

The reception by French physicians of Chagas' discovery of *Trypanosoma cruzi* and American trypanosomiasis (1909-1925)

A recepção dos médicos franceses à descoberta do Tripanosoma cruzi e da tripanosomíase americana (1909-1925) por Carlos Chagas

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Abstract

As soon as they were published early in 1909, Chagas's articles on *Trypanosoma cruzi* and American trypanosomiasis became the topic of discussions in France. The description of *T. cruzi* and Chagas disease was added to parasitology textbooks as early as 1912, and elicited active research, particularly on the part of French parasitologist Emile Brumpt. He contributed towards elucidating the lifecycle of *T. cruzi* and the different ways it could infect humans. Laboratory research on *T. cruzi* was interrupted by First World War and was not resumed afterwards on the same scale, although interest in the epidemiology of Chagas disease continued.

Keywords: Carlos Chagas disease, Emile Brumpt, Félix Mesnil, American trypanosomiasis, *Trypanosoma cruzi*.

Resumo

Assim que os artigos de Carlos Chagas sobre o *Tripanosoma cruzi* e a tripanosomíase americana foram publicados em 1909, passaram a ser tema de discussões na França. A descrição do *T. cruzi* e da doença de Chagas foram adicionadas a livros de parasitologia ainda em 1912, e ajudaram a elucidar pesquisas, particularmente as que vinham sendo desenvolvidas pelo parasitologista Emile Brumpt. Ele contribuiu para o esclarecimento do ciclo de vida do *T. cruzi* e as diferentes maneiras que poderiam infectar os seres humanos. Pesquisa de laboratório sobre o *T. cruzi* foi interrompida durante a Primeira Guerra Mundial e não foi retomada mais tarde na mesma escala, a despeito do fato de os estudos epidemiológicos sobre a doença de Chagas continuarem despertando muito interesse.

Palavras-chave: Carlos Chagas, doença de chagas, Emile Brumpt, Félix Mesnil, Tripanosomíase americana, *Tripanosoma cruzi*.

The description by Carlos Chagas (1878-1934) in the winter and early spring of 1909 of a new pathogenic flagellate, *Trypanosoma cruzi*, and the disease it caused, American trypanosomiasis, did not pass unnoticed by French parasitologists. Félix Mesnil (1868-1938), one of the leading French 'trypanosomologists', published a note in the May 30th, 1909, issue of *Bulletin de l'Institut Pasteur* summarizing the descriptions made by Chagas of *T. cruzi* and American trypanosomiasis (Mesnil, 1909a). *Bulletin de l'Institut Pasteur*, a journal devoted to the review of papers judged important by the editorial board, was distributed to a wide readership of researchers. A later article published by Chagas in the June 1909 issue of *Bulletin de la Société de Pathologie Exotique* reinforced the information previously given (Chagas, 1909c). By the end of 1909, the discoveries made by Chagas had been acknowledged in France as major contributions to the fields of parasitology and tropical medicine.

However, the die was not cast. Chagas disease proved far more complex than its initial description had suggested, and very different from sleeping sickness. The general history of Chagas disease, its context and the arguments underlying nearly 25 years of controversies about it have been described in detail in several articles and books (Benchimol, Teixeira, 1994; Perleth, 1997; Coutinho, Dias, 1999; Delaporte, 1999; Stepan 1997; Kropf, Azevedo, Ferreira, 2003). In the present paper, we focus on the way Chagas disease was received far from Brazil by the French scientific community. From 1909 to around 1925, two gradually divergent lines developed about how to view *T. cruzi* and American trypanosomiasis. The first one, led by Mesnil and later endorsed by M. Blanchard¹, based only on the published literature with no personal experience or clinical context to back it up, merely relayed the descriptions made by Chagas and his co-workers. The second line, whose proponents were Brumpt and his colleagues, made a more nuanced appreciation of the biology of *T. cruzi* and the nature of Chagas disease based on their own laboratory, clinical and epidemiological studies. French parasitologists ceased being directly involved in research on Chagas disease soon after the First World War. The forum for debates and controversies had by then moved wholesale to South America. French scientists had never been genuinely involved in the complexities of Brazilian institutional life. Most of them saw Chagas disease merely as a new and complex epidemiological situation to study, a trypanosomiasis that was very different from the sleeping sickness they were familiar with. The way Chagas disease was perceived in France can thus help better define the questions and answers which ultimately led to its accepted nosography.

French scientists and their study of trypanosomes before the discovery of *Trypanosoma cruzi*

The trypanosomes of invertebrates and cold-blooded vertebrates are not usually pathogenic to their hosts. They were identified by examining smears during zoological studies. In his *Titres et travaux*, physician and parasitologist Emile Brumpt (1877-1951) wrote he had described several such parasites prior to 1909 (Brumpt, 1934). This remark, which held true for most European parasitologists of the moment, was not insignificant. It denoted widespread laboratory studies of *Trypanosoma sp.* as well as expertise in

discriminating them morphologically and defining their particular cyclic forms through microscopic examination and transfer from one animal species to another. Comparative parasitology was part of their training, as was the identification of the morphological features of hundreds of different parasites.

However, with the exception of the global presence of *Trypanosome sp.*, responsible for equine and camel trypanosomiasis (dourine, surra, mal de Cadeiras, nagana, debab, aïno etc., see Laveran, Mesnil, 1904, 1912 and note 2; Brumpt, 1903, 1904, 1913), French parasitologists' knowledge of pathogenic trypanosomes was based solely on their colonial experience of sleeping sickness in tropical West Africa. Due to the epidemic proportion of *Trypanosoma* infection in this region, several scientific missions had been sent there to study sleeping sickness and the insect vectors of human and cattle trypanosomes. The first French mission was most probably that of du Bourg de Bozas in 1903, of which Brumpt was a member (Brumpt, 1903a and cited in Brumpt, 1934). The most significant scientific mission was certainly that of Emile Roubaud (1882-1962) and colleagues between 1906 and 1909 which initiated long-term campaigns against sleeping sickness in French West Africa (Opinel, 2008a, 2008b).

These laboratory studies and missions resulted in the emergence of a group of French scientists who were well informed about various trypanosomes and the diseases they caused. These specialists were based at Institut Pasteur, around the figures of Alphonse Laveran (1845-1922), Mesnil and Roubaud, and at the Faculty of Medicine in Paris, around Raphaël Blanchard (1857-1919) and Brumpt. In addition there were physicians trained in tropical medicine, most of whom were military physicians working in French Africa in recently created overseas Instituts Pasteur (Brazzaville, Dakar) and their mobile units in the bush. Their accumulated knowledge was divulged through numerous publications and books on trypanosomes and sleeping sickness, such as the reference book written in 1904 by Mesnil and Laveran. Finally, knowledge on trypanosomes and sleeping sickness was taught at the Faculty of Medicine of Paris (Institut de Médecine Coloniale and chair of parasitology, by Blanchard and Brumpt), Institut Pasteur (Mesnil and Laveran, later by Roubaud) and Ecole d'Application de la Marine du Pharo near Marseilles, after 1906 (Opinel, 2008a).

It is therefore clear that when Chagas made his discovery of *T. cruzi* and American trypanosomiasis, a group of biologists and physicians already existed in France who had in-depth knowledge on trypanosomes and trypanosomiasis thanks to their active laboratory and clinical research. Their only experience of any human disease caused by a trypanosome was African sleeping sickness, with its well-defined pathognomonic clinical signs of damage to the nervous system associated to the recurrent presence of the parasite in the patients' blood, lymph nodes and cerebrospinal fluid. They were also very familiar with the trypanosomes responsible for various animal diseases.

French parasitologists had access to the work undertaken by their Brazilian colleagues. Indeed, *Brazil Medico* had been available at the library of the Faculty of Medicine of Paris since 1891 and at the Institut Pasteur library since 1908. *Memórias de Instituto Oswaldo Cruz* had also been available at these libraries and at that of the Faculty of Pharmacy since its first issue. German scientific and medical journals which carried many papers by Brazilian scientists were all available. However, this broad availability of scientific information from

Brazil did not mean that Brazilian parasitology was of much interest to the French institutions. The role of Institut Pasteur in the creation of Manguinhos and the importance granted to the mission by Marchoux, Salimbeni and Simond to study yellow fever in Brazil between 1902 and 1905 (Lima, Marchand, 2005; Löwy, 2001) should not mask the fact that contact between Brazilian and French scientists was sporadic and generally lacked the length and depth normally provided by coordinated institutional collaboration. Marchoux's mission, which certainly proved successful in terms of scientific collaboration between Rio and Institut Pasteur, was organized at the behest of the Gouvernorat Général de l'Afrique de l'Ouest, making it part of French colonial policy and not a request for help from the state of Rio de Janeiro. Collaborative research between the two countries on yellow fever was discontinued after the mission reached its natural end. Actually, Brazilian medical entomology looked more towards the UK and the US than to France (Benchimol, in press). Moreover, methods and concepts in Brazilian parasitology had largely been shaped by German parasitologists (e.g. Prowazek and Hartmann) and chemists (e.g. Giemsa), who spent long periods at Manguinhos on its invitation (Sá, 2005). French institutional influence may have been dominant at the Brazilian Academy of Medicine², where 32 of the 49 foreign members in 1916 were French professors of medicine, but it was certainly much weaker elsewhere on the institutional and scientific levels in view of the active policy to promote German science.

However, exchanges of information and specimens did exist between Brazil and France, denoting the existence of contact between individuals on several parasitology-related issues. As an example concerning equine trypanosomiasis, Lutz (cited in Sá, 2005) wrote in 1908 that he had sent the parasite to Laveran and Mesnil. Concerning the same disease, also known as *quebra bunda* or *mal de Cadeiras*, a letter dated June 17th, 1909, from Raoul and Albert Engelbard of Belem, northern Brazil, to Mesnil asked for his opinion concerning the administration of Atoxyl to kill the trypanosome. The description of the disease to Mesnil was made by Alphonse Bonnetterre, who was in charge of Engelbard's properties on Marajó island. Mesnil replied by confirming that the disease was the same as the one previously observed in Paraguay and asked for blood of infected horses or smears.³ Also, Brumpt obtained live parasites from Brazilian monkeys, *Trypanosoma vickersae* and *T. minasense*, from diverse Brazilian sources, plus triatomas infected with *T. cruzi* in 1912 from Piraja da Silva in Bahia, north-eastern Brazil (Brumpt, 1912). French parasitologists were thus individually rather than collectively aware of what was going on in Brazilian parasitology.

The approach taken by French scientists towards American trypanosomiasis before First World War

The bibliographical approach

Chagas's studies first came to the attention of French scientists and physicians through bibliographical notes and review papers published in French journals that dealt with parasitology and tropical diseases.⁴ Although each of them reflected a different view on tropical diseases, reference to Chagas's work can be found in all these journals. The most consistent reporting on the disease was, however, found in *Bulletin de l'Institut Pasteur*, in

which news on parasites and parasitic diseases was most often reported by Mesnil. It is worth noting that these notes and reviews were all written by parasitologists who had had no direct contact whatsoever with patients suffering from Chagas disease.

There is no mention of an American trypanosome from 1905 to 1907. Then, in 1908, Mesnil reports on the discovery of *Trypanosoma prowazeki*, a trypanosome infecting monkeys which morphologically resembles *T. gambiense* (Mesnil, 1908).

On May 30th, 1909, Mesnil published a note in volume 7 of the *Bulletin* concerning the discovery in February of that year of *Trypanosoma minasense* Chagas, a non-pathogenic monkey parasite that had been published in February 1909, and also concerning the discovery of *T. cruzi*, published on April 22 in Brazil (Mesnil, 1909 quoting Chagas, 1909a, 1909b). He mentions that Chagas suspected *Conorhinus* of transmitting a disease particular to children through nocturnal bites "produisant une forte anémie et une déchéance organique accentuée; il y a de la fièvre, de l'œdème sous palpébral et plus généralement un engorgement ganglionnaire". *T. cruzi* had been found in the blood of one child: "Nous aurons à revenir sur cette importante découverte". Mesnil had other sources than publications, as he exchanged letters with Oswaldo Cruz. In a letter to Mesnil dated September 1st, 1909, Cruz announced that Chagas had sent him microscope slides showing the two forms which, according to Chagas (Cruz did not commit himself), represented male and female gametes.⁵ In another letter to Mesnil dated November 2nd, 1909, Cruz commented he had also sent him microscope slides showing all of the intermediate forms of the *T. cruzi* cycle.⁶

In mid 1909, Chagas published a review article in *Bulletin de la Société de Pathologie Exotique* in which he described *T. cruzi* and American trypanosomiasis (Chagas, 1909c). This paper can be regarded as the message Chagas wished to convey to his fellow French parasitologists. Briefly, he explained that numerous flagellates had been found in the intestine of a *Conorhinus* caught in Minas Gerais; these flagellates proliferated in a monkey (*Hapale penicillata*) and turned into a trypanosome different from *T. minasense*, which Chagas named *Trypanosoma cruzi*. *T. cruzi* proliferated in some other vertebrates (Chagas mentions guinea pigs, rabbits and dogs, and in general "les animaux domestiques qui vivent dans la maison") where it caused a disease (not described) that was sometimes lethal. The search for *T. cruzi* in wild monkeys had been unsuccessful. Chagas had been told that a certain disease known locally as Opilação existed in Minas, which "se manifeste par une anémie très forte, accompagnée d'augmentation du volume de la rate, d'œdème sous palpébral et souvent généralisé, d'engorgement ganglionnaire ... entraînant une déchéance physique accentuée et chez les enfants un arrêt du développement". *T. cruzi* was found in the blood of a two-year-old patient and grown *in vivo* and *in vitro*. Thus "il existe au Brésil une affection à trypanosomes, désignée vulgairement ici sous le nom d'Opilação, et confondue jusqu'ici par les cliniciens avec l'ankylostomiase", a surprising conclusion indeed since the etiology of hookworm disease had much earlier been unambiguously established by Wucherer and the Brazilian physicians of the Escola Tropicalista de Bahia⁷. The role of *Conorhinus sp.* in the transmission of *T. cruzi* was discussed.

In 1910, Mesnil reported on two papers by Chagas in *Bulletin de l'Institut Pasteur*. The first dealt with his important paper of December 1909 on the sexual cycle of *T. cruzi* in

man and bugs, supported the adoption of the name *Schizotrypanum*, and confirmed the transmission of the parasite by bites. The disease was being defined with increasing precision:

Une maladie des enfants caractérisée par une forte anémie, une sorte d'infantilisme, des oedèmes soit généralisés, soit localisés, de l'hypertrophie ganglionnaire, de l'hypertrophie splénique et parfois hépatique, retard dans l'intelligence pouvant aller jusqu'à l'imbécillité. Cette maladie conduit souvent à la mort qui est précédée soit de convulsions, soit de phénomènes d'hydropisie, rappelant alors l'ankylostomiase désignée dans ce pays sous le nom de Opilçao et de Cangaury (Mesnil, 1910a).

The second note reported on the parasitic etiology of goiter associated with infection by *T. cruzi*: "On ne saurait incriminer l'eau, puisqu'on observe l'association des symptômes de la maladie à *Schizotrypanum* et du goitre chez des enfants à la mamelle" (Mesnil, 1910b). A year later, Mesnil discussed the paper by Chagas and Vianna concerning the cycle of *Schizotrypanum cruzi* in man, insisting on the sexual phase of the cycle and the role of the invasion of peripheral tissues, including heart and endocrine glands, in the symptoms developed by the patients (Mesnil, 1911). Chagas also authored a paper on the sexual cycle of *T. cruzi* in *Bulletin de la Société de Pathologie Exotique* (Chagas, 1911).

1912 was a pivotal year for the description of Chagas' disease as presented to French readers. Mesnil published two notes in *Bulletin de l'Institut Pasteur* concerning articles by Chagas and Vianna. These two papers defined Chagas' disease as a distinctive nosological entity. Mesnil summarized Chagas' description (Chagas, 1911) as "la maladie en question rappelle par ses caractéristiques les divers syndromes de l'insuffisance des glandes à sécrétion interne et plus particulièrement les syndromes de l'insuffisance thyroïdienne et de l'insuffisance rénale. C'est une thyroïdite parasitaire". Thus, a constant hypertrophy of the thyroid gland was added to the previously described symptoms. Moreover, opotherapy with thyroid extracts often proved efficient (written by Mesnil, 1912). "Dans une dernière partie, l'auteur regroupe les faits qui lui permettent de rattacher le goitre endémique de l'état de Minas Geraes à la schizotrypanosomiase". Chagas insisted there were differences between Brazilian goiter and European goiter: "Dans ce dernier, le crétinisme est une modalité de l'hypothyroïdisme tandis qu'au Brésil les troubles de l'intelligence ... relèvent directement des lésions du système nerveux" (Mesnil, 1912a). The second paper analyzed by Mesnil was that of Gaspar de Oliveira Vianna (1885-1914) on the anatomopathology of the disease in man and laboratory animals (Vianna, 1911). For Mesnil, the point was the colonization of cardiac fibers, the thyroid and sexual and adrenal glands by a round parasite with a rod-shaped centrosome. An acute inflammatory reaction and subsequent necrosis were observed around sites of parasite proliferation. "L'altération profonde de la thyroïde explique les phénomènes de goitre sur lesquels Chagas a vivement attiré l'attention" (Mesnil, 1912b).

Annales d'Hygiène et de Médecine Coloniale did not publish much on American trypanosomiasis until 1912. Then, a large review was published by Maurice Blanchard, *médecin aide major des troupes coloniales*. Blanchard mainly worked in Africa and had become a specialist on sleeping sickness. As he summarized it, Chagas disease was dominated by the destruction of the thyroid and adrenal glands. Acute forms in childhood were most often lethal. When patients survived, they suffered paralysis, heart problems and cretinism.

Blanchard stressed the increased size of the thyroid gland in infected infants, as well as the swelling of their faces and the pseudo-myxoedematous aspect of their skin. According to Blanchard, goiter was always present in chronic forms, and the nervous signs were reminiscent of those observed in African trypanosomiasis. Blanchard, the first physician to write a review on Chagas disease, had clearly distorted the original message of Chagas's and Vianna's papers by exaggerating the frequency and severity of the symptoms.

Chagas' disease in French medical education

Were the nosography and etiology of Chagas' disease taught in specialized courses at university? Lectures on parasitology delivered by Mesnil at Institut Pasteur after 1909 included one on trypanosomes in general, one on sleeping sickness, but none on American trypanosomiasis. *T. cruzi* and Chagas' disease were only briefly mentioned in the *Cours de Parasitologie de l'Institut Pasteur* once it resumed in 1921 after the interruption of its publication since 1914.⁸

The 1912 edition of *Trypanosomes et trypanosomiasis* by Laveran and Mesnil included a 16-page-long chapter on American trypanosomiasis, succeeding the 82 pages devoted to sleeping sickness (Laveran, Mesnil, 1912). The chapter basically repeated the content of the notes in the *Bulletin de l'Institut Pasteur* discussed above. Chagas' disease was a parasitic thyroiditis and its clinical signs were those associated with the faulty functioning of the thyroid gland. Behavioural and neurological signs were due to lesions of the nervous system caused by parasites proliferating in the brain. Other physicians also occasionally learnt of Chagas disease and some of its clinical signs. For instance, the nosological value of the radiological signs in the chronic cardiac forms of Chagas' disease (appreciation of heart size anomalies) had been sufficiently documented to be presented by Henrique de Toledo Dodsworth (1865-1916)⁹ at the 7th International Congress of Radiology held in Lyon (France) on July 27th-31st, 1914, in a lecture entitled "Contribution radiographique sur une nouvelle trypanosomiase humaine, la trypanosomiase sud-américaine ou maladie de Chagas" (Toledo Dodsworth, 1914).¹⁰

It would therefore appear that the existence of Chagas' disease could have been known to physicians, although precise information on the disease did not spread much beyond parasitology circles and small groups of specialists, and certainly did not come to the attention of most general practitioners.

The experimental approach

Emile Brumpt was certainly the dominant figure in France when it came to Chagas' disease and experimental studies on *T. cruzi*. Because he was a researcher and a physician, he did not accept unquestioningly what Mesnil, a zoologist, had so readily taken as given. Human and animal trypanosomes and trypanosomiasis were the topic of more than one third (47 out of 130) of the papers published by Brumpt before First World War. Research on *T. cruzi* and its vectors was a dominant topic of choice between 1909 and 1914, with 18 papers out of a total of forty during that period. The World War interrupted research then in progress in São Paulo, which was not resumed afterwards. After the war, Brumpt's

interest in trypanosomes declined. He published few (13) papers on the description of new animal parasites and on the testing of new drugs between the two world wars. Discussion of *T. cruzi* and Chagas disease had been demoted to review papers and book chapters. Brumpt's direct personal involvement in *T. cruzi* studies in Brazil (see below) thus lasted five years.

The 1913 edition of Brumpt's treatise on parasitology

Brumpt's attitude was quite different than Mesnil's in how he presented Chagas' disease and *T. cruzi* in the second edition of his treatise on parasitology (Brumpt, 1913). The treatise was written after Brumpt had completed his first experimental work on the cycle of *T. cruzi*, before he visited Brazil. The chapter on American trypanosomiasis can be divided into two parts. The first concerned the biology of the parasite. Brumpt had no doubt about the existence of a new human blood parasite, *Trypanosoma cruzi*. However, due to his previous studies on trypanosomes, he was sceptical about the sexual cycle proposed by Chagas. The theories of the German school of parasitology had played a critical role in the interpretation of Chagas' results (Delaporte, 1999; Sá, 2005). Brumpt's studies on the *T. cruzi* cycle came to be replaced in the general effort by most European and Brazilian scientists to overcome Schaudinn and Prowazek's theories on the sexual cycle of trypanosomes and, more generally, the opinion that malaria was the only paradigm for parasitological studies. Brumpt's contribution to the definitive elucidation of the *T. cruzi* cycle was also facilitated by his earlier extensive studies into the biological cycle of several other animal trypanosomes, including one affecting the South American monkey, *T. minasense*, identified by Chagas in 1909. Brumpt experimentally defined the cycle of *T. cruzi* in man and insects, showing that it did not involve gametes or fecundation, a significant breach in Chagas's proposed system. As a consequence, he did not mention the sexual cycle postulated by Chagas in the treatise, and reported instead on the asexual cycle he had evidenced in *T. cruzi* obtained from Bahia via Piraja da Silva. Also, unlike Chagas, Brumpt and M. and P. Delanoe were unable to grow the parasite *in vitro*. Brumpt's opinion that *T. cruzi* entered the human body through the faeces of *Conorhinus* deposited in the vicinity of ocular mucosa (Brumpt, 1912) has largely been discussed elsewhere (Delaporte, 1999). It certainly conflicted with Chagas's opinion that *T. cruzi* penetrated by insect bites, in much the same way as occurred in malaria, but was in agreement with the findings of other Brazilian researchers such as Arthur Neiva.

The second part of the chapter of Brumpt's treatise concerned the clinical signs of American trypanosomiasis. Brumpt had not yet had any contact with the medical reality of Brazil's parasitic diseases. His description of acute cases fitted the 1909 description by Chagas. However, when it came to chronic cases, Brumpt remained elusive and did not openly endorse the clinical description of chronic American trypanosomiasis. Thus, the clinical description of American trypanosomiasis offered by Brumpt in his treatise was in line with Chagas's, although he clearly held some reservations, referring to Chagas' opinion with some circumspection: "Chagas est convaincu qu'une foule de cas de paralysie, de déchéance intellectuelle, d'infantilisme, de crétinisme relèvent de cette trypanosomose".

The background to Brumpt's Brazilian experience

It could be said that Brumpt reached São Paulo with general expertise in trypanosomes and particular knowledge of *T. cruzi* which challenged the initial descriptions of the parasite's cycle made by Chagas. Prior to his move to São Paulo, Brumpt had also learned from Pasteurian researchers that the parasites observed in the thyroid of animals infected with *T. cruzi* were not an evolutionary form of *T. cruzi* but belonged to an altogether different parasite species, namely *Pneumocystis carinii* (Delanoe, Delanoe, 1912), an error that Chagas (1913) subsequently acknowledged and explained. Brumpt had also shown that infected triatomas could be found 1000km away from Lassance, in Bahia for instance (Brumpt, 1912). He was also aware, through contact with Brazilian colleagues such as Piraja da Silva and Rocha-Lima and on the basis of published literature, that a controversy already existed concerning the histological studies and the proposed link between goiter and *T. cruzi* infection. Several new problems appeared concerning the diagnosis and epidemiology of the disease, the distribution of the vector(s) and the link between organ infestation and clinical signs. If he had not been aware of the existing discrepancies between published conclusions and bedside observations, he was most probably informed of them upon his arrival in São Paulo.

Actually, medical files show that as late as 1915 at least, the nosography of the disease was still being built up in Brazil. The medical documents kept at the archives of the Fundação Oswaldo Cruz¹¹ contain about eighty files of patients from the former Hospital Oswaldo Cruz, now Hospital Evandro Chagas (opened in 1918) and patients treated at Santa Casa de Belo Horizonte after 1909. The former patients (predominantly adults diagnosed with 'chronic forms' of the disease) were from different parts of Minas Gerais. The latter patients (mostly children below five diagnosed with "acute cases of Chagas' disease") were nearly all from the Lassance area, the place where the first case of Chagas' disease was identified in 1909, which was directly connected to Belo Horizonte by a 220km long railroad track. The subdivision of acute and chronic cases is used as a guideline to appreciate the criteria used by physicians and the symptoms they entailed. The files of 13 acute cases were kept.

The disease affected five-month- to five-year-old children, of whom two died a few days after their admission. *T. cruzi* was systematically searched for in the blood of the patients and its presence was noted in 12 out of 13 patients. Attention was paid to the children's home environment: all but two came from a coffee plantation and lived in an area rich in *Triatoma* infected by *T. cruzi* but believed to be free of malaria; the two exceptions suffered from malaria and no mention was made of their living conditions. All the patients displayed rather unspecific clinical signs, such as moderate fever, enlarged lymph nodes, particularly the axillary and inguinal nodes, and moderately enlarged liver and spleen. Mental retardation is mentioned in two cases. The presence of an enlarged thyroid is mentioned three times but may have been a symptom prior to infection (EMN case). Other clinical signs due to a possible thyroid dysfunction were not constant either: the mention of myxoedema-like skin was mentioned in five of the 13 cases. By contrast a distinctive swollen face was described as a striking and constant clinical sign, as noted by Chagas. More importantly in the context of the present study, physicians described with

great precision a major unilateral palpebral edema extending over one eyeball. It was sometimes associated with acute conjunctivitis. Irritating skin lesions near the affected eye were noted in the latter cases and attributed to *Triatoma*. The marked occurrence of a swollen face associated with fever seems to have prompted the parents to seek medical attention. It thus comes out that Brazilian physicians tended to suspect acute Chagas' disease when children displayed a typical swollen face. The unilateral palpebral edema was impressive enough to be described in detail. It is unclear, however, whether this sign was recognized as an early indication of infection by *T. cruzi* as Romana did in 1935. The parasite itself was consistently found in the blood of these patients and its presence finally led to the diagnosis of 'American trypanosomiasis', or 'Chagas' disease', both expressions being used. In contrast, signs of thyroid failure were not constant and appear to have been of little nosographical value for the physicians.

An analysis of the files reporting chronic cases in adults reveals a different story. The first striking evidence is the absence of a clear-cut rationale for diagnosing one Chagas' disease: the disease is said to be the 'cardiac form' or 'neurological form' in a local context favoring Chagas' disease, but without making mention of any positive evidence for an earlier or ongoing *T. cruzi* infection. One cannot exclude the possibility of the diagnosis having previously been made elsewhere. It is more likely, however, that the diagnosis of chronic Chagas' disease in adults had largely been based on presumptions: indeed, as if there were indeed some ambiguity concerning its diagnosis, the words *moléstia de Chagas* [Chagas' disease] were written across the top and first page of most of the files in a different hand from the rest of the document. This suggests that someone other than the physician who made the observations had made the diagnosis. Anyhow, assuming the cases were cardiac forms of chronic Chagas' disease, patients suffered from a broad range of ordinary, non-specific clinical signs, such as palpitations, arrhythmia, extra-systoles, effort problems, anxiety, enlarged heart evidenced by x-ray and heart failure.

Several cases of sudden death were reported after which heart lesions were physically described. Scant mention was made of other symptoms, such as goiter or cretinism, a fact which can be explained by the specific focus put on heart disease or, more simply, by their absence. Only two cases were not 'cardiac forms'. It cannot be decided from the data if heart problems were prevalent among people living in *T. cruzi*-infested areas. The files might have been selected somehow, since they nearly all concerned patients suffering from cardiac forms of the disease even though other forms were known at the time. In that respect, clinical papers published during the same period of time show that cardiac forms accounted for about 80% of the patients diagnosed as having 'chronic Chagas' disease'. Physicians also searched for clinical signs or biological parameters (blood and urine samples) that could help shape the features of Chagas' disease in adults. Cezar Guerreiro (1912) searched for urinary parameters that could be associated to the disease and concluded that none existed. In the cohort he studied, he noted the absence of goiter and the difficulty of studying pure cardiac forms of the disease, most being associated with other clinical signs. Eliezer Dias (1912), from Belo Horizonte, was well aware of the difficulty in studying 'pure' cases of Chagas' disease: out of the 57 cases he studied, only 19 did not have other parasites, in contrast to the others with various helminthic diseases and malaria.

The author, who noted the increased frequency of eosinophiles (5%-12%) and circulating mastocytes (0.4%), wrote that the enlarged thyroid and its associated symptoms could also be due to malaria and hookworm disease.

It thus appears from the study of medical files that Brazilian physicians were well aware that the coexistence of several diseases in the same patients obscured the significance of the signs they presented. They were aware that 'pure' forms of the disease were needed. The diagnosis of chronic cases was severely impaired by the lack of specific tests or clinical signs. Since *T. cruzi* was rarely observed in the blood of chronic patients, the diagnosis of a chronic form of the disease relied on a set of assumptions. All this opened to question the interpretation of these very diverse symptoms as deriving from a single infection. Moreover, the observations of acute cases did not consistently lead to the notion of dysfunction of the thyroid gland.

This clinical overview shows that the nosography of Chagas' disease, particularly its chronic forms, was, at the time Brumpt was in Brazil, not as firmly established as Chagas (followed by Mesnil in France) had suggested. Brumpt could not have been unaware of the developing and in-flux state of knowledge concerning Chagas' disease. His travels and observations kept in his notebooks and recorded in photographs taken during the two years he spent in Brazil (1913 and 1914) as a professor of parasitology in São Paulo were clearly designed to acquire first-hand information on Brazil's parasitic diseases so he could make up his own mind about them. Brumpt's contribution to the development of knowledge on Brazilian diseases has already been described (Opinel, Gachelin, 2005), while his relationship with the Brazilian scientific community and its institutions is currently under study.

Brumpt's experience in Brazil

Here we will focus only on the way Brumpt approached Chagas' disease *in situ*. Four steps in his work can be identified.

The first step taken by Brumpt was to improve diagnosis by introducing a technique known as xenodiagnosis. Actually, identifying *T. cruzi* in the blood of putative patients was not an easy task except in acute cases where *T. cruzi* was easily observed in the blood. Few or no trypanosomes circulated in the blood of chronic patients, which made their diagnosis almost impossible. As a consequence, acute cases of infection were unambiguously diagnosed whereas most chronic cases remained uncertain. To overcome this limitation, laboratory animals in which *T. cruzi* could proliferate, mainly guinea pigs, were injected with suspect blood to amplify *in vivo* the number of parasites and make them visible under the microscope. The technique was slow, controversial and inefficient. Brumpt introduced a practice he had developed earlier to Brazil, whereby uninfected triatomas were allowed to suck the blood of patients. If the patient was infected, *T. cruzi* proliferated in the insect and was recovered in huge numbers from the animals after just a few days. The introduction of Brumpt's test, known as xenodiagnosis, was important for diagnosing chronic patients. Though still revealing only a fraction of the infected patients, xenodiagnosis successfully identified the presence of *T. cruzi* in some of them. It continued to be used until the introduction of PCR in the late 1990s.

The second step, the distribution of vectors and the disease, reflected Brumpt's interest in medical entomology. He described several potential vectors of *T. cruzi* in Brazil and studied the virulence of *T. cruzi* strains propagated by different insects in various animals. The description of infected triatomas in areas with no human presence for dozens of kilometres around prompted him to conclude that the natural mammalian host of *T. cruzi*, i.e. armadillos, lived in those areas and that man was a secondary, accidental host.

Epidemiological studies on the relationship between goiter and Triatomas, the third and little-known step, can be seen from Brumpt's notebooks, photographs and letters. A visit with Mello (dates unknown), a Brazilian physician from São Paulo, to what they called 'vallée des goitreux' in Pantano, in the vicinity of Bauru (Figure 1), was originally intended for the study of the vector of cutaneous leishmaniasis, but turned into a study of the epidemiology of goiter. Were Brazilian goiters, as proposed by Chagas, different from European goiter and always associated with the presence of infected triatomas? In other words was goiter a clinical sign of Chagas' disease? The results expressed in the letters from Mello to Brumpt were clear: goiter was by no means associated with the presence of *T. cruzi*.¹² It could have an infectious origin – such a hypothesis was quite frequently expressed at the time¹³ – but if so, the infectious agent in Brazil was not necessarily *T. cruzi*. Obviously, a link between trypanosomes and goiter as a unique trait of patients in the

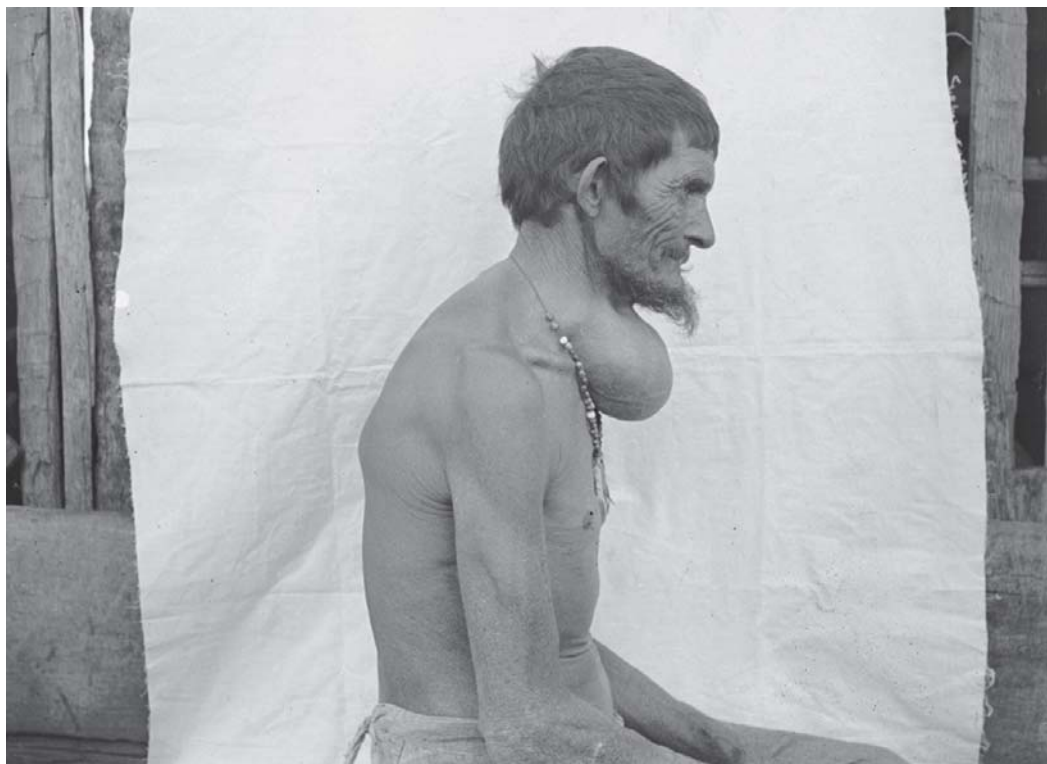


Figure 1: A middle-aged man with prominent goiter. Case 17, "Vallée des Goitreux", near Pampano, São Paulo (Brumpt, 1914). The photograph was used by Brumpt in his treatise on parasitology (1922 ed.) with the caption: "Homme présentant un goitre endémique n'ayant aucun lien étiologique avec le *Trypanosoma cruzi*. Environs de Bauru (Brésil)"

Lassance area could not be excluded, but it would have been wrong to generalize this conclusion to all goiters. Moreover, Brazilian goiter did not differ from European goiter. The conclusion was that goiter was not pathognomic of Chagas' disease in Brazil.

The last step was the visit paid to Carlos Chagas in Lassance in July 1914. In the knowledge of Mello's results, Brumpt visited the region of endemicity, described its 'epidemiological landscape' in his notebooks and took numerous photographs. The description of the mountains around Lassance notes that there was vegetation infected with triatomas found in the wild (Figure 2). The local houses, particularly those made out of wood and cob, in which triatomas proliferate, were extensively photographed (Figure 3). Interestingly they were no different from houses in the so-called 'vallée des goitreux' in Goitre valley in Pantano, also photographed by Brumpt. More informatively, Brumpt was given the opportunity to see patients treated by Chagas and to photograph them, mostly in groups. However the pathological features they displayed are hardly visible, except for the evidence that they were profoundly disabled (Figure 4). Only the young patient named Gregorio was photographed close enough for his retarded condition to be clearly visible, although his overall aspect was not at all indicative of any particular etiology (Figure 5). We have not uncovered the commentaries made on Brumpt's visit to Lassance, if such commentaries exist. The notebook only contained the list of the photographs Brumpt took.



Figure 2: Photograph of the Serra do Cabral mountain range (Brumpt, 1914). An almost identical photograph of the same ecosystem was included by Brumpt in his treatise on parasitology (1922 ed.) with the caption: "vue du point de la Savane des Monts de Cabral (800 m. alt., 12km. de Lassance, Brésil) où fut trouvé *Triatoma chagasi* (cliché E. Brumpt)"



Figure 3 : “Chaumières à triatomas. Environs de Lassance (Brésil)” (Brumpt, 1914). This is one of the photographs taken by Brumpt in Lassance illustrating the kind of housing where triatomas proliferated



Figure 4: Photograph entitled “Chagas with a group of patients. Lassance”, taken by Brumpt in 1914. Actually, the man in the picture was not Chagas



Figure 5: Two young chronic patients, including Gregorio (left), treated by Chagas. Photograph taken by Brumpt in 1914. Three similar pictures were used by Brumpt in his treatise on parasitology (1922 ed.) with the caption: "Maladie de Chagas. Formes chroniques. Enfants soignés par C. Chagas à Lassance (Brésil)"

Post-First World War: latent opposition between Chagas and Brumpt

First World War cut short Brumpt's stay in Brazil. It also interrupted all research on *T. cruzi* in France. Brumpt, however, made a kind of summary of the work he had carried out during his stays in Brazil at a lecture he delivered in 1919 at the Academy of Medicine in Paris (Brumpt, 1919). His perception of the disease can be deduced from the changes he introduced to the 1922 edition of his treatise on parasitology (Brumpt, 1922).

Brumpt had become France's leading expert on Chagas' disease, a position strengthened by his studies undertaken in Brazil. His lecture was largely based on his observations of the biology and distribution of various Reduviidae, the family Triatomas belong to, as well as on the ability of *T. cruzi* to proliferate in a diversity of other insects and the role these insects play in spreading *T. cruzi*. The question asked by Brumpt dealt with the observed discrepancy between the large geographic distribution of vectors infected with *T. cruzi* in Brazil, Venezuela etc. and the apparently very narrow distribution of the disease. He concluded that because of their different ability to transmit infectious *T. cruzi*, the diversity

of vectors, could explain this discrepancy, along with some ill-defined climatic traits. Actually, Brumpt also pointed to the small number of well-defined cases of Chagas' disease, and therefore to the marginal quantitative importance of the disease.

The chapter of the 1922 treatise devoted to American trypanosomiasis, or *maladie de Chagas*, is indicative of Brumpt's ambivalence. The chapter devoted to *T. cruzi* was primarily the same as in 1913, with the exception that transmission by faeces was emphasized and transmission by biting (referring to Chagas's opinion) was considered minor. The description of the disease was even less emphatic than in the 1913 edition, although the latter had already been rather cautious. The notion of parasitic thyroiditis had ceased to be central and was now the opinion of "certains auteurs": "peu d'auteurs ont suivi Chagas sur ce terrain ... le type myxoedémateux est difficile à distinguer du goitre endémique". Clearly, the association of hypothyroiditis with *T. cruzi* infection was not, in Brumpt's view, the most obvious conclusion to draw. The text goes on to point out other differences. Children may now survive acute infection without any apparent sequelae. The chronic stages involved a great variety of clinical signs but diagnosis remained difficult to establish and Brumpt added his voice to others concerning the wrong attribution of signs (e.g. pseudo-myxoedema) to Chagas' disease. As for the prognosis of the disease, Brumpt opposed Chagas' opinion of the extreme severity of the illness, concurring, rather, with the more widely-held view whereby the prognosis is good except when organic lesions have progressed (heart failure). Brumpt insisted on the difficulty of establishing a diagnosis "en l'absence de diagnostic étiologique précis établi par la découverte de trypanosomes dans le sang ou dans les tissus, il faudra se montrer très réservé" (p.282). The photographs were also informative: Brumpt showed the epidemiological landscape and the houses where barbeiro bugs proliferated. He depicted a man "avec un goitre endémique n'ayant aucun lien étiologique avec le *Trypanosoma cruzi*" (Figure 1). He produced several photographs of his own depicting groups of profoundly disabled children with "formes chroniques. Enfants soignés par C. Chagas à Lassance". The choice of this photograph was particularly surprising in view of the wealth of documents he used from his missions and the precision of the details evidenced for the reader. Actually, Brumpt did not focus on any detail of the diseased bodies, as if none among these patients that were presented to him, including Gregorio (Figure 5), showed clinical signs Brumpt could accept as being pathognomonic of American trypanosomiasis. Through his photographs, Brumpt pointed to the principal difficulties met in describing chronic forms of Chagas disease and later in accepting the disease *per se*: the extreme breadth of the symptoms supposedly suffered by patients, but which could equally be attributed to other diverse causes. Thus, in contrast to sleeping sickness and its neurological signs, or cutaneous leishmaniosis with its characteristic lesions, or even malaria with evidently enlarged spleen and liver, chronic forms of Chagas' disease could not be unambiguously represented. Brumpt concluded by mentioning the low frequency of cases. In the absence of archive data, it is difficult to determine from Brumpt's writings alone whether he agreed, albeit partially, with Chagas' opinion that a single disease could cause so many symptoms. He clearly referred to Chagas' descriptions and assertions in his books and articles but did not commit himself in his discussions of *T. cruzi*, Chagas and Chagas' disease. In any case, the present paper is not intended to describe

the participation Brumpt could have had in the debates which were then underway. A convergent line of evidence suggests that Brumpt minimized his contact with Chagas and Manguinhos.

An interesting piece of information that confirms the differences between Brumpt and Chagas was produced by Chagas himself. Chagas had few opportunities to express his views on American trypanosomiasis in Europe. The text of a lecture he gave at Institut Pasteur on October 23rd, 1925, on the joint invitation of the Institute and Faculté de Médecine, Chaire d'Hygiène et de Bactériologie was published in 1926 (Chagas, 1926). Brumpt attended the talk along with Mesnil, Albert Calmette (1863-1933), Emile Roux (1853-1933) and Joseph Babinski (1857-1932). In other words, the cream of Paris's physicians attended the presentation, which was subsequently publicized: the topics covered by Chagas were reported by Brumpt on October 29th, 1925, in *La Gazette du Brésil* (Brumpt, 29 oct. 1925), while on October 24th, 1925, an anonymous contributor wrote the article "Un grand savant à Paris. Le Docteur Chagas. Il a fait hier une conférence sur la maladie qu'il a découverte" in *Le Matin*, which came accompanied by a photograph of Carlos Chagas (Anonymous, 24 oct. 1925).

To the best of our knowledge, this was the first time the existence of Chagas' disease would have reached a wider, non-scientific readership. Chagas offered the public and later the readers a coherent view of three aspects of the disease: the existence of a neurotropic strain of *T. cruzi*, the existence of hereditary transmission of *T. cruzi*, and the host of the parasite in the outside world, all of which was preceded by a general overview of the disease. On the whole the paper was intriguing for its mixture of bald statements and a clearly defensive stance. The paper states several points as established fact which had already been shown by others either to be incorrect or marginal. In the overview, he states that the number of infected people in a given house was proportional to the number of infected triatomas; that *T. cruzi* was transmitted by biting and "c'est la présence du parasite dans les glandes salivaires qui détermine le pouvoir infectant de l'hématophage ... le mécanisme normal de l'infection est la piqûre de l'insecte"; and that it was justifiable to create a new genus, *Schizotrypanosoma*. The cardiac forms are described in great detail, but emphasis is rather put on the nervous forms, with Chagas insisting on the role of *T. cruzi* in mental retardation, cretinism, etc., which were frequently observed where *T. cruzi* was endemic, and defects in thyroid functions which contributed to the symptoms of the disease: "j'ai acquis la conviction que le goitre est aussi un symptôme de cette maladie ... je n'ai connaissance d'aucune région de l'intérieur du Brésil dans laquelle le goitre sans la présence du Triatome, soit rencontré".

The frequency of mental retardation and neurological signs in infants is attributed to hereditary transmission of *T. cruzi* from mother to child. Chagas says that cystic forms of the parasite were transferred from the mother's bloodstream to the fetus and that the transplacental transfer of *T. cruzi* would explain the high frequency of early nervous forms and mental retardation, due to the early destruction of the brain. Finally, Chagas proposes that the armadillo was the reservoir. It can thus be concluded that by and large Chagas adhered to the malaria model for transmission (as well to that of African trypanosomiasis) while also maintaining the clinical description he had given of the disease in 1912. Whatever

the scientific and psychological¹⁴ reasons which compelled him to describe the biology of *T. cruzi* (except its sexual cycle) and the disease in more or less the same way as he had before First World War, the contents of his talk were clearly the scientific message that Chagas wanted to convey to French parasitologists, even at a time when a heated debate still abounded in South America concerning the epidemiology, frequency, severity and even the existence of American Trypanosomiasis.

The 1922 edition of Brumpt's treatise actually closed the pre-war period more than it opened up something new. The 1925 lecture by Chagas had set his clear-cut opinion on the meaning of his discoveries. If we set aside the issue of parasitic thyroiditis (hypothyroidism caused by the parasite remained Chagas' main clue to most clinical signs and still underpinned the rationale of his lecture), a comparison between Brumpt's and Chagas's texts would suggest that their differences largely resided in the weight attributed to clinical signs and the possibility of diverse etiologies. Deeper, perhaps, and more meaningful are Brumpt's reservations and *caveat*, in stark contrast with the sharply affirmative form adopted by Chagas, suggesting that the French parasitologist could not write the chapter differently, although he was most probably convinced that the symptoms displayed by chronic cases did not have *T. cruzi* infection as their only etiology.

In 1914, Brumpt was on the way to sorting out the different clinical signs associated with chronic Chagas disease and attributing them to different diseases, such as malaria, endemic goiter or hookworm disease. In that respect, he was in tune with the Brazilian clinicians describing acute and chronic cases (see note 9). It would have been premature for Brumpt to draw any conclusions on the basis of his own observations. Thus, maintaining his intellectual stance, Brumpt set forth what he had confirmed by himself and with co-workers, and introduced enough nuances in the texts to make the reader understand that things were not entirely clear or had not been definitively established. The debate, since a debate indeed existed, had remained civil throughout.

A progressive loss of interest by most French researchers

From the beginning of First World War, active experimental and epidemiological research on Chagas' disease passed entirely into the hands of South American scientists. The debate which raged over the existence of the disease and the importance of Chagas' contribution to the discovery of *T. cruzi* was noted by French scientists, but they did not participate in it. In 1925, Joyeux (1925) commented on the conclusion reached by the Commission whose task had been to settle the conflict between Chagas and his opponents, which had concluded in favor of Chagas, despite some reservations concerning the extent of the disease. But by now the French were no longer active participants in the history of Chagas' disease. The ambivalent wait-and-see attitude of Brumpt, which remained in the 1927 edition of his treatise, was typical of the French parasitology community. The obituary of Carlos Chagas written by Félix Mesnil (1934) is a good example of the attitude shared by most French parasitologists towards his work: "Cette découverte suscita un grand enthousiasme qui déterminait, comme c'est souvent le cas, une forte réaction: celle-ci alla jusqu'à la négation du rôle causal du trypanosome Il s'était fait trop laissé influencé

par l'école protozoologique allemande Quoi qu'il en soit, l'essentiel reste: la maladie de Chagas existe; elle est bien due au trypanosome découvert par lui". French physicians were made aware of the developments by occasional notes, particularly when the clinical meaning of Romana's sign was elucidated in 1935. The definitive nosological scheme of Chagas' disease was made known to French scientists around 1935-36.

The absence of significant French publications on Chagas' disease after the Great War did not mean Brumpt and others had lost interest in the matter. A large number of letters concerning Chagas' disease are present in Brumpt's archives.¹⁵ The majority of them were indicative of an active exchange of letters with physicians working in Argentina, Uruguay, Chile, Colombia, Venezuela and Mexico. No correspondence on Chagas' disease was exchanged with Brazilian scientists. Brumpt's correspondents were all searching for the possible vectors of *T. cruzi*, their level of infestation by the parasite, and the number of well-characterized cases of Chagas' disease in their respective countries. From Brumpt's answers, it can be concluded that he had in mind that the frequency and severity of the disease reduced gradually from Brazil to Mexico in the north and Chile in the south. The same archives contain the text of several lectures given in Europe and South America and concern overviews of Chagas' disease, its epidemiology, etc.¹⁶ Some late letters (1938) concern the use of a drug synthesized by Bayer Leverkusen (Bayer 7602) in attempts to cure Ms. Herr, who was working with Brumpt at that moment and was contaminated with *T. cruzi*. This implies at the very least that the parasite was being manipulated in Brumpt's laboratory in 1938. The absence of letters from Brazil is rather puzzling, as are Brumpt's visits to Brazil without visiting Manguinhos.

It can be concluded that French parasitologists in general had their interest in *Trypanosoma cruzi* awakened as soon as its description was published. Before First World War, they made significant contributions to establishing the biology and epidemiology of the parasite, its cell cycle, etc. American trypanosomiasis was at first an exciting new disease, but their interest soon clearly dwindled (with the remarkable exception of Brumpt), presumably because the disease appeared to be restricted to certain areas of Brazil, seemed too ill-defined as a clinical entity and because they had no opportunity to observe acute or chronic patients infected with *T. cruzi*. Also, and probably most importantly, malaria and African trypanosomiasis were the major tropical parasitic diseases they were facing: after all, most French parasitologists active on the field were military physicians whose duties took them to Africa and South-East Asia rather than to Minas Gerais in Brazil.

NOTES

¹ Homonymous to Raphaël Blanchard (1857-1919), professor of parasitology at the Faculty of Medicine in Paris, Maurice Blanchard was an army physician who became an authority on African tropical diseases after First World War and later head of the French colonial services.

² Determined by the authors from the lists of members and foreign members of the Brazilian Academy of Medicine kept at the library of the Academy, Rio de Janeiro. *Annaes de Academia de Medicina*, 1912-1916.

³ AIP, fund SPE2, file Médecins et Scientifiques Brésiliens, 1909-1922, folder Raoul and Albert Engelbard.

⁴ The *Archives de Médecine Navale et Coloniale*, founded 1864 and the *Annales d'Hygiène et de Médecine Coloniale* founded 1898, expressed the views of colonial physicians. The *Revue d'Hygiène et de Police Sanitaire* founded 1879 dealt more with hygiene problems and rules. The *Archives de Parasitologie* founded

1895 reflected R. Blanchard's opinions. The *Bulletin de l'Institut Pasteur* founded 1903 was a purely bibliographical journal in which the editorial board summarized the papers it judged important. Finally, the *Bulletin de la Société de Pathologie Exotique* founded 1908 was a journal devoted clinical practice and research in tropical areas.

⁵ AIP, fund Mesnil, box 09.

⁶ AIP, fund Mesnil, box 09.

⁷ The polysemy of the word Opilação would be worth investigation.

⁸ AIP, fonds Ramon, boîte RAM.46. Summary of courses from 1911 until the current day are kept in the archives.

⁹ Henrique de Toledo Dodsworth (1865-1916) member of the Brazilian Academy of Medicine in 1911, professor of medical physics at the Faculty of Medicine of Rio de Janeiro. He created the Instituto de Raios X e Eletricidade Médica in 1911 in Rio de Janeiro.

¹⁰ The participation of Brazil in the manifestations in Lyon was significant. Four Brazilian physicians attended a meeting of 66 members. Two papers were presented in addition to one dealing with radiography and Chagas' disease. They concerned X-ray departments and clinical radiography and the use of X-rays to treat Chyluria and Hematochyluria, two helminthic tropical diseases. In addition, several clinical radiographies taken at Instituto de Raios X e Eletricidade Médica of Rio de Janeiro were displayed at the Lumière laboratories, Lyon. A film describing the 'extinction' of yellow fever in Brazil was shown by Theophilo Torres at the Exhibition Internationale Urbaine, where Brazil had a stand.

¹¹ Fundo Instituto Oswaldo Cruz, seção Hospital Evandro Chagas, caixa 1, 1909-1922.

¹² AIP, fund Brumpt, box BPT.D1, letters from Mello to Brumpt, 19 mar. 1914 and 24 jun. 1914.

¹³ As a contemporary example: Dr. Jouveau-Dubreuil (1911, p.203) comments that 25% of the population had goiter but not cretinism. He mentioned the possibility of an infection by *Entameba histolytica*, excluded it, and mentioned the Grassi hypothesis, according to which "le goitre serait dû à la présence d'un agent infectieux dans les maisons, humides, sales et obscures". This description is basically used to describe poor housing in Minas, as it could most probably be used in the entire world. The conclusion was that poverty equals goiter.

¹⁴ It can easily be imagined how distressing an experience it would be to appear before a commission charged with establishing one's contribution to a discovery, even if the validity of one's contribution were finally recognized.

¹⁵ AIP, fund Emile Brumpt, BPT, files B10, B11, D7, D17.

¹⁶ AIP, fund Emile Brumpt, BPT, files B10, B11, D1, D7, D11, D15, F2, GF1, H.

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