance in Brazil because of yellow fever. The immediate demonstration that this disease was also transmitted by mosquitoes strongly boosted the process which was already underway in the dissemination of medicine, one which I shall call "Koch-Pasteurian" to emphasize the leadership of France and Germanic Europe in this process. In both public and private spheres, in cities embedded within the globalization of laboratory medicine, institutions multiplied in order to diagnose diseases, produce serums and vaccines, conduct basic and applied research, and in some cases, teach bacteriology and other disciplines. Discoveries related to malaria and yellow fever provided more exposure to teams and institutions from various countries, and brought entomology and other branches of medical zoology to the forefront, alongside new sanitary practices directed at controlling the vectors of diseases transmitted by blood-sucking insects. New networks were created by doctors, biologists, and even laymen who studied these insects (BENCHIMOL; SÁ, 2006; SANJAD, 2003, p. 85-111).

The Amazon region was the backdrop for important events in the overall process of disseminating tropical medicine, partly because of the imbroglío I shall describe below.

In 1899, soon after Ronald Ross, Giovanni Battista Grassi, and Grassi's Italian colleagues discovered how malaria was transmitted, the Liverpool School of Tropical Diseases began operations and was soon followed by the London School of Tropical Medicine.<sup>1</sup> In June 1900, Herbert Edward Durham and Walter Myers journeyed to Belém do Pará on the fourth overseas expedition of the Liverpool School to investigate yellow fever. They stopped in Havana, the capital of the former Spanish colony which had only recently been occupied by the Americans (1898), to see the work that the United States Yellow Fever Commission was doing there. The British hypothesized that yellow fever was transmitted by mosquitoes, which had been proposed nearly two decades earlier by the Cuban physician Carlos Juan Finlay (1965, p. 247-261). This hypothesis gained more credibility after Durham and Myers spent time in discussions with Cuban and American doctors at that leg of their journey. Soon after their visit, Lazear (a member of Reed's commission) began experiments with mosquitoes provided by Finlay, while Carroll and Agramonte, members of the same group, continued their studies of the supposed bacillus of yellow fever, which was the priority at that time. In September, Lazear died after an accidental bite. The commission headed by Walter Reed restructured its experimental strategy according to the time of incubation in the human host and in the insect – a *Culex* mosquito which was later reclassified as *Stegomyia fasciata* and then *Aedes aegypti* – from an *as-yet unknown organism*, and still obtained successful experimental cases (STEPAN, 1978, p. 397-423; DELAPORTE, 1989; BENCHIMOL, 2010, p. 315-344). The analogies with malaria led various researchers to the assumption that the agent of yellow fever was also a protozoan.

Durham and Myers arrived in Belém in August 1900. Five months later, they contracted yellow fever, and Myers died in January 1901. In February, Durham announced the conclusions they had reached. They had been unsuccessful in their attempts to locate a protozoan, and their searches had turned up a bacillus in fatal cases of yellow fever. "The endeavor to prove a man-to-man transference of yellow fever by means of a particular

kind of gnat by the recent American Commission is hardly intelligible for bacillary disease," admitted Durham and Myers (1901, p. 450; see also DURHAM, 1902).

Durham left Belém in May of 1901. In April 1905, two other researchers from the School of Liverpool, Harold Howard Shearme Wolferstan Thomas and Anton Breinl, arrived in Manaus to investigate yellow fever.

The University of Liverpool and its School of Tropical Medicine paid the expenses related to research and overseas expeditions that originally targeted malaria, although with great difficulty. In July 1899, Ronald Ross, Henry Edward Annett, Ernest Edward Austen (of the British Museum), and G. Van Neck (of Belgium) went to Sierra Leone; that same year, Robert Fielding Ould continued to the Gold Coast and Lagos; the third expedition, which consisted of Annett, John Everett Dutton, and J. H. Elliott, was sent to Nigeria in March 1900. Yellow fever was the object of the fourth expedition, Durham and Myers's trip to Pará. During the trip to Gambia in 1902, Dutton demonstrated the presence of a trypanosome in the blood of a patient who had sleeping sickness. At that time, an epidemic had killed thousands of people in Uganda and Congo. The Liverpool School's expedition to Senegambia (1902) and the Congo (1903-1904) were already focused on this human trypanosomiasis. These expeditions are referred to in Miller (1998), Maegraith (1972, p. 354-368), Allmand (1921, p. 1-47), and analyzed in greater detail in Power (1999).

The latter expeditions are linked to the decision by the Liverpool School of Tropical Medicine to hire Wolferstan Thomas, a physician born on May 29, 1875 in Montreal, Canada and trained at the McGill University School of Medicine in the same city.<sup>2</sup> Although yellow fever was the reason behind his 1905 trip to Manaus, the main subject of this article is his contribution to treating trypanosomiasis in Africa and the multiple connections which can be made between this issue and the therapy adopted to treat the diseases which dominated Brazil, particularly in the Amazon. For this reason, an overview of the state of the art with regard to this medical and veterinary topic in the era when Thomas began to work with these diseases is important.

### Trypanosomiasis in animals

In 1890, a disease known as *n'gana* laid waste to herds in southern Africa and threatened the way of life of the Zulus, whose main activity was raising livestock, and whose insurrections had represented a serious threat to British colonial ambitions in the region. The governor of Zululand invited Captain David Bruce, a surgeon in the British Army Medical Service, to investigate the disease. In 1894 he and his wife, Mary Bruce (who was also his collaborator) settled in Ubombo. The Zulus attributed *n'gana* to cattle eating food contaminated by wild animals. Meanwhile, the Europeans who hunted these animals often lost the mounts they rode, which they believed were 'poisoned' by the bite of the tsetse fly that infested the region (COX, 1996, p. 184).<sup>3</sup>

Bruce initially looked for a bacterium in sick animals, but in their blood he found a spindle-shaped hematozoan with an undulating membrane and extensive motility – a 'trypanosome,' the name proposed by David Gruby in 1843 to designate the parasite he had found in the blood of a frog (*Trypanosoma sanguinis*). Since that time, trypanosomes had

been seen in the blood of fish, amphibians, and mammals. In 1877, Timothy Lewis, a surgeon in the Royal Army Medical Corps (within the Army Medical Service), described a protozoan in rats which he classified as *Trypanosoma lewisi*. A veterinary surgeon who also lived in India, Griffith Evans, found similar parasites in 1881, in the blood of camels and horses that died from a disease known in that country as *surra* (*Trypanosoma evansi*). The discovery of two trypanosomes in the same region which were difficult to distinguish using the culture and staining methods available at that time led to confusion in papers published by these and other researchers mentioned in the book that was to become the main reference on the subject, *Trypanosomes et trypanosomiasis*, by Charles Louis Alphonse Laveran and Félix Mesnil (1907).<sup>4</sup>

In 1894-1895 in southern Africa, Bruce demonstrated (with the help of Mary) the relationship between the trypanosome found in the blood of sick animals and *n'gana* by inoculating infected blood into healthy horses, oxen, and dogs, which produced the characteristic signs and lesions of the disease. The suspicion that *n'gana* was identical to the disease spread by the tsetse fly, mentioned by hunters and explorers, was proven by Bruce when he kept unaffected cattle and horses on a fly-infested plain and confirmed the presence of the trypanosome in the blood of these animals (COX, 1996, p. 184-185).

Bruce published a preliminary report in 1895 and another more complete report in 1897. He incriminated *Glossina morsitans* as the vector of the protozoan, which was soon classified as *Trypanosoma brucei*, and identified the antelope and buffalo as its wild reservoirs.<sup>5</sup>

In 1903, in North Africa, the bacteriologists Etienne and Edmond Sergent of the Pasteur Institute of Algiers related *debad* (a camel disease) to *Trypanosoma berberum*, identifying flies from the family Tabanidae (horseflies) as its means of transmission. At the same time in South America, a horse disease known as *mal de cadeiras* was linked to *T. equinum*.

## Sleeping sickness

At the turn of the twentieth century, the impacts on the ecosystem and on African social formations produced by Europeans and their local partners in subjugating the native peoples and animals in agricultural, extractive, infrastructure-related, or trade endeavors led to the outbreak of deadly epidemics of a human disease that was well known and would soon also be recognized as trypanosomiasis (LYONS, 1992; WORBOYS, 1994, p. 89-102).

In an October 1898 lecture at Charing Cross Hospital, where he had examined two Africans hospitalized with this illness, Patrick Manson hypothesized that the disease was caused by a *Filaria* – not the *F. sanguinis* of elephantiasis, but *F. perstans*, which had recently been identified in the blood of Europeans and natives in areas of Africa where sleeping sickness was endemic (MANSON, 1898, p. 1672-1677). Another doctor in the hospital, Frederick Walker Mott, examined the cases of “Congo disease” on which Manson’s hypothesis was based and described lesions in the nervous system, proposing that they be used to differentiate that African lethargic encephalitis from the nervous manifestations of syphilis, the initial diagnosis (MOTT, 1899, p. 1666-1669). Manson’s hypothesis went counter to the various etiological assumptions of that time: heatstroke, excessive consumption of

palm wine by the Africans, their excessive venereal activity, and “banzo,” a melancholic affliction of Black slaves. Manson also refuted the prevailing theory of the time that sleeping sickness (like yellow fever) was caused by a bacterium.

As shown by Amaral (2008, p. 301-328; 2012, p. 1275-1300), António de Oliveira Figueiredo found bacilli in 1889, in a hospitalized patient in Lisbon. In 1897, Antoine Cagigal and Charles LePierre also identified a bacillus in the blood of an Angolan hospitalized in Coimbra. The high incidence of sleeping sickness in the provinces of São Tomé, Príncipe, and Angola led the Portuguese government to send a mission to Angola in 1901, headed by Annibal Bettencourt, director of the Camera Pestana Royal Institute. They identified a *Hypnococcus* in samples of blood and cerebrospinal fluid of patients with the disease. In Coimbra, António de Pádua and LePierre challenged the observations made by Bettencourt’s team.

As this controversy played out, sleeping sickness took on epidemic proportions in Uganda, a British protectorate, and in neighboring territories. Fearing that it could reach the Nile River Valley, Suez, and even India, with disastrous economic consequences, the Foreign Office, Colonial Office, Royal Society, and the Liverpool and London schools made great efforts to understand and control the problem. The Germans, French, and Americans also made important contributions to the efforts to find a cure for sleeping sickness (LYONS, 1992, p. 70-71; DUTHIE, 1946, p. 56).

The uncertain epidemiological data produced at that time are impressive. In Busoga, the region with the highest population density in Uganda, 200,000 of its 300,000 inhabitants fell victim, spreading the epidemic to the east and west. In 1905, a researcher from the Royal Society (Dr. Nabarro) estimated that approximately 100,000 people in Uganda had died in each of the previous three years. And Todd, of the Liverpool School, was informed that over the four years prior, the disease had stricken roughly 250,000 Africans on the outskirts of Entebbe, the capital of British protectorate. Dutton and Todd confirmed that 30 to 50% of the populations of many villages in Uganda and Congo were infected, and that few survived. These data appear in Lyons (1992, p. 24-25, 70-71). According to this author, sleeping sickness continued to rage unabated until 1910, causing tremendous demographic upheavals in the region. Duthie (1946, p. 55-56), in turn, states that it caused nearly half a million deaths in Congo alone between 1885 and 1915, reducing extensive areas around the great African lakes by half or two-thirds (see also BERRANG-FORD *et al.*, 2006, p. 226-231).

In 1902, the Royal Society sent a Sleeping Sickness Commission to Uganda, which was comprised of George Carmichael Low, Cuthbert Christy, and Aldo Castellani (LEDERMANN, 2011, p. 276-281). They began their work in July, months after the Liverpool School’s malaria expedition landed in Gambia. Low, Christy, and Castellani confirmed that the *Filaria perstans* which Manson had blamed was common in the blood of Africans who were not stricken by sleeping sickness. In October 1902, Castellani sent a note to the Royal Society claiming the discovery of a *Streptococcus* that he believed to be the agent of the disease. Although it was not published, because the Society did not consider this proof sufficient, the majority of the medical authorities considered bacterial etiology to be probable (COX, 1996, p. 186).

While Castellani and the previously mentioned Portuguese and French bacteriologists continued their dispute for priority, the relationship between sleeping sickness and trypanosomes strengthened due to the following circumstances.

In May 1901, at Bathurst (now Banjul) in Gambia, the physician and surgeon Robert Michael Forde began to treat the captain of a ship that regularly navigated the Gambia River, the main river in the British colony. Kelly's malaise and fever suggested malaria, but Forde dismissed this diagnosis when he noted that the patient did not respond to treatment with quinine and he was unable to find that disease's protozoan in his blood. Forde did, however, find another unfamiliar parasite (1902, p. 261-263). In December 1901, Joseph Everett Dutton (1903), of the Liverpool School came to Gambia to study malaria, and Forde asked him to examine Kelly. Dutton soon realized that the micro-organism he saw was a trypanosome, which he immediately reported to the Liverpool School in early 1902.<sup>6</sup> Considering the patient's origin, the protozoan was called *T. gambiense*.

Losing no time, that same year the Liverpool School sent Dutton and John Lancelot Todd to Senegambia to study trypanosomes. And in March 1903, another Sleeping Sickness Commission from the Royal Society set off for Entebbe, the capital of Uganda, involving Bruce, the bacteriologist David Nabarro, and Edward Grieg, the captain sent by the government of India to study the problem. It appears that Bruce and Castellani met in Entebbe, and the Italian bacteriologist continued his etiological research in England. Dutton's finding led Bruce and Castellani to focus their attention on the protozoan that had already been appearing in the fluids examined by the young Italian bacteriologist, which he considered to be merely commensals without any pathogenic significance (according to the prevailing opinion among his peers). Castellani's 1903 announcement that trypanosomes were the agents of the cases investigated in Uganda<sup>7</sup> definitively transformed sleeping sickness into the hottest topic in European tropical medicine.

Meanwhile, Dutton and Todd were called back to Liverpool from Senegambia and then sent to the Etat Indépendant du Congo (Free Congo), a neighboring territory of Uganda, in 1903. It was more of a private property belonging to King Leopold II of Belgium than a colony subject to the control of the Belgian state, as shown in the exceptional study by Hochschild (1999). Alfred Jones, the chairman of the executive committee of the Liverpool School, maintained close relations with Leopoldo II. A branch of Jones's navigation company, the Compagnie Belge du Congo, controlled the lucrative trade between Congo and Antwerp. Jones was the president of the Africa section of the Chamber of Commerce of Liverpool, and also the consul of Free Congo in the same city (LYONS, 1992, p. 70).

The two members of the Liverpool School's twelfth expedition soon joined Christy, a former member of the first Sleeping Sickness Commission, and a former student at the Liverpool School, Inge Heiberg, who was connected to the Congolese health service. The expedition was established in the capital, Boma, on September 13, 1903, and officially remained in the colony for 18 months, although Christy returned to England earlier. Dutton died in the Congo in February 1905 (LYONS, 1992, p. 74).

## Thomas and the Runcorn laboratory

Even though the Belgian government contributed 650 pounds to fund the expedition, this effort worsened the financial situation of Liverpool School (LIVERPOOL..., 1920, p. 29-32). Nevertheless, a new laboratory for studies in tropical veterinary medicine was created in a rural area near Liverpool. Part of the capital came from an Anglo-Canadian pharmaceutical company, Evans Sons Lescher & Webb Ltd., which was founded in 1902 from the merger of pharmaceutical wholesalers in Liverpool and London. This coalition of interests involving the university, the municipality, the Chamber of Commerce, and the shipping companies in Liverpool led to the creation of the Incorporated Institute of Comparative Pathology in 1903, which would operate until 1911 at the University of Liverpool, and the Runcorn Research Laboratory, which was founded in a rural area in Crofton Lodge, Runcorn, 16 miles from that port city (PROCÓPIO, 1953, p. 372).<sup>8</sup>

According to the plan developed by Rubert William Boyce and Charles Scott Sherrington, professors of pathology and physiology, and Henry Edward Annet, who was a lecturer in comparative pathology at that time, the profits generated from the sales of products developed by the new Institute would return to fund research at the university and the School of Tropical Medicine.<sup>9</sup>

In September 1904, the tropical veterinary laboratory was inaugurated, and featured pastures and stables for the experimental animals. Strains of trypanosomes and other pathogenic parasites (or suspected organisms) which had been collected by the school's expeditions were brought to the new laboratory, especially from the tenth expedition to Senegambia in 1902-1903 (LIVERPOOL..., 1920, p. 31).

The choice of Thomas to direct the work in Runcorn was the initiative of his countryman and friend John Lancelot Todd, who had been part of the expedition and would be included in next one, which was sent immediately to the Congo. Todd came from a family that earned its fortune in the Canadian fisheries, and offered the school £200 for 12 months (and another year, if necessary) to pay Thomas's wages if he was invited to work in the Johnston Laboratories (the Runcorn laboratory had not yet been established) during the journey Todd would make with Dutton and Cuthbert Christy to Congo. Todd's letter was read at a meeting of the school's executive committee on August 10, 1903, amid discussions on the previously mentioned financial difficulties, and the young Canadian doctor's proposal was readily accepted.<sup>10</sup>

The two groups of observers, one headed by Bruce in Uganda and the other in the Congo from the Liverpool School, worked in close contact, and cases of sleeping sickness were sent to Liverpool so that comparable data could be obtained (DUTTON *et al.*, 1904).

Throughout 1903 and 1904, Bruce kept his peers informed on the state of knowledge in relation to sleeping sickness (BRUCE; NABARRO, 1903, p. 11-39; BRUCE, 1904, p. 367-369).<sup>11</sup> When monkeys were inoculated with cerebrospinal fluid from patients with neurological signs of disease, or blood from those who were still asymptomatic but had trypanosomes, the animals exhibited all the signs of the disease. Besides finding strong evidence connecting the disease with the trypanosomes, these were also seen to be identical to those found in sick patients on the west coast of Africa and in Uganda. The disease appeared to be limited

to areas where the tsetse fly (*Glossina palpalis*) occurred, since where these flies were not present the disease did not occur. The so-called "trypanosome fever" was the first stage. The parasite did not seem to undergo any metamorphosis in the body of the vector; it was simply transferred mechanically from one human or animal to another. This issue remained controversial until 1909, when Friedrich Kleine demonstrated that *Glossina* flies played a crucial role in the evolutionary cycle of trypanosomes (COX, 2002, p. 595-612).

Bruce's reports were partially based on the results of the Liverpool School's expedition to Congo. Dutton made epidemiological, clinical, and parasitological observations; Austen, the British Museum entomologist, reported on the tsetse fly, and Thomas and his assistants, reported on the comparative studies conducted in Runcorn with trypanosomes collected in different parts of Africa.

### The discovery of atoxyl's therapeutic properties

The Runcorn laboratory and the Institute of Comparative Pathology, which were created simultaneously at the University of Liverpool, were related to the more general process of growing involvement by microbiological and chemical-pharmaceutical laboratories in developing drugs for human and animal diseases associated with protozoa and other parasites. A good inventory of the historiography in this respect can be found in Cavalcanti (2013).

Thomas, as reported by Thomson and Sinton (1912, p. 331-356), was the first to cultivate strains of trypanosomes pathogenic to humans both *in vitro* and *in vivo*. With the help of Stanley Fox Linton and Anton Breinl, he showed that the trypanosomes found in spinal fluid and blood of patients with sleeping sickness in Uganda and the Congo were identical to the *T. gambiense* described by Dutton (THOMAS; LINTON, 1904b, p. 1337-1340; 1904a, p. 75-86). For Thomas, this name covered the trypanosomes from various regions of Africa, but in 1909-1910 Stephens and Fantham described *Trypanosoma rhodesiense*, which was responsible for the acute type of sleeping sickness.<sup>12</sup>

In addition to studying and comparing strains which were pathogenic to humans and animals (*T. evansi*, *T. brucei*, *T. equinum*, and *T. equiperdum*), Thomas and his assistants did extensive research on treating trypanosomiasis. He knew that immunity to the infection was not acquired, and that it was not transmitted to offspring. As early as 1902, Thomas was experimenting with sodium arsenide and other substances in animals infected with *T. brucei* and *T. lewisi*. Substances tested by H. Wendelstadt, William Everett Musgrave, Moses Tran Clegg<sup>13</sup>, and other researchers were retested in Runcorn by Thomas's team, which added sodium fluoride, potassium, and ammonia to the list, along with fluorescein, chrysoidine, and various silver and mercury preparations. At the Pasteur Institute in Paris, Laveran and Mesnil (1902, p. 786-817) verified that arsenous oxide had a tenuous sterilizing effect in small animals infected with *T. brucei*, the agent of *n'gana*, and *T. equinum*, which was responsible for *mal de cadeiras*, a horse disease in South America which had recently been associated with trypanosomes.

The medical use of arsenic extends far into the past (RIETHMILLER, 1999, p. 28-33); when syphilis erupted in fifteenth-century Europe, highly toxic inorganic arsenic



compounds were used. David Livingstone treated sick animals with *liquor arsenicalis*, a widely-used medicine also known as Fowler's solution (named for Thomas Fowler, a British physician who mixed arsenous acid, potassium carbonate, and water flavored with lemon balm).<sup>14</sup> In 1852, the French chemist Pierre Jacques Antoine Béchamp developed an inexpensive method for producing aniline by reducing nitrobenzene, and in 1863 synthesized a compound from aniline and arsenic acid which he called atoxyl, alluding to its lower toxicity. In the early twentieth century, atoxyl was placed on the market as a remedy for asthma, but interest in this and other arsenic compounds was limited to doctors and laboratories who gave them new meanings within the context of tropical medicine (DUTHIE, 1946, p. 40, 46). According to Duthie (1946), arsenic had been supplanted by mercury, although it was still used internally to treat a series of conditions ranging from asthma to anemia.

In India, during research on *surra* in the 1890s, Alfred Lingard demonstrated that arsenic compounds had some curative properties. Bruce then tried to fight n'gana by adding varying doses of arsenic (in the form of sodium arsenite) to animal feed, but the trypanosomes only disappeared temporarily from the blood of the animals, extending the lives of those which were already sick (LAVERAN; MESNIL, 1907, p. 169 and ss.; LAVERAN; MESNIL, 1902, p. 786-787).

Thomas tested several arsenic compounds, and came to the conclusion that atoxyl was the most effective.<sup>15</sup> *Trypanroth* (trypan red), which had been developed by Paul Ehrlich and his assistant, Kiyoshi Shiga, also showed some efficacy. This dye was the product of a line of research that the physician and chemist had pursued for quite some time.

When Ehrlich entered medical school in the 1870s, his cousin, Carl Weigert, conducted innovative experiments with synthetic dyes. The selective staining of tissues and cells from animals and bacteria was at the heart of advances in histology and bacteriology (see BENCHIMOL, 2004, p. 40-152).<sup>16</sup> At the Charité Hospital in Berlin, which he had entered in 1878, Ehrlich tested dyes in blood smears he examined under a microscope and reshaped previous thinking on normal and pathological forms of blood cells. In 1882, when Koch discovered the tuberculosis bacillus, Ehrlich soon developed a diagnostic technique to show that this bacillus, when stained with heated fuchsin solution (a red dye), behaved differently than other microorganisms, resisting subsequent discoloration from acids. Still in the 1880s, after verifying that methylene blue stained nervous tissue selectively, he injected this compound into patients suffering from severe neuralgia to see if the concentration of dye in the nerves would halt pain or illness. After demonstrating that the living malaria protozoa were selectively stained by the dye, Ehrlich injected it into patients with quinine-resistant malaria; this therapeutic strategy was based on the assumption that the concentration of dye in the parasite (and not in the host cells) would lead to its destruction, and he obtained some degree of success.<sup>17</sup> Selective staining of bacteria and parasites in the living body of the host guided the chemotherapeutic research of Ehrlich and other researchers for several years (DUTHIE, 1946, p. 37-38).

In different institutions, especially the Royal Institute for Sorootherapy in Frankfurt (where he became director in 1899), Ehrlich devoted himself to the study of bacterial toxins and their antibodies, the antitoxins, particularly those employed against diphtheria and tetanus.

These studies also involved the selective action of chemical substances in the body's cells; toxins were molecules that attacked certain tissues rather than others because of chemical affinities, and antibodies were molecules which bound themselves to active groups in the toxin molecules (also because of chemical affinities) and neutralized them.

The circumstances that highlighted sleeping sickness led Ehrlich and Shiga to dwell on the trypanosomes. By testing and altering the molecules in a series of dyes derived from benzidine, in 1904 they arrived at trypan red, which was especially active in infections caused by *T. equinum* in mice, but ineffective against this parasite in other animals and against *T. brucei* in any animal. Nevertheless, the experiments showed that by modifying the structure of a dye, it could be transformed into a treatment for diseases.

Of the concurrent experiments in Runcorn involving the parallel path of experimentation with arsenic and other chemical substances already known to chemists, Thomas drew the following conclusions: atoxyl was the only drug which could offer any hope of a cure for animals and humans. In humans, treatment was to be prolonged and at doses as high as the patient could stand, and it was important to take measures to invigorate the patient's body. Trypan red was useful to some extent, but had excessively toxic effects. Thomas believed that subsequent investigations into treating trypanosomiasis should look for less toxic arsenic compounds suitable for injection into human patients, and proposed a short-term treatment involving atoxyl combined with a refined version of trypan red (THOMAS, 1905a, p. 62-63).

Thomas published his final work on this subject in May and October of 1905, when he was in Manaus with his collaborator Anton Breinl. Both contracted yellow fever; Breinl returned to England, resumed his research on pathogenic protozoa in the Runcorn laboratory, and took over as its director in May 1907. It appears that after accidentally infecting himself during his experiments that year, he was the first European to overcome sleeping sickness, after injecting himself with atoxyl (DOUGLAS, undated).

From October 1905, the Liverpool School began distributing the drug to doctors and missionaries working in Africa for them to test, and it was used in Europe at the same time, with conflicting results. In an article published in 1907, Breinl and Todd made special mention of the communication by Ayres Kopke to the XV International Congress of Medicine held in Lisbon in April 1906 (BREINL; TODD, 1907, p. 132-134). In the following year, this Portuguese physician reported auspicious results from the first large-scale application of drugs in victims of sleeping sickness on the island of Príncipe.<sup>18</sup>

At the same time, as part of a Sleeping Sickness Commission sent to Africa by Germany, Robert Koch was investigating atoxyl in an archipelago of Lake Victoria in Uganda, the Sse Islands. He found that injecting 0.5 g of atoxyl caused the parasite to disappear from the bloodstream within six to eight hours; the same dose given on two successive days prevented it from reappearing for ten days. However, 22 of the 1,622 individuals treated demonstrated atrophy of the optic nerve and blindness. Koch presented these results to Ehrlich in 1907, advising him to improve atoxyl, as reported in Steverding (2008, p. 4). Even so, and although the infection often recurred when the drug was discontinued, Koch recommended it be administered on two successive days, every six days, over four or six months (DUTHIE, 1946, p. 41).

Therefore, the first journalistic records of Thomas's presence in Brazil include congratulations, after Koch confirmed the effectiveness of atoxyl in treating sleeping sickness.<sup>19</sup>

## Experiments with atoxyl in Pará

The drug was also tested in northern Brazil. In 1907, his last year as director of the Bacteriological Institute of São Paulo, Adolpho Lutz was hired by the government of Pará to study the diseases that ravaged the region (BENCHIMOL; SÁ, 2006, p. 109-119). When he reached Belém on August 18, Lutz was received by the directors of the Pará Agricultural and Industrial Union and several physicians. They went to the mansion of the governor, Augusto Montenegro, and then to the Goeldi Museum, where the director, Dr. Jacques Hüber, awaited them. Lutz was introduced to Vincent Francisco de Miranda, who placed his farms on the island of Marajó at his disposal (AS EPIZOOTIAS..., 1907, p. 1).

In a tugboat belonging to the Booth Line, a Liverpool company, Lutz then sailed to the Tuyuyu Farm, on the banks of the Arari River (DR. LUTZ, 1907, p. 1). He found trypanosomes in horses and cattle in the region, and in an interview with the newspaper *A Província do Pará* three months later, Lutz confirmed the relationship between *mal de cadeiras*, the disease that attacked horses in that part of the Amazon, and sleeping sickness (O MAL..., 1907, p. 1). Lutz showed the journalist a "beautiful preparation of trypanosomes" and a recently published article by Rubert Boyce (1907, p. 624-625) on treating trypanosomiasis with atoxyl and mercury-based drugs. Lutz had administered atoxyl to a monkey inoculated with the *mal de cadeiras* trypanosome, which was in better condition than other monkeys which had not received this treatment.

During his four months in Pará, Lutz visited other livestock-raising areas (Cachoeira, Chaves, Soure, and Óbido). Vital Brazil (1907, p. 2-4), his assistant, had just published a study on *mal de cadeiras*, which was raging in the states of São Paulo and Mato Grosso as well as in Paraguay, Uruguay, and the River Plate. The studies Vital Brazil and Adolpho Lutz used as references were published by Dr. Miguel Elmassian (1901, p. 1-16; 1902, p. 122-148), who had discovered *Trypanosoma equinum*, the agent of *mal de cadeiras*, in Paraguay. This work was published in Asuncion and Buenos Aires, and soon reverberated in Germany and England.<sup>20</sup> Elmassian and Migone (1903, p. 241-267) published a more extensive article on the subject in the *Annales de l'Institut Pasteur de Paris*.

Elmassian was connected to the Pasteur Institute in Paris, and was hired by the Paraguayan government in 1899 to found the National Institute of Bacteriology in Asuncion. The immediate objective was to produce serum against the pandemic wave of bubonic plague which had reached that country, not unlike the circumstances leading to the creation of the serotherapy institutes in Manguinhos (Rio de Janeiro) and Butantã (São Paulo) that same year in Brazil. Elmassian became a professor of bacteriology and histology in the Medical School at the National University of Asuncion. The school's first graduating class in 1904 included Luis Enrique Migone Mieres, who had investigated the *mal de cadeiras* protozoan while he was still a student. Migone would go on to further study in Paris at the Pasteur Institute and return to Paraguay in 1906, where he would teach parasitology and medical zoology at the Asuncion School of Medicine.<sup>21</sup>

Elmassian and Migone's results were confirmed by Otto Voges, José Lignières,<sup>22</sup> Joaquín Zabala, Félix Mesnil, and Alphonse Laveran, as well as by Vital Brazil and Adolpho Lutz.

In addition to verifying that the trypanosome which had been isolated in Pará was the same one described in Paraguay, Lutz confirmed the popular observation that capybaras were susceptible to the disease; in fact, they were the wild reservoir of the parasite. Lutz demonstrated that several mammals were susceptible to experimental infection, such as sloths and squirrel monkeys (*Saimiri sciureus*).

Lutz tested atoxyl, potassium iodide, and mercury bichloride combined with atoxyl, trypan red, and certain colors of aniline, but did not find a reliable cure in any of these agents. Trypan red and atoxyl did make the trypanosomes disappear from the blood, but they reappeared days later; the other preparations were even less effective. Prophylaxis was consequently the only recourse for farmers, although it was almost as difficult as curing the disease.<sup>23</sup>

Adolpho Lutz returned to São Paulo in December 1907, convinced that the main transmitters of *Trypanosoma equinum* were two species of horseflies abundant where horses were bred: *Tabanus importunus* and *Tabanus trilineatos* (LUTZ, 1907, p. 356-362; 2007, p. 83-100).

At the end of October, Lutz traveled to Manaus to meet with Thomas. They certainly talked about trypanosomiasis and other topics that interested them both. Later I shall return to this trip.

## Atoxyl and its derivatives against protozoa and spirochetes

In the Amazon, Thomas used atoxyl as an adjuvant of quinine in cases of quinine-resistant malaria. By this time, atoxyl was used to treat infections related to spirochetes, which gained evidence from 1905 when the protozoologist Fritz Richard Schaudinn and dermatologist Erich Hoffman announced the discovery of the agent of syphilis, *Treponema pallidum* (*Spirochaeta pallida*). Birds with chicken spirillosis (*Spirillum gallinarum*) responded well to atoxyl, and the drug prevented or healed lesions which appeared after monkeys and rabbits were inoculated with the syphilis germ. It was also used to treat human syphilis, which until then had been combated with mercury, as well as relapsing fever (*Borrelia recurrentis*). The results were encouraging, but many patients developed permanent blindness. The combination of mercury and atoxyl did not prove safer or more effective (DUTHIE, 1946, p. 40-41, 47).

A classic work in the historiography of tropical medicine states that Ehrlich visited Thomas's laboratory in Runcorn, and that his own studies with this arsenic compound led to salvarsan in 1910, the first medicine effective against syphilis. Ehrlich's visit to Runcorn has not been proven, however.<sup>24</sup> To better understand the studies connecting atoxyl to salvarsan, I will use the excellent work by Duthie (1946, p. 37 and ff.).

Ehrlich and Shiga had tested atoxyl in 1903, but when they saw that it had no effect whatsoever on trypanosomes cultivated *in vitro*, they abandoned the compound. Thomas's work led Ehrlich to attempt to alter the atoxyl molecule in order to preserve its parasite-

killing properties while reducing the impact on the host. Ernest Forneau, a chemist at the Société Anonyme des Établissements Poulenc Frères (founded in 1900), had just deciphered the chemical structure of atoxyl, describing it as an arsenic acid anilide in which the arsenic atom is bound to the nitrogen in the aniline's amine group. Ehrlich found that this formula was incorrect: the arsenic atom was not linked to the nitrogen atom, but rather to one of the carbon atoms in the benzene ring; this structure was easier to modify than the one suggested by the French chemist.<sup>25</sup> Various derivatives of atoxyl then emerged, which were tested by Ehrlich's team and by other researchers with regard to their anti-trypanosome and anti-spirochete properties. A modification of the atoxyl molecule, with the introduction of an acetyl group (CH<sub>3</sub>) in the hydrogen amine, created the compound acetyl-arsanilic acid or arsacetin, which was less toxic than the original drug but still capable of destroying the optic nerve in patients.

Neither atoxyl nor arsacetin, which was used to combat sleeping sickness in 1908, had significant activity against trypanosomes cultivated *in vitro*, although they were very active in living hosts. This led Ehrlich to deduce that the arsenic compound lost oxygen atoms within the host and that the pentavalent form was reduced to the trivalent, which was active against parasites and toxic to the host.

Ehrlich and his colleagues were also attentive to the phenomenon of resistance displayed by the trypanosomes (and, in general, protozoa) to drugs used against them. When the dose of an arsenic compound was not sufficient to kill trypanosomes in mice and was repeated several times, the parasites acquired resistance to this and other arsenic derivatives. Ehrlich theorized that the hypothetical point where the resistant trypanosomes linked to drugs (the 'arsenoceptor') was damaged. He sought to circumvent this phenomenon by using a drug containing other groups which could connect to the trypanosome at other points – the acetic acid group, for example, and the 'aceticceptor' (DUTHIE, 1946, p. 45-47).

Preparation 418 (sodium salt of p:p'-arsenophenylglycine) was developed in 1909; this compound was much less toxic, but easily oxidizable by air outside the body, transforming it into a very toxic substance. Like atoxyl and arsacetine, arsenophenylglycine was used with varying success in animals and humans to treat spirochete infections such as relapsing fever and syphilis. The risk of blindness for patients remained, however.

By carefully testing several compounds, Ehrlich, Sahachiro Hata, and other collaborators synthesized the compound dihydroxydiaminoarsenobenzol, the 606th derivative of atoxyl, in May of 1909. It would become famous the world over as salvarsan (DUTHIE, 1946, p. 47-50).<sup>26</sup>

That year Ehrlich received the Nobel Prize for Medicine, and was received with great acclaim at the International Congress of Medicine held in London in 1913. The drug was then widely used to treat syphilis and other infections such as relapsing fever and yaws.

## Therapeutics in American trypanosomiasis

One question inevitably arises. Was atoxyl or any of its derivatives used to treat victims of the other human trypanosomiasis, the second type discovered by Carlos Chagas in 1909?

It would appear so, but a preliminary examination of sources is puzzling in this respect.<sup>27</sup>

The discovery of Chagas disease brings us back to the transformations within the Sorotherapy Institute, which was created in Rio de Janeiro ten years before to produce serums and vaccines against bubonic plague. The appointment of its director, Oswaldo Cruz, to head the Directorate-General of Public Health and the campaign against yellow fever in Rio de Janeiro (based on the recently-proven theory that this disease was transmitted by a species of mosquito) created an opportunity for this small laboratory to become a center of research similar to the Pasteur Institute in Paris (STEPAN, 1976; BENCHIMOL, TEIXEIRA, 1993). Its activities expanded in three directions; manufacture of biological products, research, and teaching are still pillars of the Oswaldo Cruz Foundation today. Investigations into diseases involving humans and animals (and to a lesser extent, plants) put the institution into contact with different clients and research communities, reinforcing its social bases of support. Expanding frontiers also had a geopolitical connotation, as it did for the institutes which worked in the European colonial territories. When they delved into Brazil's *sertão* badlands to study and combat malaria, at the service of railroads, hydroelectric plants, and other enterprises (BENCHIMOL; SILVA, 2008, p. 719-762), scientists from the Institute headed by Oswaldo Cruz encountered pathologies that were barely known or even unknown, broadening the horizons of tropical medicine in Brazil.

After facing malaria in the states of São Paulo and Rio de Janeiro, Chagas was moved to Minas Gerais, where the Brazilian Central Railway was extending its routes. In June 1907, he began work against malaria near the Bicudo River, a tributary of the Velhas River between Corinto and Pirapora. In the village of São Gonçalo das Tabocas, which was renamed Lassance after the inauguration of the railway station in 1908, Chagas installed a small laboratory in a train car. Alongside his anti-malaria activities, he observed the local fauna, motivated by two topics that dominated the research group he was associated with: medical zoology and protozoology. In 1908 he identified a protozoan he classified as *Trypanosoma minasense* in the blood of a marmoset, which was not pathogenic to the animal.

A railroad engineer, Cantarino Mota, suggested that Chagas examine an insect that lived in the gaps of wattle-and-daub houses and emerged at night to suck the blood of the inhabitants and their domestic animals. It preferred to attack the human face, which led it to be called *barbeiro*, the barber, in Portuguese (and kissing bug in English). In a subsequent report, Chagas would say that he had been identifying anomalies in the pathological framework in the region. He arrived there to fight a familiar disease, malaria, but faced signs which were difficult to interpret. "Something new, in the fields of pathology, lingered there unknown, and gripped our curiosity" (CHAGAS, 1922, p. 68).

When he searched for parasites in the digestive tube and salivary glands of the triatomine insect, he found a protozoan. Chagas sent *barbeiro* specimens to Oswaldo Cruz in Rio de Janeiro. After Cruz fed them on marmosets raised in the laboratory (which were free of infection), he found an unknown species of trypanosomes in the blood of the animals that became sick, which Chagas named *Trypanosoma cruzi*. In December 1908, he wrote a note on this discovery, which was published in the journal of the Hamburg Institute of Maritime and Tropical Diseases.

In Lassance, the laboratory and hospital which would be housed in a dedicated building and more sophisticated installations under construction at the Institute (which came to be called the Oswaldo Cruz Institute in 1908) was the setting for Chagas to study the biology of the parasite and the forms it took in vertebrates and in its vector. He also began to systematically examine the blood of domesticated and wild animals and people who lived in homes with triatomine insects, until he found flagellates in the blood of a critically ill child with morphology similar to the *T. cruzi* found in the triatomines and lab-infected primates. According to Chagas Filho (1993, p. 84), this took place on February 14, 1909. The name of this child, Berenice, entered the history books along with this discovery, since she was the vertebrate host in which the puzzle found in Minas Gerais was finally deciphered.

Chagas reported this first human case in *Brazil-Medico*, and on April 22, 1909, a communication from Chagas was read by Oswaldo Cruz at the National Academy of Medicine (CHAGAS, 1909a, p. 161; 1909b, p. 188-190). The discovery of the new tropical disease was published that same year in important journals in Germany and France.

Nearly all the researchers in the Institute concurred with the consolidated discovery of the new human trypanosomiasis, deepening knowledge of this disease from a range of perspectives. Despite quarrels that would erupt at the Institute, their work supported Oswaldo Cruz's policy to publicize Chagas, solidifying his discovery within Brazil and abroad, thus earning greater benefits for the Institute in the form of prestige, resources, and visibility, which each researcher capitalized for his or her own professional strategy.<sup>28</sup>

In 1910, the National Academy of Medicine hailed Chagas as a full member, and he came in first in a competitive examination held at the Oswaldo Cruz Institute to fill the important position as head of the service. The following year, at the International Exhibition of Hygiene and Demography in Dresden, the Brazilian pavilion highlighted American trypanosomiasis. In 1912, the Institute of Maritime and Tropical Diseases of Hamburg granted Chagas the Schaudinn Protozoology Award, and in 1913, he was nominated for the Nobel Prize in Medicine (COUTINHO, 1999, p. 519-549).<sup>29</sup>

Max Hartmann, a protozoologist at the institute founded by Koch in Berlin, was at the Oswaldo Cruz Institute in 1909 and helped systematize the parasitic and anatomopathological aspects of that human trypanosomiasis. Also at the IOC were two teachers from the Hamburg school, the protozoologist Stanislas von Prowazek and the chemist Gustav Giemsa, Hermann Duerck, professor of anatomic pathology at the University of Jena, and the protozoologist Viktor Schilling. The *Memórias do Instituto Oswaldo Cruz*, first published in 1909, began to disseminate studies carried out at the institution in Portuguese and German (SÁ, 2005, p. 309-317).

The communication to the Academy of Medicine in 1909 sought to distinguish the disease produced by *Trypanosoma cruzi* from other pathologies it could be confused with: sleeping sickness, hookworm disease, and malaria. Fusing the name of the new trypanosomiasis with its discoverer was the suggestion of Miguel Couto, who also named American trypanomiasis. Lutz called it coriotrypanosis, and Miguel Pereira used parasitic thyroiditis. These names connote aspects of the discovery which would lead to controversy in the 1920s: the authorship of the discovery, the location of the parasite in the human thyroid (leading to the assumption that goiter was one of its clinical manifestations), and

its wide geographical range, which had been postulated from the beginning but not yet supported by data. The name of the parasite was also the subject of controversy. The first name that Chagas adopted was *Trypanosoma cruzi*. Subsequently, with the collaboration of Prowazek and Hartmann, the genus *Schizotrypanum* (i.e. a trypanosome that reproduces via schizogony) was created to accommodate *S. cruzi*. Chagas supposed that the parasite had two forms of reproduction, binary and schizogony; this latter form was related to the observation of parasitic forms in the lungs of infected monkeys which he considered to be stages in the evolution of the human parasite. But Henrique Aragão observed the same forms in the lungs of rabbits and other experimental animals which were free from *Schizotrypanum* infection. This and other findings led Chagas to reconsider the classification of the trypanosome in 1913.

These investigations helped clarify the role of hematophagous insects in transmitting this group of protozoans to vertebrates, strengthening Kleine's theory that there was a vital biological relationship (not only a mechanical exchange) between the sleeping sickness trypanosome and tsetse flies (KROPF; SÁ, 2009, p. 13-34).

In 1910, Chagas classified the clinical forms of the American disease as acute and chronic, distinguishing four categories: pseudomyxedematous, myxedematous, cardiac, and nervous. More comprehensive studies on the life cycle of *Trypanosoma cruzi* were published during this period.

The importance of this trypanosomiasis led Chagas to take on the position of director of the Institute after the death of Oswaldo Cruz in February 1917, a position he would hold until the end of his life in 1934.

In the works he published, we find detailed analyses of different aspects of the disease that bears his name, but there are few references to the prophylactic actions which were genetically aimed at residences where the vector hid. And Chagas only very rarely addressed the therapies utilized in the hundreds of cases which were the object of his observations over the years. His silence on this aspect is surprising, especially when reading clinical reports intended to spread understanding about the new pathology among Brazilian physicians, enabling them to recognize it but not providing any assistance regarding what to do with the patient.

In an article published in 1910, "Nova entidade mórbida do homem" ["New morbid entity of man"], Chagas (1910, p. 433-437) did not address public health measures to be taken since he did not yet have data on the geographical distribution of the disease. In the following article, he promised to outline a "general plan for a prophylactic campaign, applicable to known outbreaks" (CHAGAS, 1911b, p. 221), but did not do so. In a lecture at the National Academy of Medicine in August 1911, he avoided any responsibility for presenting plans to prevent the disease, the distribution of which was still poorly known (CHAGAS, 1911a).<sup>30</sup> But the experience in Lassance had shown that modifying homes to avoid contact between humans and the triatomine insect was essential. The main epidemiological characteristic of American trypanosomiasis was the coexistence of man and the insect in residences, and this was theoretically easy to halt. "In the African continent, where lethargy endemically rages among the blacks, a disease similar to ours, the transmitting fly lives



outside, which produces almost extreme difficulty in prophylaxis for this disease,” wrote Chagas (1911a, in PRATA, 1981, p. 27/191).

The historiography shows the same situation, that the two fundamental components of the policies adopted by the colonial authorities against African trypanosomiasis in sick natives were therapy associated with segregation measures, both of which were essentially compulsory and draconian (although European patients received more benign procedures).

As for American trypanosomiasis, Chagas made only rare comments on therapeutics. In the cited 1910 article, he expressed his intention to test “arseno-phenyl-glycine, the medication sent by professor Ehrlich, which produced positive results in treating sleeping sickness” (CHAGAS, 1910, p. 437). This was the 418<sup>th</sup> compound derived from atoxyl (mentioned above), and soon supplanted by number 616, salvarsan. The results of these drugs must not have been satisfactory, since there is no other reference to them in Chagas’s scientific works.

“Nous n’avons trouvé, dans les mémoires publiés jusqu’ici, aucun reinsegnement sur le traitement de la maladie humaine dont le pronostic est très grave,” wrote Laveran and Mesnil (1912, p. 811). Experimental therapeutic trials had been conducted at the Hamburg Institute by Martin Mayer and Henrique da Rocha Lima with atoxyl, quinine, trypan red, salvarsan, tartar emetic, and fuchsin, but without any noteworthy results. Manson (1919, p. 192), in turn, wrote: “We know no specific remedy. Arsenicals and antimony have failed in experimental animals. Treatment, therefore, must be on general lines.” And in a leaflet on Chagas disease produced a few years later, Emmanuel Dias (1944, p. 11) said: “unfortunately, there is not yet a drug capable of definitively curing the disease.”

“Symptomatic medication might alleviate the diarrhea,” wrote Chagas (1916, p. 55) amid observations on case no. 22, a seven-month-old mixed race boy living in Lassance. But even this type of record is scarce, and the hundreds of cases in his scientific articles progressed to death, to chronicity, to relapse or to uncertain outcomes, without the course of the disease being influenced in any way by the prescribed treatment.

This situation only changed with the use of atropine in the cardiac forms of the disease starting in 1922, with Chagas and Villela (1922, p. 16-17) registering very promising results from experiments utilizing this drug in relation to the arrhythmias associated with the disease. This is the only medication mentioned the first time that an article by Chagas (published in Germany) presented a section specifically dedicated to ‘therapy’ (CHAGAS, 1925, p. 1367-1386).

Atropine is the alkaloid of a plant in the family Solanaceae, *Atropa belladonna* L., popularly known as belladonna. The name is linked to the fact that women historically used the juice of the plant as eyedrops as a beauty treatment, to dilate their pupils.<sup>31</sup> The use of the alkaloid in Chagas disease was related to the better knowledge of its cardiac manifestations, especially after the great controversy in the National Academy of Medicine in 1922-1923. As Kropf observed, the most prominent clinical signs of heart failure, arrhythmias, began to be seen as a better way of assessing the epidemiological extent of the disease; this was disputed by Chagas’s opponents, who also contested goiter and thyroid involvement as a guideline for the differential diagnosis. Chagas was the first doctor in the Brazil to use a

cardiograph machine, which he purchased in 1910, adds Kropf (2009b, p. 145-146, 240-241). This equipment was installed in the hospital at the Oswaldo Cruz Institute, and was important to obtain the graphic representations of cardiac rhythms which he presented in his 1922 article.

Recent research by Costa Santos (2016) using records from the hospitals created in Lassance and the Oswaldo Cruz Institute show more vivid and 'tumultuous' therapeutic procedures adopted for patients with Chagas disease.<sup>32</sup> We can see that atropine and the arsenicals had been used since the 1910s in combination with several other drugs. This "polypharmacy" or "polytherapy" refers to an important aspect of the difficulty in obtaining a specific therapy for American trypanosomiasis, namely the diversity of its clinical manifestations. This "polytherapy" was also a characteristic of the treatment adopted in yellow fever and other infections. In the medical records which have already been examined, there is also considerable variation in the regimens adopted according to the clinician responsible for the patient, and also because of other illnesses which manifested concomitantly with Chagas disease in those people who were generally poor rural workers coming or brought in from small Brazilian villages.

### Chagas disease and the Amazon: connections

The correlations between Chagas disease and sleeping sickness do not seem to have been deeply explored by historians. To my knowledge, no one has mapped the circulation of knowledge, protocols, techniques, professional staff, or biological inputs among the research communities which dealt with these pathologies. A quick survey of the papers published at the time shows that there were exchanges, but nevertheless Chagas disease and sleeping sickness remained separate from the geographical, epidemiological, clinical, and therapeutic points of view.

Examination of Chagas's publications shows no dialog with Thomas, even when Chagas visited the city where he lived, despite his very relevant experience with the African trypanosomiasis. Chagas was in the Amazon when the rubber plantations organized by the British in Asia superseded this industry in Brazil. In January 1912, the Brazilian Congress (belatedly) approved the Rubber Defense Plan to modernize not only the extraction and processing of this product, but also the labor process, through measures to reduce the high morbidity and mortality rates in the workforce. From October 1912 to March 1913, Carlos Chagas, Pacheco Leão, João Pedro de Albuquerque, and a photographer traversed a good portion of the Amazon basin aboard a small steamship (ALBUQUERQUE *et al.*, 1991). As Schweickardt and Lima observed (2007, p. 31), in Manaus, the starting point of the successive river trips, the commission was in the Santa Casa de Misericórdia charity hospital and examined cases of leishmaniasis, beriberi, and yellow fever, and was accompanied by Figueiredo Rodrigues, the only physician from the city cited in the expedition's report (CRUZ, 1913). There is no reference to Thomas, even though he was connected to the hospital and headed a laboratory which was very active in the city. In the introduction to *Sobre o saneamento da Amazônia* [On the sanitation of the Amazon], Djalma da Cunha Batista (CRUZ; CHAGAS; PEIXOTO, 1972, s.p.) expressed surprise that he did not find any reference to "great physicians who pontificated in Manaus at that time" in the report or in

the lecture given by Chagas in October 1913 in Rio de Janeiro. Schweickardt (2011, p. 85) attributed this to ignorance of the work carried out there or the “choice by the Manguinhos scientists to not position themselves in relation to the type of work performed by the doctors in the Amazon.”

Such assumptions conflict with the evidence presented by Schweickardt himself, that the medical elite in Manaus was in line with the ideas of science and civilization, and with the paradigms of microbiology and tropical medicine reigning in Europe and among the Europeanized intellectuals and doctors from southeastern Brazil. It could be assumed that there were only small repercussions in the Brazilian capital for the works published in *Amazonas Médico*, the journal founded in 1909,<sup>33</sup> the same year that *Memórias do Instituto Oswaldo Cruz* appeared. But certainly the efforts by Alfredo Augusto da Matta and other Amazonian physicians to combat malaria and yellow fever (along with Thomas) were known, and followed the same guidelines adopted by Oswaldo Cruz and his team in campaigns against the latest disease in Rio de Janeiro (1903-1906) and in Belém do Pará (1909), and the concomitant campaigns of Chagas, Neiva, and other sanitarian-scientists from the IOC against malaria, in the southeast and soon after in northern Brazil.

It is true that the links between these characters cannot be inferred only from their publications. Many ideas, information, and even objects circulated in correspondence, in trades during scientific meetings, in personal contacts made during travel, etc. Correspondence is scarce in the Carlos Chagas file in the archives at the Oswaldo Cruz House. The documentation by Alfredo da Matta seems to have been destroyed, and Thomas's correspondence, which is archived in the Liverpool or London Schools, is limited. No evidence has been found there about possible conversation between Chagas, Thomas, or other doctors working in Manaus. On the other hand, it is necessary to consider that tropical medicine, microbiology, and public health involved different networks with their own dynamics which depended on skills, diseases, and national affinities. The researchers who turned to medical entomology, for example, established their own network of exchanges. The fact that the Amazonian characters in this narrative were in closer contact with the French and British, and that the Oswaldo Cruz Institute was closer to the Germans, might help explain this question mentioned by Schweickardt and Batista.

To Chagas (CRUZ; CHAGAS; PEIXOTO, 1972, p. 160), the Amazon was the region of Brazil where tropical diseases appeared “with their true characteristics,”<sup>34</sup> a reference above all to the superlative manifestations of malaria, beriberi, and a pathology that began to place researchers from the southeast and north of Brazil in the international spotlight. I refer to the leishmaniasis, an intriguing set of pathologies which, as shown by Jogas Junior (2017), emerged as the subject of research within a network which seemed to center around the Société de Pathologie Exotique and its *Bulletin*, created in 1908 by Alphonse Laveran and Félix Mesnil.

Cutaneous ulcers afflicting Europeans and locals in cities in Asia and Africa had received dozens of names alluding to the time and place in which they were acquired; oriental sore was the most widely known.<sup>35</sup> In 1903, this phenomenon was related to a protozoan classified as *Helcosoma tropicum* by James Homer Wright. Meanwhile, a disease called kala-azar raged in urban centers and rural areas of India; this very lethal

disease particularly affected the liver and spleen, and many considered it a severe form of malaria or an anomalous form of hookworm disease. In 1903 William Boog Leishman and Charles Donovan (each working independently) identified an associated protozoan. A new genus, *Leishmania*, was then created to accommodate this parasite that Laveran and Mesnil classified as *Leishmania-Donovani*. Three years later, the German Max Luhe showed great morphological similarity between *Leishmania-Donovani* and *Helcosoma tropicum*, and this latter species was reclassified as *Leishmania tropica*. Two morphologically indistinguishable protozoa caused diseases with completely different symptoms and courses. Kala-azar affected the internal organs and had a high mortality rate, while oriental sore manifested as cutaneous ulcers lasting approximately a year and often resolving spontaneously.

In 1909, Antonio Carini and Ulisses Paranhos of the Pasteur Institute of São Paulo and Adolpho Lindenberg of the Bacteriological Institute in the same city published almost simultaneous articles reporting the discovery of *Leishmania* in the so-called 'Bauru ulcers.' These lesions affected workers in forest areas who were constructing the Brazilian Northwest Railway, which would connect São Paulo and Mato Grosso (JOGAS JUNIOR, 2017; BENCHIMOL; SILVA, 2008, p. 719-762). In these early diagnoses of leishmaniasis in South America, the parasite was also associated with severe lesions in the mucous membranes. Similar lesions were soon described in other regions of Brazil and Latin America, most notably in studies undertaken in Amazonas by Alfredo da Matta (1910, p. 440).<sup>36</sup>

In 1911, Carini (1911, p. 289-290) suggested that a specific protozoan was responsible for the leishmaniasis which attacked the mucosae in the nose, mouth, and throat, and mainly occurred in forests and wild areas. In a note published that same year, Gaspar Vianna (1911, p. 411-412), a pathologist from Pará who worked at the Oswaldo Cruz Institute, proposed the new species *L. braziliensis*. Alfredo da Matta, in articles published in 1915-1916 in Brazil, France, and Venezuela, proposed a new taxonomic division of the *Leishmania* species which included Vianna's *L. braziliensis* (DA MATTA, 1916, p. 494-503; JOGAS JUNIOR, 2017, p. 84-85).

He would later describe two cases of "nodular and pseudoverrucous" leishmaniasis treated at the Manaus charity hospital (DA MATTA, 1918, p. 14-17). The "bacterioscopic" diagnosis was made by Thomas, who he acknowledged. Da Matta based his assumptions on the work of the Canadian doctor regarding a syndrome he had classified as 'mossy foot' (THOMAS, 1910-1911a, p. 95-104). Nodular, warty lesions were affecting the legs of Amazon dwellers. Thomas had managed to reproduce this infectious condition (which he had also observed in Pará) in a rabbit model. His work featured several photographs, one supplied by a doctor in British Honduras, J. H. H. Harrison.<sup>37</sup> Alfredo da Matta considered his cases identical to those of Thomas and Harrison and those described by the Peruvian Julián Arce and by Adolpho Lutz. "What they suspected, I had the opportunity to determine with certainty, and with the microscopic and clinical diagnosis to be 'Mossy foot of Amazon or Pie Muscoso,' a cutaneous leishmaniasis, nodular and pseudoverrucous variation, the hypertrophy of tissues very probably due to the access of erysipelas, a complication that I believe is quite often still not properly indicated" (DA MATTA, 1918, p. 17).<sup>38</sup>

In the expedition to the Amazon River Valley in 1912-1913, Carlos Chagas showed the high endemicity of leishmaniasis, which was known there as *ferida brava* [wild ulcer], and considered it one of the greatest obstacles to work in the region (CRUZ, 1913; CRUZ; CHAGAS; PEIXOTO, 1972, p. 170). Chagas tested the therapy proposed by Gaspar Vianna, which leads us to another thread tying together researchers at the Oswaldo Cruz Institute and in Manaus, particularly Thomas.

Gaspar Vianna's decision to experiment with tartar emetic in treating leishmaniasis was motivated by studies by researchers in Britain and other colonial centers on the use of compounds derived from antimony, mercury, and arsenic to treat diseases caused by protozoa. The anti-trypanosome properties of tartar emetic, a trivalent antimonial which was used against fevers for some time, were recognized in experiments with mice conducted in 1907 by Henry George Plimmer and J. D. Thomson (1907, p. 505-516; 1908, p. 1-11). These experiments sponsored by the Royal Society tested various substances, including atoxyl and trypan red. As we have seen, Thomas's results with the arsenic derivative atoxyl led Ehrlich to salvarsan. At the 7th Brazilian Congress of Medicine held in Belo Horizonte in April of 1912, Gaspar Vianna (1912, p. 426-428) compared the results he obtained with this drug, which was the most common at that time for treating the leishmaniasis, with the new method he proposed based on tartar emetic. To minimize problems from its high toxicity, he diluted the substance in saline solution and then injected it into the patient intravenously over several sessions, making the drug tolerable, if very painful.

In the Amazon, Chagas and Alfredo da Matta (independently) obtained very favorable results from tartar emetic to treat leishmaniasis (CRUZ, 1913, p. 170; DA MATTA, 1918, p. 14-17), helping to spread the use of the drug to treat not only leishmaniasis but also malaria and schistosomiasis in Brazil and in other parts of the world, a process which still remains poorly studied by historians. This took place at a time when interactions between researchers in the north and southeast of Brazil solidified through the ties that interconnected them to the international leishmaniasis network, and also through synergies that lead us to yellow fever.

### Thomas and yellow fever

In October 1907, as mentioned, Adolpho Lutz traveled from Pará to Manaus to meet with Thomas. They certainly talked about trypanosomiasis and another topic that interested them both. Thomas had just published a note about inducing yellow fever in a chimpanzee using laboratory-reared female *Stegomyia fasciata* (THOMAS, 1907b, p. 138; 1907c, p. 15-16), which contradicted the results of the Paris Pasteur Institute mission, which had unsuccessfully tried to infect primates with the still-unknown agent of yellow fever in Rio de Janeiro.<sup>39</sup> Thomas's experiment, which was linked to the effort to find this agent, threatened what up to that point had been the consecrated strategy to combat yellow fever: this strategy was based on the assumption that no other animal besides man was susceptible to the disease and that *Stegomyia fasciata* was the only transmitter, only in urban areas, especially on the coast. The implications of Thomas's work would only be recognized in the late 1920s, when the prophylactic deductions of the Finlay-Reed theory collapsed in West Africa.

In 1902, amid heated discussions about the transmission of yellow fever exclusively by *Stegomyia fasciata* involving physicians and other social actors, Rodrigues Alves was elected president of Brazil on the promise to clean up the capital, Rio de Janeiro. An engineer was appointed mayor with exceptional powers to put into motion the urban reforms conceived in light of the old miasmatic hygiene, but Oswald Cruz was nominated as the head of public health, and he pledged to combat yellow fever based on the controversial 'Havana theory.' Smallpox and bubonic plague were also targets of the director-general of public health (BENCHIMOL, 2003, p. 231-286).

In September 1905, Oswaldo Cruz began trips to inspect Brazil's main maritime and river ports with an eye to reorganizing health services in the rest of the country. These trips, which were extensions of the cleanup in the capital, represent an episode of economic and cultural expansionism of the southeast, and were the first expression (in the republican context) of a national health project that would only crystallize in the 1920s. The underlying national project for the visit to Manaus and the other ports was based on the assumption that epidemic diseases did not respect borders; the victory against yellow fever in Rio de Janeiro would be ephemeral if it was not extended to other cities. This vision did not link into the political workings of that federal republic, which granted autonomy to the oligarchic groups which were dominant in the states and were averse to actions by the central government (HOCHMAN, 1998).

On November 11, 1905, the director-general of public health left Belém, and after quick visits to Santarém, Óbidos, and Parintins landed in the capital of Amazonas. Thomas was among the doctors and authorities who received him there. When the fifteenth expedition of the Liverpool School (comprising Thomas and Breinl) arrived in the Amazonian capital in April,<sup>40</sup> the rubber economy and the modernization of the city were at their zeniths, with the filling in of small streams (*igarapés*), construction of avenues, installation of tram services and electricity, telegraph, and telephone, and construction of docks and iron bridges as well as water and sewer networks. The prosperity resulting from the extractive economy was reflected in the greater circulation of ideas and the formation of a group of physicians who were active in public health and in line with the scientific discussions concerning microbiology and tropical diseases (SCHWEICKARDT, 2011).

In the 1890s and the first two decades of the twentieth century, four committees successively occupied themselves with the sanitation of Manaus, with malaria and yellow fever as priorities. Thomas and Breinl arrived in Manaus amid the activities of the second sanitation committee, led by Márcio Nery (1904 to 1906).<sup>41</sup> From 1902, the mosquito theory came to guide the fight against these diseases, adding new aspects to important facets of sanitation policies: filling in streams and other projects where water could collect and allow the transmitters of malaria and yellow fever to procreate. A similar shift in meaning occurred in Rio de Janeiro (BENCHIMOL, 2003, p. 231-286).

The head of the Manaus health commission put a ward in the Santa Casa de Misericórdia hospital at the disposal of the British doctors; this ward housed cases of yellow fever, malaria, beriberi, and other infectious diseases. But in July 1905 Thomas and Breinl contracted *yellow jack* (as yellow fever was known), Breinl seriously. "I fervently hope that history does not repeat," wrote the executive secretary of the Liverpool School, alluding

to the death of Myers in Belém (MILNE, 1905). In September, Breinl returned to England. The ship in which he traveled sank, and the unfortunate doctor lost all his belongings (LIVERPOOL..., 1920, p. 35). Thomas remained in Manaus, taking care of the Liverpool School laboratory alone.<sup>42</sup>

After confirming that malaria was abundant in Manaus, especially the malignant tertian variety, Thomas used atoxyl as an adjuvant of quinine in cases resistant to this drug. "As in other places," he wrote to Ross (THOMAS, 1905c), "treatment with quinine is neglected as soon as the fever recedes, and the patients refuse to take the injections." In another letter sent four months later, Thomas stated (1905c) that he had been treating many patients "with a combination of atoxyl and quinine, both administered intravenously," and obtained "good results" from this therapy. It was used in Iquitos, in Peru, when Thomas was there.

He studied other diseases of Manaus: amoebic dysentery, leprosy, beriberi, and also filariasis, which was found among Italians who had resided in southern Brazil or workers from the East Indies recruited for the local projects and the construction of the Madeira-Mamoré Railroad. Thomas attached great importance to hookworm infection: he verified that it had a high prevalence in Manaus, with a high mortality rate when it occurred together with amebiasis.

In December 1905 Thomas visited Iquitos, the capital of Loreto, the largest of Peru's departments. There were close links between this port city (which had roughly 15,000 inhabitants) and Manaus and Belém, the main links in the British hegemony of trade in the Amazon basin. Since the beginning of the rubber boom in the 1880s, also known as the "white gold rush," Colombians, Ecuadorians, Peruvians, and Brazilians flocked to this border region of Amazonia, where the government had almost no presence and the workforce was exploited brutally, almost as brutally as in Leopold II's grim possession cynically named Free Congo.

The slavery regime established there to exploit rubber, ivory, and other products was the target of an international campaign led by the British journalist and writer Edmund Dene Morel and the Irish poet and diplomat Roger Casement. They were able to mobilize humanitarian and abolitionist organizations and force the Parliament of the United Kingdom, Belgium, and other governments to take a position against Leopold II around 1908 (HOCHSCHILD, 1999). Shortly thereafter, a similar process was launched against the *caucheros* of the river basin controlled by the port of Iquitos, notably Julio Cesar Araña, the founder of the Peruvian Amazon Company, with offices in London and Manaus. Heading this campaign were the American engineer Walter Ernest Hardenburg (2017), author of an accusation against Araña's empire, which had great repercussion, and Casement, who from 1906 occupied the post of British consul in Santos, Belém do Pará, and Rio de Janeiro.<sup>43</sup>

Thomas had gone to Iquitos with a mission: to investigate the disease known as *vômito negro* (black vomit), to see if it was yellow fever. He consequently paid careful attention to the systems for sewage and wastewater drainage and the supply and storage of drinking water, as well as the sanitary conditions of public spaces and households. He made a distinction between the habits and practices of poor and wealthy people, always attentive to the breeding of yellow fever and malaria mosquitoes as well as the transmission of bacteria and worms through water and other means. Although he did not see any cases of *vômito*

*negro*, information provided by two doctors there and the fact that *Stegomyia fasciata* was abundant in the city and in the surrounding villages led Thomas to conclude that yellow fever had arrived in the region. Having found a few *Anopheles* in the city, Thomas collected blood from hundreds of people of all social ranks and found that the majority of those infected with plasmodium lived in the rubber plantations on the riverbanks.

In the water sources that supplied the population, Thomas found many hookworm eggs, confirming that almost all the native children and a large number of adults were hosts of the parasite. Thomas's report (1907) included other human and animal diseases and made several recommendations concerning sanitation improvements in the Peruvian port city.

Although his mission was determined by the interests of the Liverpool shipping companies, an accentuated concern with the living conditions of the local population of workers can be seen, and certainly was not part of the scope of the commissioned study.

Thomas (1910-1911b) also published a more extensive report on the sanitary conditions and the prevailing diseases in Manaus, the most complete (and perhaps the only) epidemiological study that historians can find on the capital of Amazonas during the height of the rubber boom. Other works by Thomas appeared in the same issue of the *Annals of Tropical Medicine and Parasitology*, including a study he did with Robert Newstead on mosquitoes in the Amazon (NEWSTEAD; THOMAS, 1910-1911, p. 101-110).

Had Thomas tested atoxyl in patients with yellow fever? I ask the question considering that after World War I, doctors in the United States and other countries treated the disease with arsenicals such as salvarsan. The reason for this leads us to the studies mentioned by Ehrlich and the discovery of the syphilis microbe in 1905.

The Reed Commission maintained the suspicion that yellow fever was caused by a "filterable virus," but we should not consider the modern concept of a virus when we hear this idea. In 1904, on the eve of the discovery of *Spirochaeta pallida*, Shaudinn found life forms that were able to cross the filters that trapped the smallest bacteria, whose life cycles could include mosquitoes as intermediate hosts. The German protozoologist then surmised that a spirochete could also be the agent of yellow fever (it should be added that these microorganisms were then considered protozoa). This hypothesis was investigated in Rio de Janeiro by two doctors from the Hamburg Institute of Maritime and Tropical Diseases, where Schaudinn worked.<sup>44</sup>

Arthur Marston Stimson (1907, p. 541), of the United States Public Health Service, described *Spirochaeta interrogans* found in a victim of yellow fever. Thomas (1909, p. 56-57) was the author of the communication of this discovery to the Society of Tropical Medicine in London.

He had returned to England in 1909 to negotiate more substantial support for his laboratory. During the nearly four years he stayed in Manaus, Thomas worked in close harmony with the local medical elite. He conducted around 7,000 microscopic examinations for the Health Service and the hospitals in the city, and another 2,000 in Iquitos. His interest in yellow fever did not keep him away from ancylostomiasis, and he confirmed that more than 50% of the Manaus's population suffered from the disease. WOLFERSTAN..., 1909, p. 1).



In the records of the Liverpool School, Thomas is actually associated with two expeditions: the fifteenth, in 1905, and the twenty-sixth, in 1910, which had the objective of "sanitation," no more, no less. In the middle of that year, the Yellow Fever Research Laboratory was reopened, now with a small hospital that mainly served foreigners. In 1919, Thomas obtained resources from the Booth Steamship Company to hire three assistants, the doctors Robert Mccoll Burnie, Rupert Montgomery Gordon, and Charles James Young, who only remained in Manaus until 1922. After this time, the Liverpool School laboratory was definitively overshadowed by Thomas himself, and fades in the documentary records.

In Japan during the first World War, Inada et al. identified *Spirochaeta icterohaemorrhagica japonica* nov. sp as the agent of a disease that affected many soldiers in the trenches, which would become known as leptospirosis and had two symptoms in common with yellow fever: jaundice and bleeding. Schaudinn's hypothesis was confirmed by Hideyo Noguchi, a bacteriologist from the Rockefeller Institute; in 1918, he described a spirochete as the agent of yellow fever and created new genus, *Leptospira*, to accommodate *Leptospira icteroides*, from the disease transmitted by *Aedes aegypti* and the *Leptospira* of the trench disease transmitted by rats. This was the theory that reigned during the yellow fever eradication campaign conducted by the Rockefeller Foundation after the first World War in Latin America and then on the west coast of Africa (BENCHIMOL, 2011, p. 199-338).

We find Thomas in the 1920s in northeastern Brazil, working in the service of Liverpool shipping companies to treat yellow fever patients with the serum and vaccine developed by Noguchi. The Brazilian doctors, starting with Henry Aragão of the Oswaldo Cruz Institute, adopted salvarsan and neosalvarsan in massive doses to treat patients with yellow fever. At the end of that decade, some of the pillars of the campaigns conducted up to this point against yellow fever began to collapse. In West Africa and then in Brazil, the disease was confirmed to be caused by a virus that could be transmitted by other mosquitoes besides *Aedes aegypti*, and hosted by vertebrates other than humans, especially the monkeys involved in the cycle of the disease known as sylvatic yellow fever.

## Epilogue

The Liverpool School of Tropical Medicine's laboratory in Manaus closed its doors after Thomas's death in May 1931 from "alcoholic sclerosis,"<sup>45</sup> an event that had no repercussions among the international scientific community. Even so, the archives at the Liverpool School contain various documents (or rather, inquiries) about this character that new generations of researchers have forgotten: this "corpulent, elegant, and bearded man," reads one letter, who had become "completely Spanish" after leaving for the city amid the Amazon jungle (RIDING, 1952). Interest in Thomas stirred in 1950, when he was granted a portion of an award instituted by King Baudouin of Belgium: one million francs, to be divided among several researchers. One hundred thousand went to Thomas's heirs for the discovery of the trypanocidal qualities of atoxyl; the remainder of the prize was divided among scientists linked to research and development of trypanamide. The chemists Walter A. Jacobs and Michael Heidelberger each received 100,000 francs for the discovery of this drug at the Rockefeller Institute in 1915-1919; another 200,000 francs were given to the heirs of the biologist Wade H. Brown, "co-author of the first experiments in laboratory

animals," and 500,000 francs went to the biologist Louise Pearce, "the co-author of the first experimentation of this product in laboratory animals and author of its first application in the treatment of human sleeping sickness in the Belgian Congo."<sup>46</sup>

The prize generated a feverish search for information on Thomas. He was brought back from oblivion again 20 years later by the parasitologist Wallace Peters, dean of the Liverpool School. In 1971, when studying the chemotherapy of malaria, he traveled to the Amazon and found bits of information that piqued his curiosity.<sup>47</sup> Thanks to Peters, new facts and objects related to Thomas began to be added to the Liverpool School archives.

My interest in Thomas was stirred by a small biographical article based on materials collected recently by Peters (SMITH, 1976, p. 4-6). A copy of this work reached the president of Fiocruz in 1993, and a copy of the copy arrived at the desk of the author of this meandering article linking sleeping sickness, Chagas disease, syphilis, leptospirosis, malaria, and yellow fever.<sup>48</sup>

Thomas, as we have seen, *for some time* provides us a good thread for us to follow through the work in the laboratory and field which occurred simultaneously in the Americas, Europe, and Africa, involving synergies which only recently have begun to be unveiled through the social history of tropical medicine, or what is known as transnational history. Thomas became involved with the local problems of the Amazon and with doctors who were at the forefront of experimental medicine and public health in the region, without losing sight of the reasons which led to his trip there. But over the years he distanced himself from the medical and scientific issues of the Liverpool School on the one hand, and from the social structures in which his peers lived and thought, on the other, including their search for prestige and positions. This in my view differs from the course taken by the majority of doctors from imperial metropolises who ventured out to the tropics on expeditions.

The sources show that until the late 1910s Thomas left notable records of what he was doing in the Amazon in British academic forums, but the evidence regarding this physician's trajectory after the 1920s becomes increasingly fragmented.

Thomas chose to live in a city deep in the Amazon jungle, at a time when it was transitioning from opulence to destitution. When he arrived there, Manaus was the Paris of the tropics, where the fortunes made in all of the areas of the extractivist rubber economy were spent on all sorts of luxury, and even (as Thomas wrote) on kickbacks paid to state authorities and officials.<sup>49</sup> These fortunes depended on the import, subjugation, and physical annihilation of large masses of miserably poor people in the capital of the state as well as in the ports, villages, and rubber plantations, which were difficult or nearly impossible to access through the network of rivers that snaked through the vast forest. Thomas had an up-close view of the collapse of that opulent era associated with the rubber crisis, and only from afar witnessed the devastation caused by World War I, which was so traumatic for his contemporaries.

The economic impoverishment of the Amazon frayed the intimate economic and cultural connection between its elites and the cities of Europe, which was largely ensured by the shipping companies, particularly those from Liverpool, which maintained the School

of Tropical Medicine and its representative in Manaus. These factors certainly explain the lack of interest and distancing with relation to Thomas, but not his decision to remain in Manaus, which by the educated people of Europe and even southeast Brazil was considered to be the end of the world.

The Canadian doctor, who could have easily been a character out of Somerset Maugham, traversed three worlds: Europe, the Europeanized world of the Amazonian *baré* bourgeoisie, and the world of the workers and the poor, whether they were from Manaus or came from afar to treat their illnesses in the Amazonian capital, at the few institutions that offered free treatment where Thomas worked for many years as a volunteer. He did this because the patients hospitalized at these institutions were the raw material for studies with which the group of doctors Thomas had allied himself had distinguished themselves. He also did it because he was a man imbued with the philanthropic spirit that we find in his family origin, a cultural tendency which may be strong among the elites of Canadian and British society but is very tenuous in Brazil and even more so in Amazonas. The prevailing mentality there involved strong mercantile greed, class snobbery, and a profound lack of interest in the sort of people condemned by that social structure to misery and disease.

These are the provisional conclusions I have reached in this study, which is still ongoing.

**English version by Tracy Smith Miyake.**

## References

ALBUQUERQUE, Marli B. *et al.* *A ciência a caminho da roça: imagens das expedições científicas do Instituto Oswaldo Cruz ao interior do Brasil entre 1911 e 1913*. Rio de Janeiro: Fiocruz/Casa de Oswaldo Cruz, 1991.

ALLMAND, Dorothy. Liverpool School of Tropical Medicine. Scientific Record. *Annals of Tropical Medicine and Parasitology*, London, v. 15, n. 1, p. 1-47, 27.4.1921.

AMARAL, Isabel. Bactéria ou parasita? A controvérsia sobre a etiologia da doença do sono e a participação portuguesa, 1898-1904. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 19, n. 4, p. 1275-1300, out.-dez. 2012.

AMARAL, Isabel. The emergence of tropical medicine in Portugal: The School of Tropical Medicine and the Colonial Hospital of Lisbon (1902-1935). *Dynamis*, Granada, v. 28, p. 301-328, 2008.

ARRÉTÉ ROYAL de 15.4.1953, intitulado *Prix pour la decouverte du remede contre la maladie du sommeil*. Cópia fornecida à Liverpool School of Tropical Medicine pelo Ministère des Colonies da Bélgica (2 pag. datil., francês). Archives of the LSTM – TM/14/ThW 13.1-5b:1 May-11 June 1953 – docs 187 e 188.

AS EPIZOOTIAS EM MARAJÓ. *A Província do Pará*, Belém, 19 e 20.8.1907, p. 1.

BENCHIMOL, Jaime L. Hideyo Noguchi e a Fundação Rockefeller na campanha internacional contra a febre amarela (1918-1928). In: BASTOS, Cristiana; BARRETO, Renilda (Orgs.). *Impérios, centros e províncias: a circulação do conhecimento médico*. Lisboa: Imprensa de Ciências Sociais, série digital, 2011. p. 199-338.

BENCHIMOL, Jaime L. Bacteriologia e medicina tropical britânicas: uma incursão a partir da Amazônia (1900-1901). *Boletim Museu Paraense Emílio Goeldi. Ciências Humanas*, Belém, v. 5, n. 2, p. 315-344, maio-ago. 2010.

BENCHIMOL, Jaime L. Adolpho Lutz e a dermatologia em perspectiva histórica. In: BENCHIMOL, Jaime L.; SÁ, Magali Romero (Orgs.). *Adolpho Lutz, obra completa*. v. I, livro 3: *Dermatologia & Micologia*. Rio de Janeiro: Ed. Fiocruz, 2004. p. 40-152.

BENCHIMOL, Jaime L. Reforma urbana e revolta da vacina na cidade do Rio de Janeiro. In: FERREIRA, Jorge; NEVES, Lucília de A. *O Brasil republicano. Economia e sociedade, poder e política, cultura e representações*. Rio de Janeiro: Editora Civilização Brasileira, 2003. v. 1, p. 231-286.

BENCHIMOL, Jaime L.; SÁ, Magali R. *Adolpho Lutz e a entomologia médica no Brasil (apresentação histórica)*. *Adolpho Lutz, obra completa*. v. II, livro 3. Rio de Janeiro: Ed. Fiocruz, 2006.

BENCHIMOL, Jaime L.; Sá, Magali R. Insetos, humanos e doenças: Adolpho Lutz e a medicina tropical. In: Benchimol, Jaime L.; Sá, Magali R. (Orgs.). *Adolpho Lutz, obra completa*. v. II, livro 1: *Febre amarela, malária & protozoologia*. Rio de Janeiro: Ed. Fiocruz, 2005. p. 43-244.

BENCHIMOL, Jaime L.; SILVA, André F. C. Ferrovias, doenças e medicina tropical no Brasil da Primeira República. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 15, n. 3, p. 719-762, 2008.

BENCHIMOL, Jaime L.; TEIXEIRA, Luiz A. *Cobras, lagartos e outros bichos: uma história comparada dos institutos Oswaldo Cruz e Butantan*. Rio de Janeiro: UFRJ; Casa de Oswaldo Cruz, 1993.

BERRANG-FORD, Lea *et al.* Sleeping sickness in Uganda: revisiting current and historical distributions. *African Health Sciences*, Kampala, v. 6, n. 4, p. 226-231, Dec. 2006.

BOYCE, Rubert. The treatment of sleeping sickness and other trypanosomiasis by the atoxyl and mercury method. *British Medical Journal*, London, v. 2, n. 2437, p. 624-625, 14.9.1907.

BOYD, John. Sleeping Sickness – the Castellani-Bruce controversy. *Notes and records. The Royal Society Journal of the History of Science*, London, v. 28, n. 1, p. 93-110, 1973.

BRAID, James. Arsenic as a remedy for the bite of the Tse-Tse, etc. *British Medical Journal*, London, v.s4-1, n. 63, p. 214-215, 13.3.1858a.

BRAID, James. The bite of the Tse-Tse: arsenic suggested as a remedy. *British Medical Journal*, v.s4-1, n. 59, p. 135, 13.2.1858b.

BREINL, Anton; TODD, John L. Atoxyl in the treatment of trypanosomiasis. *The British Medical Journal*, London, v. 1, n. 2403, p. 132-134, 19.1.1907.

BRUCE, David. Discussion on trypanosomiasis. *British Medical Journal*, London, 11, v. 2, n. 2277, August 20, p. 367-369, 1904.

BRUCE, David; NABARRO, David. Progress report on sleeping sickness in Uganda. *Reports of the Sleeping Sickness Commission of the Royal Society*, London, Harrison and Sons, n. 1, p. 11-39, August 1903.

CAPONI, Sandra. Coordenadas epistemológicas de la medicina tropical. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 10, n. 1, p. 113-149, jan.-abr. 2003.

CARINI, A. Leishmaniose de la muqueuse rhino-bucco-pharyngée. *Bulletin de la Société Pathologie Exotique*, Paris, v. 4, n. 5, p. 289-290, 1911.

CARRARA, Sérgio. *Tributo a Vênus: a luta contra a sífilis no Brasil, da passagem do século aos anos 40*. Rio de Janeiro: Editora Fiocruz, 1996.

CASTELLANI, Aldo. On the discovery of a species of *Trypanosoma* in the cerebrospinal fluid of cases of sleeping sickness. *Proceedings of the Royal Society of London*, v. 71, p. 501-508, 1903a.

CASTELLANI, Aldo. Presence of *Trypanosoma* in sleeping sickness. *Reports of the Sleeping Sickness Commission of the Royal Society*, London, Harrison and Sons, n. 1, p. 3-10, August 1903b.

CAVALCANTI, Juliana M. *A trajetória científica de Rudolf Kraus (1894-1932) entre Europa e América do Sul: a elaboração, produção e circulação de produtos biológicos*. Rio de Janeiro: Pós-Graduação em História das Ciências e da Saúde da Casa de Oswaldo Cruz-Fiocruz, 2013.

CHAGAS, C. Die amerikanische Trypanosomiasis. In: BERGMANN, G. V.; STAEHELIN, R. *Handbuch der Innere Medizin*. Berlin: Verlag von Julius Springer, 1925. p. 1367-1386.

CHAGAS, Carlos. Descoberta do *Tripanozoma cruzi* e verificação da Tripanozomíase Americana. *Memórias do Instituto Oswaldo Cruz*, t. XV, fasc. 1, p. 67-76, 1922.

CHAGAS, Carlos. Tripanosomíase americana. Forma aguda da moléstia. *Memórias do Instituto Oswaldo Cruz*, t. VIII, 1916, p. 37-60 mais 5p. com fotos.

CHAGAS, Carlos. Moléstia de Carlos Chagas. Conferência realizada em 7 de agosto na Academia Nacional de Medicina. *Brazil-Medico*, Rio de Janeiro, v. 25, n. 34, p. 340-343; n. 35, p. 353-355; n. 37, p. 361-364, 373-375, 1911a.

CHAGAS, Carlos. Nova entidade mórbida do homem. Resumo geral dos estudos etiológicos e clínicos. *Memórias do Instituto Oswaldo Cruz*, t. III, fasc. II, p. 219-275, 1911b.

CHAGAS, Carlos. Nova entidade mórbida do homem (continuação). *Brazil-Medico*, Rio de Janeiro, ano XXIV, n. 44, p. 433-437, 22.11.1910.

CHAGAS, Carlos. Nova espécie mórbida do homem, produzida por um *Trypanozoma* (*Trypanozoma cruzi*): nota prévia. *Brazil-Medico*, Rio de Janeiro, v. 23, n. 16, p. 161, 1909a.

CHAGAS, Carlos. Trabalho do Instituto de Manguinhos sobre uma nova tripanossomíase humana. *Anais da Academia de Medicina do Rio de Janeiro*, Rio de Janeiro, v. 75, p. 188-190, jan.-dez. 1909b.

CHAGAS, Carlos; VILLELA, Eurico. Forma cardíaca da Trypanosomíase Americana. *Memórias do Instituto Oswaldo Cruz*, Rio de Janeiro, t. XIV, fasc. I, p. 5-61, 1922.

CHAGAS FILHO, Carlos. *Meu pai*. Rio de Janeiro: COC/Fiocruz, 1993.

CHAGAS FILHO, Carlos. Histórico sobre a doença de Chagas. In: CANÇADO, J. Romeu (Org.). *Doença de Chagas por um grupo de colaboradores especializados*. Belo Horizonte: Imprensa Oficial do Estado de Minas Gerais, 1968. p. 7-15.

COSTA SANTOS, Renata Soares da. *Doenças entre dois mundos: médicos-cientistas e pacientes no Hospital de Manguinhos (1909-1930)*. Rio de Janeiro: Dossiê de qualificação. Pós-Graduação em História das Ciências e da Saúde da Casa de Oswaldo Cruz-Fiocruz, 2016.

COUTINHO, Marília. Ninety years of Chagas Disease: a success story at the Periphery. *Social Studies of Science*, Kingston/Thousand Oaks, v. 29, n. 4, p. 519-549, 1999.

- COX, Francis E. G. History of human parasitology. *Clinical Microbiology Reviews*, Washington, v. 15, n. 4, p. 595-612, Oct. 2002.
- COX, Francis E. G. (ed.). *Illustrated history of tropical diseases*. London: The Wellcome Trust, 1996.
- CRUZ, Oswaldo G. *Relatório sobre as condições médico-sanitárias do valle do Amazonas apresentado a s. ex<sup>a</sup> o snr. dr. Pedro de Toledo, ministro da Agricultura, Indústria e Comércio*. Rio de Janeiro: Typ. do Jornal do Commercio, 1913.
- CRUZ, Oswaldo. Carta a Adolpho Lutz, 6.1.1907. BR. MN. Fundo Adolpho Lutz, pasta 213.
- CRUZ, Oswaldo; CHAGAS, Carlos; PEIXOTO, Afrânio. *Sobre o saneamento da Amazônia*. Manaus: Philippe Daou, 1972, s.p.
- DA MATTA, Alfredo. Considerações sobre a leishmaniose nodular e pseudo-verrucosa. *Amazonas Medico*, Manaus, ano I, p. 14-17, mar. 1918.
- DA MATTA, Alfredo. Sur les leishmanioses tégumentaires. Classification générale des leishmanioses. *Bulletin de la Société Pathologie Exotique*, Paris, v. 9, n. 7, p. 494-503, 1916.
- DA MATTA, Alfredo. Leishmaniose trópica (Nota clínica do primeiro caso observado em Manaus). *Revista Médica de São Paulo*, São Paulo, n. 7, p. 440, 1910.
- DELAPORTE, François. *Histoire de la fièvre jaune*. Paris: Payot, 1989.
- DIAS, Emmanuel. *Doença de Chagas – noções*. Rio de Janeiro: Ministério da Educação e Saúde, Serviço Nacional de Educação Sanitária, 1944.
- DOUGLAS, R. A. Breinl, Anton (1880–1944), *Australian Dictionary of Biography*, National Centre of Biography, Australian National University, s.d. Disponível em: <<http://adb.anu.edu.au/biography/breinl-anton-5342/text9031>>. Acesso em: 19 maio 2015.
- DR. LUTZ. *A Província do Pará*, 22.8.1907, p. 1.
- DR. WOLFERSTAN THOMAS. *Amazonas*, Manaus, ano XLV, n. 11, p. 1, 12.1.1909.
- DUREN, A. Prix institué pour la découverte du remède contre la Trypanosomiase. Institut Royal Colonial Belge. *Bulletin des Séances*, Bruxelles, v. XXIV, n. 2, p. 741-763, 1953.
- DURHAM, Herbert E. *Report of the Yellow Fever Expedition to Pará*. Liverpool School of Tropical Medicine – Memoir VII. London, New York, Bombaim: Longmans, Green & Co, 1902.
- DURHAM, Herbert E.; MYERS, Walter. Liverpool School of Tropical Medicine: Yellow Fever Expedition. (Abstract of Interim Report). *The British Medical Journal*, London, v. 1, n. 2095, p. 450-451, 23.2.1901.
- DUTHIE, Edward S. *Molecules against microbes*. London: Sigma Books Limited, 1946.

DUTTON, John Everett. *Report of the Malaria Expedition to the Gambia – 1902*. Liverpool School of Tropical Medicine – Memoir X. London: Longmans, Green & Co., 1903.

DUTTON, John E. *et al. Reports of the Trypanosomiasis Expedition to the Congo 1903-1904*. Liverpool School of Tropical Medicine – Memoir XIII. London: William & Norgate, August 1904.

DUTTON, Joseph E. Preliminary note upon a trypanosome occurring in the blood of a man. *Thompson Yates Laboratories Report*, Liverpool, v. 4, p. 455-468, 1902.

EHRlich, Paul. Experimental researches on specific therapy. Chemotherapeutic Studies on Trypanosomes. Third Harben Lecture. London: Lewis, 1908. (Reproduzido em *The Collected Papers of Paul Ehrlich* in four volumes including a complete bibliography compiled and edited by F. Himmelweit, with the assistance of Martha Marquardt, under the editorial direction of Sir Henry Dale. London, Oxford, New York, Paris: Pergamon Press, 1960, v. III, p. 130-134.)

ELMASSIAN, Miguel. Mal de caderas, flagelosis pasesiante de los equideos. *Revista de la Sociedad Médica Argentina*, Buenos Aires, v. 10, n. 53, p. 122-148, jan.-fev. 1902, 1pl., figs. 1-17.

ELMASSIAN, Miguel. Mal de caderas. Conférence faite au Conseil National d'Hygiène le 19 mai, Asunción, le 19.5.1901. *Anales de la Universidad Nacional*, Asunción, 1901, t. I, n. 1, 16p.

ELMASSIAN, Miguel; MIGONE, Luis Enrique. Sur le mal de caderas ou flagellose parésiante des équidés sud-américains. *Annales de l'Institut Pasteur*, Paris, v. 17, n. 4, p. 241-267, 25.4.1903.

FAJARDO, Francisco. Carta a Adolpho Lutz, 13.6.1900. BR. MN. Fundo Adolpho Lutz, pasta 176.

FINLAY, Carlos J. El mosquito hipoteticamente considerado como agente de transmisión de la fiebre amarilla. Trabajo leído en la Real Academia de Ciencias Médicas, Físicas y Naturales de la Habana, sesión del 14.8.1881. *Obras completas de Finlay*, Havana, t. I, p. 247-261, 1965.

FORDE, Robert M. Some clinical notes on a European patient in whose blood a trypanosoma was observed. *The Journal of Tropical Medicine and Hygiene*, London, v. 5, p. 261-263, 1902.

GARCIA, Domingos S. da Cunha. *Território e Negócios na "Era dos Impérios": os belgas na fronteira oeste do Brasil*. Brasília: Fundação Alexandre de Gusmão, 2009.

GIBAUD, Stéphane; JAOUENT, Gérard. Arsenic Based Drugs: from Fowler's solution to modern anticancer chemotherapy. *Medicinal Organometallic Chemistry. Topics in Organometallic Chemistry*, Berlin, v. 32, p. 1-20, October 2010.

GREEN, Paul. Evans Sons, Lescher & Webb Ltd. In: The Herb Museum (History – Medicine – Botanicals). Vancouver, British Columbia, Canada: s.d. Disponível em: <<http://www.herbmuseum.ca/content/evans-sons-lescher-webb-ltd>>. Acesso em: 16 fev. 2016.



- HARDENBURG, Walter. *O paraíso do diabo*. São Carlos: Editora Scienza, 2017.
- HOCHMAN, Gilberto. *A era do saneamento: as bases da política de saúde pública no Brasil*. São Paulo: Hucitec/Anpocs, 1998.
- HOCHSCHILD, Adam. *King Leopold's Ghost: a story of greed, terror, and heroism in Colonial Africa*. Boston: Houghton Mifflin Company, 1999.
- JOGAS JUNIOR, Denis. *Uma doença americana? A leishmaniose tegumentar e a medicina tropical no Brasil (1909-1927)*. Curitiba: Editora Prismas, 2017.
- KESTEVEN, W. B. Arsenic eating as a prophylactic for the bites of venomous reptiles, *British Medical Journal*, London, v.s4-1, n. 64, p. 251, 27.3.1858.
- KOPKE, Ayres. Traitement de la trypanosomiase humaine. Rapport présenté au XVI Congrès International de Médecine. *Archivos de Hygiene e Pathologia Exoticas* publicados pela Escola de Medicina Tropical de Lisboa, v. II, p. 219-224. Lisboa: Imprensa Nacional, 1909a.
- KOPKE, Ayres. Trypanosomiase Humaine. Separata da *Medicina Contemporanea*, 1909b (10p.). Pasta Ayres Kopke, Instituto de Higiene e Medicina Tropical, Lisboa, 616.937 (Cx/ Separatas 47, n. 7).
- KOPKE, Ayres. Traitement de la maladie du sommeil. *Archivos de Hygiene e Pathologia Exoticas*, Lisboa, v. 1, n. 3, p. 299-349, 1907.
- KOPKE, Ayres. Investigações sobre a doença do somno. *Archivos de Hygiene e Pathologia Exoticas* publicados pela Escola de Medicina Tropical de Lisboa, v. I, fasc. 1, p. 1-65, 1.10.1905.
- KROPF, Simone P. Construindo a doença e a nação: a história da descoberta da doença de Chagas. In: CARVALHEIRO, José da Rocha et al. (Org.). *Clássicos em doença de Chagas. História e perspectivas da descoberta*. Rio de Janeiro: Editora Fiocruz, 2009a.
- KROPF, Simone P. *Doença de Chagas, doença do Brasil: ciência, saúde e nação (1909-1962)*. Rio de Janeiro: Editora Fiocruz, 2009b.
- KROPF, Simone P.; SÁ, Magali R. The discovery of *Trypanosoma cruzi* and Chagas disease (1908-1909): tropical medicine in Brazil. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 16, supl. 1, p. 13-34, jul. 2009.
- LAVERAN, Alphonse; Mesnil, Félix. *Trypanosomes et trypanosomiasés*. Paris: Masson et Cie., 1912.
- LAVERAN, Alphonse; MESNIL, Félix. Recherches sur le traitement et la prévention du nagana. *Annales de l'Institut Pasteur*, Paris, v. 16, n. 11, p. 786-817, 25.11.1902.
- LAVERAN, Charles L. Alphonse; MESNIL, Félix. *Trypanosomes and Trypanosimiasés*. Chicago: W. T. Keener & Co., 1907.

LEDERMANN D., Walter. Aldo Castellani y las expediciones de la Royal Society al país del sueño negro. *Revista Chilena de Infectología* [online], Lima, v. 28, n. 3, p. 276-281, 2011.

LIVERPOOL School of Tropical Medicine. *Historical Record 1898-1920*. Liverpool: University Press of Liverpool, 1920.

LÖWY, Ilana. La mission de l'Institut Pasteur à Rio de Janeiro: 1901-1905. In MORANGE, Michel (ed.). *L'Institut Pasteur: contribution à son histoire*. Paris: La Découverte, 1991. p. 195-279.

LUTZ, Adolpho. Estudos e observações sobre o quebrabunda ou peste de cadeiras. In: BENCHIMOL, Jaime L.; SÁ, Magali R. (Orgs.). *Adolpho Lutz, obra completa*. v. III, livro 3: *Viagens por terras de bichos e homens*. Rio de Janeiro: Ed. Fiocruz, 2007. p. 83-100.

LUTZ, Adolpho. Estudos e observações sobre o quebrabunda ou peste de cadeiras. *Diário Oficial do Estado do Pará*. Belém, v. 17, n. 4780, p. 356-362, 1907.

LYONS, Marynez. *The colonial disease: a social history of sleeping sickness in northern Zaire, 1900-1940*. New York/Port Chester/Melbourne/Sydney: Cambridge University Press, 1992.

MAEGRAITH, Brian G. History of the Liverpool School of Tropical Medicine. *Medical History*, Cambridge, v. 16, n. 4, p. 354-368, October 1972.

MANSON, Patrick. *Tropical Diseases – a manual of diseases of warm climates*. 6 ed. London; New York; Toronto; Melbourne: Cassell and Company, Ltd., 1919.

MANSON, Patrick. A clinical lecture on the sleeping sickness. *The British Medical Journal*, London, v. 2, n. 1979, p. 1672-1677, 3.12.1898.

MARTINEZ, Sabrina T.; ALMEIDA, Márcia R.; PINTO, Angelo C. Alucinógenos naturais: um voo da Europa medieval ao Brasil. *Química Nova*, São Paulo, v. 32, n. 9, p. 2501-2507, 2009.

MILLER, Patricia. *Liverpool School of Tropical Medicine. An illustrated history of the Liverpool School of Tropical Medicine 1898-1998*. Liverpool: Liverpool School of Tropical Medicine, 1998.

MILNE, Alan Hay. Carta a Ronald Ross, 16.8.1905. LSHTM Archives - GB 0809 Ross/113/06/16.

MOLYNEUX, D. H. Carta a Carlos Morel em 5.3.1993. 1p. datilografada (cópia no acervo pessoal do autor).

MOREIRA, Juliano. Distribuição geográfica do botão endêmico dos países quentes. *Gazeta Medica da Bahia*, Salvador, v. 26, p. 369-374, 1895a.

MOREIRA, Juliano. Existe na Bahia o botão de Biskra? Estudo clínico. *Gazeta Medica da Bahia*, Salvador, v. 26, p. 254-258, 1895b.

MORGAN, Henry James. *The Canadian men and women of the time: a hand-book of Canadian biography and living characters*. Toronto: William Briggs, 1912. p. 1093-1094.

MOTT, Frederick W. The changes in the central nervous system of two cases of negro lethargy: sequel to Dr. Manson's clinical report. *The British Medical Journal*, London, v. 2, n. 2033, p. 1666-1669, 16.12.1899.

MUSGRAVE, William E.; CLEGG, Moses T. *Trypanosoma and trypanosomiasis, with special reference to surra in the Philippine Islands*. Manila: Bureau of Public Printing, 1903.

NEILL, Deborah J. *Networks in tropical medicine: internationalism, colonialism and the rise of a medical specialty, 1890-1930*. Stanford: Stanford University Press, 2012.

NEPVEU, Gustave. Sur un trypanosome dans le sang de l'homme. *Comptes rendu de la Société de Biologie*, Marseille, v. 50, p. 1172-1174, 1898.

NEWSTEAD, Robert; THOMAS, Harold H. S. Wolferstan. The mosquitoes of the Amazon Region. *Annals of Tropical Medicine and Parasitology*, London, v. IV, n. 1, p. 141-150, 1.6.1910-10.3.1911.

O MAL DE CADEIRAS. Cura possível pelo método combinado do atoxil e do mercúrio. *A Província do Pará*, Belém, 11.10.1907, p. 1.

OBITUARY (dat, s.d.). Archives of the LSTM, s.d. TM/14/ThW 28.2.

PENNINGTON, David. *Manaus e Liverpool: uma ponte marítima centenária*. Manaus: Edua/Uninorte, 2009.

PLIMMER, Henry G.; THOMSON, J. D. Further results of the experimental treatment of Trypanosomiasis in rats. *Proceedings of the Royal Society*, Series B, London, v. 80, n. 536, p. 1-11, 4.2.1908.

PLIMMER, Henry G.; THOMSON, J. D. A preliminary summary of the results of the experimental treatment of Trypanosomiasis in rats. *Proceedings of the Royal Society*, Series B, London, v. 79, n. 534, p. 505-516, 6.9.1907.

POWER, Helen J. *Tropical Medicine in the Twentieth Century. A History of the Liverpool School of Tropical Medicine 1898-1990*. London: Kegan Paul International, 1999.

PRATA, Aluizio. *Carlos Chagas: coletânea de trabalhos científicos*. Brasília: Ed. UnB, 1981.

PROCÓPIO, José. Harold Wolferstan Thomas: cientista canadense a serviço da medicina do Amazonas. *Revista Brasileira de Medicina*, Rio de Janeiro, v. X, n. 5, p. 371-374, maio 1953.

RAO, Carlos. Leishmaniose ulcerosa no Amazonas. *Revista Médica de São Paulo*, São Paulo, n. 7, p. 165, 1910.

*REGISTRO de Inhumações a cargo do administrador do Cemitério São João Batista*. 1931.

Archives of the LSTM - TM/14/ThW-22p-23p. Documento original: Arquivo da Secretaria Municipal de Limpeza Pública (Semulsp).

REYNOLDS, L. A.; TANSEY, E. M. (ed.). *British contributions to medical research and education in Africa after the Second World War*. London: The Wellcome Trust Centre for the History of Medicine, v. 10, April 2001. Disponível em: <[http://www.history.qmul.ac.uk/research/modbiomed/Publications/wit\\_vols/44832.pdf](http://www.history.qmul.ac.uk/research/modbiomed/Publications/wit_vols/44832.pdf)>.

RIBEIRO, Evandro L. *et al.* Cromoblastomicose: doença presente na realidade populacional brasileira. *Revista Brasileira de Análises Clínicas – RBAC*, Rio de Janeiro, v. 38, n. 3, p. 189-192, 2006.

RIDING, D. Carta ao prof. James Henri Dible, Post Graduate Medical School, University of London, Hammersmith Hospital, em 26.9.1952. 2p. Archives of the LSTM - TM/14/ThW 12.1-3e.

RIETHMILLER, Steven. Erlich, Bertheim and Atoxyl: the origins of modern chemotherapy. *Bulletin for the History of Chemistry*, Cincinnati, n. 23, p. 28-33, 1999.

SÁ, Magali Romero. The tropical medicine in Brazil: the discovery of *Trypanosoma cruzi* in the German School of Protozoology. *Parassitologia*, Roma, v. 47, p. 309-317, 2005.

SANJAD, Nelson. Da 'abominável profissão de vampiros': Emilio Goeldi e os mosquitos no Pará. *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 10, n. 1, p. 85-111, jan.-abr. 2003.

SCHOENPF, Daniel. *George Huebner 1862-1935. Um fotógrafo em Manaus*. São Paulo: Metalivros, 2000.

Schweickardt, Júlio C. *Ciência, nação e região*. As doenças tropicais e o saneamento no estado do Amazonas, 1890-1930. Rio de Janeiro: Editora Fiocruz, 2011.

SCHWEICKARDT, Júlio C.; LIMA, Nísia T. Os cientistas brasileiros visitam a Amazônia: as viagens científicas de Oswaldo Cruz e Carlos Chagas (1910-1913). *História, Ciências, Saúde – Manguinhos*, Rio de Janeiro, v. 14, supl., p. 15-50, dez. 2007.

SCIENTIFIC notes and news. *Science*, New Series, New York, v. 18, n. 465, p. 702-704, Nov. 27, 1903.

SCOTT, Harold H. *A history of tropical medicine*. London: Edward Arnold & Co., 1939. 2v.

SEM TÍTULO. *O Estado de São Paulo*, São Paulo, 30.12.1906, p. 2.

SILVA, André F. C. da; BENCHIMOL, Jaime L. Malaria and quinine resistance: a medical and scientific issue between Brazil and Germany (1907-1919). *Medical History*, Cambridge, v. 58, n. 1, p. 1-26, 2014.

SMITH, G. Joan. Our man in Manaus. *The University of Liverpool Recorder*, Liverpool, University of Liverpool, n. 71, p. 4-6, April 1976.

SNEADER, Walter. *Drug discovery: a history*. Chichester, West Sussex: John Wiley & Sons, Ltd., 2005. p. 95-96.

STEPAN, Nancy. The interplay between socio-economic factors and medical science: yellow fever research, Cuba and the United States. *Social Studies of Science*, London, v. 8, p. 397-423, 1978.

STEPAN, Nancy. *Gênese e evolução da ciência brasileira: Oswaldo Cruz e a política de investigação científica e médica*. Rio de Janeiro: Artenova, 1976.

STEVERDING, Dietmar. The history of African trypanosomiasis. *Parasites & Vectors*, Heidelberg, v. 1, n. 3, 12.2.2008, 8p.

STILES, Ch. Wardell; HASSALL, Albert. *Index-Catalogue of Medical and Veterinary Zoology*, part 5 Authors: E to Eyssel. Washington: Government Printing Office, 1903.

STIMSON, Arthur M. Note on an organism found in yellow-fever tissue. *Public Health Reports*, Washington, v. 22, n. 18, p. 541, 1907.

THOMAS, Harold H. S. Wolfestan. "Mossy Foot" of the Amazon Region, an infective verrucotic condition affecting the skin of the upper and lower limbs. *Annals of Tropical Medicine and Parasitology*, London, v. IV, n. 1, p. 95-104, 1.6.1910-10.3.1911a.

THOMAS, Harold H. S. Wolfestan. The sanitary conditions and diseases prevailing in Manaus, North Brazil, 1905-1909, with plan of Manaus and chart. *Annals of Tropical Medicine and Parasitology*, London, v. IV, n. 1, p. 1-55, 1.6.1910-10.3.1911b.

THOMAS, Harold H. S. Wolfestan. Notes on Stimson's Spirochaete found in the kidney of a yellow fever case. *Transactions of the Society of Tropical Medicine and Hygiene*, London, v. III, n. 2, p. 56-57, Dec. 1909.

THOMAS, Harold H. S. Wolfestan. *La sanidad publica de Iquitos*. London: Williams & Norgate, 1907a.

THOMAS, Harold W. Yellow fever in chimpanzee. *The British Medical Journal*, v. 1, n. 2403, p. 138, 19.1.1907b.

THOMAS, Harold H. S. W. Preliminary note on the inoculation of a chimpanzee with yellow fever / Nota preliminar sobre a inoculação da febre amarela em um chimpanzé. *Brazil-Medico*, Rio de Janeiro, v. XXI, n. 2, p. 15-16, 8.1.1907c.

THOMAS, Harold H. S. Wolfestan. *Report on Trypanosomes, Trypanosomiasis, and sleeping sickness being an experimental investigation into their pathology and treatment*. Memoir XVI. Liverpool School of Tropical Medicine. Liverpool: William & Norgate, October 1905a. p. 1-94.

THOMAS, Harold H. S. Wolfestan Some experiments in the treatment of trypanosomiasis. *The British Medical Journal*, London, v. 1, n. 2317, p. 1140-1143, 27.5.1905b.

THOMAS, Harold Wolferstan. Cartas a Ronald Ross, em 13.12.1905c e 22.8.1905c. LSHTM Archives - GB 0809 Ross/146/07/107 e GB 0809 Ross/141/02/13.

THOMAS, H. Wolferstan; LINTON, Stanley F. A comparison of the animal reactions of the trypanosomes of Uganda and Congo Free State sleeping sickness with those of *Trypanosoma gambiense*, Dutton. Liverpool School of Tropical Medicine, Memoir XIII. Liverpool: Williams & Norgate, 1904a. p. 75-86.

THOMAS, H. Wolferstan; LINTON, Stanley F. A comparison of the animal reactions of the trypanosomes of Uganda and Congo Free State sleeping sickness with those of *Trypanosoma gambiense* (Dutton). A preliminary report. *Lancet*, London, v. 163, n. 4211, p. 1337-1340, 1904b.

THOMSON, John G.; SINTON, John A. The morphology of *Trypanosoma Gambiense* and *Trypanosoma Rhodesiense* in cultures and a comparison with the developmental forms described in *Glossina Palpalis*, *Annals of Tropical Medicine and Parasitology*, v. 6, n. 3B, p. 331-356, 18.10.1912.

TODD, John L. Carta a Sir Andrew Macphail, 3.12.1920, 2p. dat. Archives of the LSTM. TM/14/ToJ – John Lancelot Todd / 7.6b.

TRYPANOSOMA IN MAN. *The British Medical Journal*, London, v. 1, n. 2140, p. 42, 4.1.1902.

VIANNA, Gaspar. Tratamento da leishmaniose pelo tártaro emético. Comunicação ao 7º Congresso Brasileiro de Medicina e Cirurgia. Belo Horizonte, Minas Gerais, 1912. *Anais...*, v. 4, n. 3, p. 426-428, 1912.

VIANNA, Gaspar. Sobre uma nova espécie da leishmania. *Brazil-Medico*, Rio de Janeiro, v. 25, n. 41, p. 411-412, 1911.

VITAL BRAZIL [Vital Brazil Mineiro da Campanha]. Mal de cadeiras em São Paulo. *Revista Medica de São Paulo*, São Paulo, v. 10, n. 1, p. 2-4, 1907.

WORBOYS, Michael. Germs, malaria and the invention of Mansonian Tropical Medicine: diseases in the tropics to tropical diseases. In: ARNOLD, D. *Warm climates and western medicine: the emergence of tropical medicine 1500-1900*. Amsterdam: Rodopi, 1996. p. 181-207.

WORBOYS, Michael. The comparative history of sleeping sickness in East and Central Africa, 1900-1914. *History of Science*, London, v. 32, p. 89-102, March 1994.

## NOTES

- 1** In 1898, Ronald Ross revealed the cycle of the bird malaria parasite in a *Culex*; in the following year, Giovanni Battista Grassi, Amico Bignami, and Giuseppe Bastinelli identified the human malaria parasite in mosquitoes of the genus *Anopheles*. This finding permitted the project which Patrick Manson defended in England to invest in the training of physicians qualified to deal with what he called tropical medicine. This theme is already well studied, by, among others, Worboys (1996, p. 181-207), Power (1999), Caponi (2003, p. 113-149) and, more recently, Neill (2012).
- 2** Information about Thomas can be found in the in the Special Collections and Archives of the Sydney Jones Library at the University of Liverpool, in the Archives of the Liverpool School of Tropical Medicine, hereafter referred to as the 'Archives of the LSTM.' It can also be found in the archives of the London School of Hygiene and Tropical Medicine, the 'LSTM Archives.' On Thomas, see also Morgan (1912, p. 1093-1094), Procópio (1953, p. 371-374), and in recent works, Pennington (2009) and Schweickardt (2011).
- 3** The explorer David Livingstone had been the first to connect *n'gana* to tsetse fly bites in his 1852 observation about the disease in the Limpopo and Zambezi River Valleys, as well as on the shores of Lakes Nyasa and Tanganyika, where all the cattle he was transporting died, reports Steverding (2008, p. 4).
- 4** The original edition in French is from 1904.
- 5** *T. congolense* and *T. vivax* would also later be proven to be pathogens of *n'gana*. In 1896-1897, Durham (who would later be sent to Belém) and the entomologist Walter F. H. Blandford joined the Tsetse Fly Disease Committee, headed by the Brazilian Alfredo Antunes Kanthack. Kanthack's team studied the life cycle of the hematozoan discovered by Bruce in laboratory animals, looking for ways to prevent or cure the disease. In this respect see Benchimol (2010, p. 315-344).
- 6** This observation was communicated to Ronald Ross by telegram, which Cox (1996, p. 185) transcribed, and was published in "Trypanosoma in man" (*British Medical Journal*, v. 1, n. 2140, 4.1.1902, p. 42). Nepveu (1898, p. 1172-1174), of the Marseilles School of Medicine, had described a trypanosome in human blood, but Dutton's observation (1902, p. 455-468) represented the first case of a trypanosome in man which was possibly related to "symptoms of great importance."
- 7** The first communication by Castellani (1903a, p. 501-508), written from Entebbe, Uganda, in April 1903, was read at the Royal Society in London on May 8. It was republished in August (CASTELLANI, 1903b, p. 3-10). In that competitive environment, Castellani was marked by the suspicion that he only considered the trypanosomes after Bruce had suggested them, states Boyd (1973, p. 93-110).
- 8** In 1907, Evans Sons Lescher & Webb began to manufacture biological products for human and veterinary use, such as serums against diphtheria, tetanus, and meningococcus, in association with the University of Liverpool. In 1911, the Incorporated Liverpool Institute of Comparative Pathology became a department of the pharmaceutical company, which in the 1920s manufactured "fine chemical products, drugs, pharmaceutical preparations and cosmetics, vaccines, pills, tablets, etc." Through developments I am unable to depict here, this company became Evans Medical PLC, which was incorporated in 1954 in Nigeria, and today is part of Glaxo Laboratories Limited and manufactures anti-malaria drugs and other products (GREEN, undated).
- 9** The administrators who participated in this plan were the university's vice chancellor (Alfred William Winterslow Dale) and the 'gentlemen' (likely entrepreneurs) K. Muspratt, Allsopp, Hughes (of the Harrison Line, a shipping company founded in Liverpool in 1853), J. J. Evans, and his son, J. H. E. Evans, who would succeed him as president of the Evans Lescher & Webb Ltd. Annet was named medical superintendent of the Institute of Comparative Pathology (after Boyce's death in 1911, he would replace him as chair of comparative pathology) (RIDING, 1952, Annex A). Riding was director of the Evans Biological Institute, Runcorn, and the Annex to his letter is an excerpt taken from *The Chemist & DRUGGIST*, 16.10.1937, p. 449.
- 10** In papers published in 1904 and 1905, Thomas presents himself as the "J.H. Todd Memorial Fellow," proof that his salary was paid from a fund created in memory of Todd's father, and which seems to have been maintained until 1909 (an addendum to the title reads as follows: "In Memoriam Jacob Hunter Todd, Died August 10, 1899, Victoria, B.C., Canada"). Thomas was initially hired as an assistant lecturer, and began working in the Johnston Laboratories at the university before assuming leadership of the laboratories in Runcorn (PROCÓPIO, 1953, p. 371; OBITUARY, typed, undated; Archives of the LSTM, undated. TM/14/ThW 28.2). In other school records, Thomas would be designated as a research assistant and director of Runcorn Laboratory (1903-1905), then director of the Manaos Laboratory (LIVERPOOL..., 1920, p. iv, 29, 31, 72).
- 11** In May 1903, Bruce learned from the entomologist Ernest E. Austen that the species present in Uganda was the same found in West Africa: *Glossina palpalis* (COX, 1996, p. 187). Bruce's first communication and the arrival of Dutton and Todd to Boma, in the Congo, are discussed in Scientific Notes and News (November 27, 1903, p. 702-704).
- 12** Currently, there are three recognized subspecies of *Trypanosoma brucei*: *T. brucei* (not pathogenic to man), *T. brucei gambiense*, and *T. brucei rhodesiense*.
- 13** Musgrave and Clegg (1903), of the Biological Laboratory in Manila, published a report on trypanosomiasis in the Philippines, especially *surra*. Wendelstad tested a dye, parafuchsin, a line of experimentation that would later be taken up by Ehrlich (1960 [1908], p. 130-134) and yield fruitful results.
- 14** This information is found in Todd's letter to Sir Andrew Macphail (3.12.1920), a professor of the history of medicine, who was surprised by Thomas's importance to the history of chemotherapy. According to Todd, *liquor arsenicalis* may

have produced effective cures, but the trypanosomes usually returned, acquiring growing resistance to the drug until the patient died from either the parasites or arsenic poisoning. Livingstone based this treatment on the letters of a squire, a member of the lower British nobility, which were published in the 1850s. Having read comments in Livingstone's narrative (*Missionary Travels and Researches in South Africa*) on the fatal disease in oxen and sheep infected by the tsetse fly, James Braid suggested arsenic to the English explorer. This idea came from another text, a report by a Dr. Honigberger (*Thirty-Five Years in the East*) on a fakir who allowed himself to be bitten by a poisonous snake and suffered no harm because of his habit of eating arsenic. Livingstone promised to test the substance on his next trip to Africa. The subject was discussed by other correspondents of the British newspaper, such as Kesteven. (BRAID, 1858a, p. 214-215; 1858b, p. 135; KESTEVEN, 1858, p. 251). See also Gibaud and Jaouet (2010, p. 1-20).

**15** The most important reference is Thomas's report published in October 1905 and entitled *Report on Trypanosomes, Trypanosomiasis, and Sleeping Sickness being an experimental investigation into their pathology and treatment*. Part VII is dedicated specifically to "The treatment of Trypanosomiasis" (p. 49-63). The composition of this report is confusing. It is described on the cover as the work of Thomas and Breinl, and reports a secondary work ("Gland Puncture in Trypanosomiasis") by Dutton and Todd. On the first page, the main work is attributed to Thomas, registering a type of addendum to Breinl: "A description of the tissue changes." The preface is by Thomas and refers to several collaborators, and the page that effectively opens the report presents the authors as Thomas and Breinl. See also the article by Thomas published in the *British Medical Journal* (1905, p. 1140-1143).

**16** The presentation that follows is based on the excellent work by Duthie (1946, p. 37 and ss.).

**17** On the malaria plasmodium's resistance to quinine, see Silva and Benchimol (2014, p. 1-26). The authors showed (p. 10) that, after the 1891 publication of Paul Ehrlich and Paul Guttman's work on the usefulness of the methylene blue, Miguel Couto recommended its use to treat malaria, which led Arthur Neiva to test the substance in the state of Rio de Janeiro. In Hamburg, Nocht and Werner obtained equally unsatisfactory results in patients who had contracted resistant malaria in the Amazon.

**18** In a 1905 work in which he reported investigations made into sleeping sickness in Africa, Kopke (1905, p. 1-65) devoted the two final pages (p. 64-65) to unsuccessful attempts to treat patients with various medications: potassium iodide, tinctures of kola, quina, and coca, colargol, and arsenic in the form of sodium cacodylate and sodium arsenate. Atoxyl was the main object of the communication to the XV International Congress of Medicine (KOPKE, 1909a, p. 219-224). Another Portuguese periodical published "Trypanosomiase Humaine" (KOPKE, 1909b, p. 1-10). In 1907, the year following the Congress, Kopke (1907, p. 299-349) published his first solid results with atoxyl in patients infected by *T. gambiense*. In this respect, and on the Portuguese missions to Africa related to sleeping sickness, see Amaral (2008, p. 301-328).

**19** It was publicized discreetly, with a telegram sent by the Liverpool Society of Tropical Medicine to Dr. Dollerstan Thomas [sic] (UNTITLED, 1906, p. 2).

**20** The article published in 1902 in the *Revista de la Sociedad Médica Argentina* was translated into German by Kaesewurm and published (in an abridged version) in 1901 in *Berliner und Münchener Tierärztliche Wochenschrift*, v. 40, October 3, 1901, p. 604, 1fig. It was also translated into English by E. P. Barry and published in the *Veterinary Journal* (Elmassian, 1903, p. 192-196). In 1903 a review of the article was published by M. Lüche in *Jahresbericht über die Fortschritte in der Lehre von den pathogenen Mikroorganismen umfassend Bakterien, Pilze und Protozoën*, a journal edited by P. von Baumgarten, in Leipzig (1901, v. 17, n. 1, p. 560.). Here I cite data from Stiles and Hassal (1903, p. 418).

**21** This information comes from Denis G. Jogas Junior, a doctoral student in the graduate program in the History of Science and Health at the Oswaldo Cruz House/Fiocruz; under the guidance of Benchimol and Simone Kropf, Jogas is developing a doctoral thesis project entitled "Between South America and Europe: tropical medicine in Brazil and the controversies surrounding the American Tegumentary Leishmaniasis (1903-1948)" (Rio de Janeiro, 2014). He is the author of the book *Uma doença americana? A leishmaniose e a medicina tropical no Brasil (1909-1927)* [An American disease? Tegumentary leishmaniasis and tropical medicine in Brazil (1909-1927)] (2017).

**22** As director of the Bacteriological Institute of São Paulo, Lutz considered hiring this veterinarian from the Alfort School. In a letter from Paris, Francisco Fajardo (1900) said that he had been with Lignières, "but he responded: here there is no desire to go to Brazil, because if you go there, then the mayor changes and all the contracts are worth nothing, and you are abandoned."

**23** Infected horses needed to be quarantined or killed before the disease showed itself through paralysis, but bacteriological diagnosis depended on the creation of zootechnical posts. Lutz suggested wiping out the capybaras and using a substance to deter horseflies. The horses' legs were to be coated with this substance, since this was where the insects preferred to attack.

**24** The Liverpool School archives contain various documents testifying to the efforts in this direction, after Thomas's work on atoxyl had been 'rediscovered.' This controversial information appears in Scott (1939, v. 2, p. 525), and is echoed by other authors: "Ehrlich, when he learned of Thomas's results of *T. gambiense* infection in mice, went to Runcorn to see the work, and when he returned to Germany he started the research that led to the preparation of arsenophenyglycine, and ultimately, salvarsan."

**25** Ehrlich called the sodium salt of arsenic acid p-amino-phenyl arsanilic acid. Ehrlich worked in a new laboratory, Georg-Speyer-Haus, which was specially built for him to advance his work in chemotherapy. The pharmaceutical company Farbwerke Cassella & Co. provided materials and an assistant, the chemist Ludwig Benda. With the help of other assistants, particularly the chemist Alfred Berthheim and Sahachiro Hata, Ehrlich devoted himself to the development of "his magic bullets" (DUTHIE, 1946, p. 41-43).



**26** Duthie (1946) describes the problems of salvarsan and derivative 914, neosalvarsan. On the use of these drugs in Brazil, see Carrara (1996).

**27** The considerations below are based on Kropf (2009a; 2009b, p. 23-30) and Benchimol and Teixeira (1993). It should be noted, however, that these and other authors gave little attention to the treatment of Chagas disease. Due to space limitations, I am not including references to many of the works by Chagas mentioned below. They can be found in the works indicated above and in Prata (1981).

**28** See also the studies by Gaspar Vianna, Ezequiel Dias, Arthur Neiva, Cezar Guerreiro and Astrogildo Machado (among others) on the anatomic pathology, hematology, transmission, and diagnosis of Chagas disease, analyzed in Kropf (2009b) and Benchimol & Teixeira (1993).

**29** Chagas Filho (1968, p. 7-8, 15) divides the history of studies on Chagas disease into four periods: the heroic, involving the diffusion of the discovery within Brazil and abroad; the period of disenchantment caused by attacks at the National Academy of Medicine, with Chagas continuing his studies along with some dedicated collaborators; the third stage coincides with his death in 1934 (and the discovery of Romaña's sign), increased interest in the disease, and proliferation of research centers; and the final stage, starting in 1950, initiating the period of "perfect national and international understanding of the problem."

**30** Reissued in Prata (1981, p. 167-192), under the title *Segunda conferência realizada na Academia Nacional de Medicina em agosto de 1911* [Second Conference held at the National Academy of Medicine in August 1911], from a brochure with the numbering p. 3-28 (reference to prophylactic plans: p. 26/190).

**31** The substance was used in Egyptian, Greco-Roman, and ayurvedic medicine, and was synthesized in 1901 by Richard Martin Willstätter. There are many studies on the interesting history of this drug, for example Martinez, Almeida and Pinto (2009, p. 2501-2507) and Sneider (2005, p. 95-96).

**32** The materials from the Oswaldo Cruz Institute Fund, namely the series pertaining to patient records from the Evandro Chagas Hospital at the Department of Archives and Documentation at the Casa de Oswaldo Cruz are surveyed by the doctoral student Costa Santos, with the help of Luciana Pinheiro and Rafael Lima de Souza, scholarship recipients participating in a project I am leading: History of the leishmaniasis (1903-2015): meanings, confrontation, and challenges of a tropical disease that became a global threat.

**33** There were only ten issues of the publication. It was relaunched in March 1918, following the creation of the Amazon Medicine and Surgery Society. It ceased in 1922, and had a brief third phase (now exclusively at the initiative of Alfredo da Matta), with only two issues (1941 and 1944). In this respect see Schweickardt (2011, p. 102-106) and Schweickardt and Lima (2007).

**34** This is the lecture *Notas sobre a epidemiologia do Vale do Amazonas* [Notes on the Epidemiology of the Amazonas Valley] given in October 1913 at the Monroe Palace in Rio de Janeiro, and published that same year in *Brazil-Médico*.

**35** In the 1890s, Juliano Moreira (1895b, p. 254-258; 1895a, p. 369-374) described "Bahia button" and proposed calling this ailment which had so many names around the world the "button endemic to warm countries."

**36** A doctor in São Paulo also published work on leishmaniasis in the Amazon based on a patient from that state who he had examined (RAO, 1910, p. 165).

**37** The other photos came from Hübner and Amaral. At the end of the nineteenth century, the German photographer Georg August Eduard Hübner opened the *Photografia Allemã* studio. In 1901, he joined the photographer Libânio do Amaral, and in 1906 both acquired the *Fidanza* photo studio in Belém. Hübner produced extensive photographic work involving the indigenous peoples of the Amazon region. See (among others) Schoenpf (2000).

**38** Ribeiro *et al.* (2006, p. 189-192) classify mossy foot as chromoblastomycosis, a common mycosis in the Amazon and other tropical and subtropical regions which went by many other names: Carrion's disease, Fonseca's disease, Fonseca-Carrion disease, Pedroso's mycosis, black blastomycosis, *figueira*, *formigueiro*, *sunda*, *susna*, *chapa*.... They included *espúndia* among in the names for chronic infections of the skin and subcutaneous tissue characterized by lesions which were often warty and mainly affected individuals who worked outdoors and went barefoot. In reporting the first descriptions of the disease, they omitted Thomas and da Matta.

**39** Oswaldo Cruz alludes to the reception of Thomas's communication in a letter to Adolpho Lutz from January 6, 1907. Paul-Louis Simond, Émile Marchoux, and Alexandre Tourelli Salimbeni had arrived in Rio in November 1901. Only Marchoux remained in the capital during the 37 months the Pasteur Institute mission lasted, until finally departing on May 3, 1905. On this topic see Löwy (1991, p. 195-279) and Benchimol and Sá (2005, p. 43-244).

**40** Around 60,000 people lived in Manaus. The population of Rio de Janeiro was 811,444 at that time; it was the only city in the country with more than 500,000 inhabitants.

**41** In 1898, the sector charged with public hygiene in Manaus gave rise to a General Board of Health Service, which Alfredo Augusto da Matta would command until 1912.

**42** The laboratory was installed in early 1906 on Rua Monsignor Coutinho n. 529/537, across from Antonio Bittencourt Square (Congress Square). In letters written in August and December 1905, Thomas used paper with the letterhead: "Liverpool School of Tropical Medicine, Expedition to the Amazon, 1905." Only afterwards would he print the reference to the Yellow Fever Research Laboratory or Observation Laboratory, Committee of the Liverpool School of Tropical Medicine or even the Manaus Research Laboratory.

**43** Some works of fiction portray these tragic and similar situations, starting with *Heart of Darkness* by Joseph Conrad, who worked in shipping and trading companies on the Congo River. Vargas Llosa portrays the life of Casement in *El sueño del celta*; Richard Collier places Araújo and Hardenburg at the center of a fictional history of the Amazon rubber boom: *The River That God Forgot*. On Leopold II's plans to occupy the right bank of the Madeira River in the north of Mato Grosso to create a 'Belgian Congo' in South America, see Garcia (2009).

**44** When Hans Erich Moritz Otto and Rudolf Otto Neumann visited Rio de Janeiro in 1904, the three researchers from the Pasteur Institute of Paris were already there (BENCHIMOL; SA, 2005, p. 43-244).

**45** The cause of death was entered in the São João Batista cemetery Burial Register (1931), in Manaus. Today the page with Thomas' name and other data pertaining to his death, photographed by Wallace Peters in the 1970s, is in tatters.

**46** By a decree on June 3, 1906, Leopold II established the prize, but it had not been awarded. Bauduin, Leopold III's successor to the Belgian throne, reinstated the 1906 decree via another on July 12, 1952, raising the prize from 200,000 to one million Belgian francs. The rules of the prize and the jury appointed by the minister of the colonies on July 18, 1952 are listed in Duren (1953, p. 741-763) and Arrêté Royal (1953).

**47** Wallace Peters worked in West Africa as a physician in the Royal Army Medical Corps in the 1940s, and the Colonial Development Corporation in Tanganyika during the following decade. He served as an entomologist and malariologist in Liberia, in the service of the WHO. He continued to work in tropical medicine at the Liverpool School as the Walter Myers Professor from 1965 to 1978, and at the London School of Hygiene and Tropical Medicine until his retirement in 1989 (REYNOLDS; TANSEY, 2001).

**48** Molyneux, the director of the Liverpool School, was concerned with the hundredth anniversaries of the two institutions, and informed Carlos Morel, the president of Fiocruz, of the expedition his institution had sent to Brazil in 1900. Richard Ward photographed the grave of Myers, after whom the School's chair in parasitology was named. Molyneux (1993) suggested to Morel that he put the historians at the Oswaldo Cruz House in contact with the recently-hired historian at the Liverpool School, Helen Power, who in 1999 would publish an important source for this present study.

**49** "A major obstacle here is that almost no governmental venture is carried out without the expenditure of large sums of money. Every employee wants his share, and consequently many projects cost twice what they should" (THOMAS, 1905).

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Submitted: 18/05/2017

Accepted: 24/11/2017