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Leishmaniasis: historical configuration in Brazil with an emphasis on the visceral disease, from the 1930s to the 1960s

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Abstract: The first cases of cutaneous and mucocutaneous leishmaniasis in the Americas were described in São Paulo in 1909; visceral leishmaniasis was only found in Brazil in 1934, by a Yellow Fever Service pathologist. The historical processes related to these forms of leishmaniasis gained institutional strength in the 1930s. While the Leishmaniasis Study Commission solidified the concept of American tegumentary leishmaniasis, the American Visceral Leishmaniasis Study Commission (headed by Evandro Chagas) gave rise to the Institute of Experimental Pathology for the North (1936) and the Large Endemic Disease Study Service (1938). Visceral leishmaniasis gained importance in northeastern Brazil in the 1950s, and control measures against its vectors using dichlorodiphenyltrichloroethane (DDT) followed in the wake of the malaria campaign. They also targeted dogs (which were killed en masse) and humans, who were treated with antimonial drugs. Large-scale undertakings in Brazil's hinterlands after the 1964 civilian-military coup transformed cutaneous and mucocutaneous leishmaniasis into a serious problem in Amazonia and other regions. Brazil and other countries saw a resurgence of all forms of leishmaniasis in rural and urban areas because of environmental changes, human migrations, chaotic urban growth, and other socioeconomic processes.

Keywords: History of cutaneous and mucocutaneous leishmaniasis in Brazil. History of visceral leishmaniasis in Brazil. Evandro Chagas. Leônidas and Maria Paumgarten Deane. Samuel Pessoa. Institute of Experimental Pathology for the North (Evandro Chagas Institute).

Resumo: Casos pioneiros de leishmaniose cutânea e mucocutânea nas Américas foram descritos em São Paulo, em 1909; somente em 1934, um patologista do Serviço de Febre Amarela encontrou a leishmaniose visceral no Brasil. Processos históricos concernentes a essas formas ganharam mais vigor institucional nos anos 1930. Se a Comissão para o Estudo da Leishmaniose consolidou o conceito de leishmaniose tegumentar americana, a Comissão Encarregada do Estudo da Leishmaniose Visceral Americana, chefiada por Evandro Chagas, deu origem ao Instituto de Patologia Experimental do Norte (1936) e ao Serviço de Estudo das Grandes Endemias (1938). A leishmaniose visceral ganhou crescente relevância no Nordeste brasileiro, nos anos 1950. Medidas de controle dos vetores por Dicloro-Difenil-Tricloroetano (DDT) ocorreram a reboque da campanha contra a malária, direcionadas também a cães, sacrificados massivamente, e humanos, tratados com drogas antimoniais. Grandes empreendimentos no interior do Brasil após o golpe civil-militar de 1964 transformaram a leishmaniose cutânea e mucocutânea em um problema sério na Amazônia e em outras regiões. No Brasil e em outros países, todas as formas de leishmaniose supostamente sob controle reemergiram em zonas rurais e urbanas e em áreas consideradas livres desse complexo de doenças endemoepidêmicas, devido a mudanças ambientais, migrações humanas, crescimento urbano caótico e outros processos socioeconômicos.

Palavras-chave: História da leishmaniose cutânea e mucocutânea no Brasil. História da leishmaniose visceral no Brasil. Evandro Chagas. Leônidas e Maria Paumgarten Deane. Samuel Pessoa. Instituto de Patologia Experimental do Norte (Instituto Evandro Chagas).

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The leishmaniasis are classified by the World Health Organization as neglected tropical diseases, and are the only illnesses in this category that continue to grow in number. Brazil has the most cases of the three forms of this disease that occur in the Americas (cutaneous, mucocutaneous, and visceral) (World Health Organization, 2017; Organização Mundial da Saúde, 2010). This article portrays how visceral leishmaniasis established itself as a public health problem in Brazil between the 1930s and the 1960s.

In India, medical records of visceral leishmaniasis (also known as kala-azar) began to multiply from the mid-nineteenth century as epidemic outbreaks worsened. This disease was initially associated with malaria or ancylostomiasis and joined the leishmaniasis group at the turn of the twentieth century, at the same time as dermatological diseases known under a wide range of local names ('oriental sore' was perhaps the most widespread).¹ This cutaneous leishmaniasis and visceral leishmaniasis became the object of intense scientific production in various parts of the world. Starting in 1909, physicians from South and Central America began to stand out in the international scientific network for their work on the unique manifestations of leishmaniasis in the skin and mucous membranes. In the Americas, the disease had another unique characteristic: unlike in the Old World, where it was acquired in urban centers, leishmaniasis was only acquired in forested regions. In the 1930s, this leishmaniasis was generally recognized as 'American tegumentary leishmaniasis,' indicating the foothold gained by Latin American researchers in the field of tropical medicine. Visceral leishmaniasis, however, was virtually absent in the Americas. One case was diagnosed in 1912 by the Paraguayan physician Luis Enrique Migone Mieres (1913) in a resident of Mato Grosso, an Italian who had worked on the construction of Brazil's Northwest

Railway. Four years earlier, this same railroad had been the setting for an outbreak of 'Bauru ulcer,' which was then recognized as cutaneous leishmaniasis, for the first time in the Americas (Lindenberg, 1909a, 1909b; Carini; Paranhos, 1909a, 1909b). In 1926, two other cases of visceral leishmaniasis were identified in Argentina (Mazza; Cornejo, 1926), but these diagnoses remained isolated events, in stark contrast to the hundreds of cases of cutaneous and mucocutaneous leishmaniasis described by Latin American physicians.

Visceral leishmaniasis erupted as a public health problem in 1934, amid a routine pertaining to another disease. The Cooperative Yellow Fever Service had recently established a laboratory in Bahia to analyze liver samples sent by hundreds of viscerotomy stations scattered across the country, taken from persons who had died from suspicious fevers. In slides from material collected in the north and northeast of Brazil which tested negative for yellow fever, the pathologist Henrique Penna identified *Leishmania* (Penna, 1934).² As a result, 41 deaths were suddenly linked to visceral leishmaniasis.

Carlos Chagas, the director of the Oswaldo Cruz Institute (IOC), charged his eldest son and director of the Institute's hospital, Evandro Serafim Lobo Chagas, with investigating the new medical and scientific problem. Using the records from the cases Penna diagnosed *post-mortem*, he found the first living Brazilian patient, a 16-year-old boy living in Aracaju, Sergipe (Chagas, E., 1936; Chagas, E. et al., 1937). In a note published shortly thereafter in March of 1936, Evandro Chagas referred to Brazilian visceral leishmaniasis as possibly differing from the disease observed in the Old World, although it was impossible to morphologically differentiate the *Leishmania* found in Brazil from *L. donovani*, the agent of kala-azar in India and other parts of Asia and Africa or *L. infantum*, the parasite incriminated by Charles Nicolle as the cause

¹ On this subject see Dutta (2009, 2008) and Jogas Junior (2017a, 2017b).

² On the yellow fever campaign in Brazil, see Löwy (2001), Benchimol (2001), and Cueto (1996).

of infantile visceral leishmaniasis in the Mediterranean (Chagas, E., 1936).³

Carlos Chagas died on November 8, 1934, and some time elapsed before Evandro could begin his research on visceral leishmaniasis. In June 1936, under the management of Antônio Cardoso Fontes, Carlos Chagas's successor as director of the Oswaldo Cruz Institute, the Commission for the Study of American Visceral Leishmaniasis (CEELVA) was created. This commission was led by Evandro Chagas and included Aristides Marques da Cunha, Gustavo de Oliveira Castro, and Leoberto de Castro Ferreira. Cecílio Romãña, who conducted studies on visceral leishmaniasis in Argentina, also participated. With financial support from the Oswaldo Cruz Institute and the businessman Guilherme Guinle,⁴ Evandro visited other locations in the northeast, but soon focused his research on Pará, in the north of Brazil. Other characters were soon incorporated into his team: the English nurse Agnes Stewart Waddel, who would become his second wife, Leônidas and Gladstone Deane, from Pará, Felipe Nery-Guimarães, and Maria Von Paumgarten, who would later marry Leônidas Deane. The efforts by this group resulted in several publications in the second half of the 1930s on various aspects of visceral leishmaniasis.⁵

In Pará, as in the northeast, Evandro Chagas and his staff continued to navigate using the reports from the pathologists of the Yellow Fever Service to guide them. Where deaths had occurred from leishmaniasis, the residents were examined, principally for early indicators like fever, anemia, and an enlarged spleen (splenomegaly). Cases considered suspect were subjected to a risky and painful procedure: liver or spleen puncture to withdraw

material for parasitological examination. Some patients were sent to hospitals in Belém or Rio de Janeiro so that material could be collected and used in animal experiments and studies on the progression of the disease and its treatment, which at that time involved two antimonial drugs, Fuadin and Neo-estibosan (Gualandi, 2013).⁶

Evandro Chagas and his team collected sandflies and other arthropods, along with animals that could host *Leishmania*. They also studied the environmental characteristics of the places they inspected, which were important to study potential vectors and hosts as well as to prove Evandro Chagas's central hypothesis about the disease: unlike in the Old World, visceral leishmaniasis in Brazil would have a wild character. The son of Carlos Chagas put a great deal of effort into demonstrating the presumptive theory that American visceral leishmaniasis was autochthonous. He attempted to follow in the footsteps of the researchers who established the concept of American cutaneous leishmaniasis, as well as those of his father, who discovered 'American trypanosomiasis' in 1909. Evandro Chagas was also influenced by the scientific ebullience caused by the discovery of forest yellow fever, and it is important to note that Henrique Penna was one of the authors of the 1933 work which changed the course of the campaign against this disease in Brazil (Soper et al., 1933).

The discovery of American visceral leishmaniasis was announced in February 1937 in three research notes published in a Brazilian journal (Chagas, E., 1937; Cunha; Chagas, E., 1937; Chagas, E.; Castro, 1937). In the north and northeast of Brazil and the province of Chaco in northeastern Argentina, visceral leishmaniasis occurred in

³ The main reference for Evandro Chagas's studies on visceral leishmaniasis is Gualandi (2013). Important information can also be found in Deane, L. (1986).

⁴ On the relationships between this businessman and philanthropist and Carlos Chagas and other Brazilian scientists, see Sanglard (2008). Evandro Chagas's relationship with this and other public and private sponsors of his activities was examined by Barreto (2012).

⁵ On research projects pursued by Evandro Chagas and his team in the Northern Institute of Pathology (Instituto de Patologia do Norte – IPEN) and the Serviço de Estudos de Grandes Endemias (Large Epidemics Study Service – SEGE/IOC) and their impact on the Brazilian public health agenda, see Barreto (2012).

⁶ When Evandro Chagas found the first living patient in Sergipe, he paid the family to obtain consent to send the boy to the Instituto Oswaldo Cruz hospital, in Rio de Janeiro. This and other information is confirmed in Deane, L. (1994, p. 155). According to Barreto (2012, p. 108) this practice was repeated with other cases.

individuals of different ages, while in the Mediterranean this disease was found mainly in children. The American disease occurred exclusively in wild or rural areas in close contact with forests, unlike kala-azar, which manifested as intense and lethal urban epidemics in India. Dogs were the main hosts of the agent of Mediterranean visceral leishmaniasis, but could not play this same role in a disease as sparse as the American variety; only wild animals acting as primary reservoirs of *Leishmania* could explain the absence of notable outbreaks. In identifying a new species as the cause of American visceral leishmaniasis, *Leishmania chagasi*, Evandro Chagas explicitly associated his discovery with that of Gaspar de Oliveira Vianna, who had described *Leishmania braziliensis*, now the recognized agent of American cutaneous leishmaniasis.

In 1911, this doctor from Pará, a researcher at the Oswaldo Cruz Institute and author of important studies on *Trypanosoma cruzi*, published a preliminary note on *Leishmania* that he had found in a patient from Minas Gerais admitted to the Hospital da Misericórdia in Rio de Janeiro. The presence of a filament – “[...] perhaps a rudimentary flagellum, which has not yet been observed [...]” – supported the hypothesis that this was a new species, which Vianna named *L. braziliensis* (Vianna, 1911, p. 411). The note, which was only published in a Brazilian periodical, was received with caution. *Leishmania braziliensis* was one of the many solutions offered to explain the unique characteristics of cutaneous and mucocutaneous leishmaniasis in the Americas. The idea of an autochthonous species of this protozoan gained strength with the finding in the 1920s that its most likely vectors of transmission were phlebotomine sand flies (Diptera: Psychodidae) that varied from region to region. Archaeological findings related to the pre-Colombian origins of cutaneous and mucocutaneous leishmaniasis (which appeared to be represented in ancient pottery vessels) had an influence, alongside the inclusion of

nationalist ideologies in the medical debate, which added to the symbolic capital of Latin American researchers within the international scientific network of tropical medicine (Jogas Junior, 2017b). Another factor which certainly contributed to this international projection was the discovery by Gaspar Vianna, who died prematurely just before World War I, that emetic tartar was an effective treatment for leishmaniasis despite its toxicity (Vianna, 1912). The use of this trivalent antimonial quickly spread across Europe and its colonies. The hegemony of *Leishmania braziliensis* as an agent of all forms of cutaneous and mucocutaneous leishmaniasis in the Americas, which was consecrated in 1930 with the concept of American tegumentary leishmaniasis, would be shattered in the 1960s and 1970s when the populations of parasites (along with their respective vectors and vertebrate hosts) were recognized as much more heterogeneous than previously imagined (Lainson, 2010).

In our view, the findings that substantiated Evandro Chagas's theory about American visceral leishmaniasis largely resulted from the fact that his studies concentrated on the Amazon region, where visceral leishmaniasis is still residual today. Chagas favored this area because his political connections were the most successful in the region, resulting in the creation of the Institute of Pathology of the North (Instituto de Patologia do Norte, IPEN) in Belém do Pará as a home for studies on visceral leishmaniasis.⁷

EVANDRO CHAGAS AND HIS TEAM IN PARÁ AND AGAIN IN NORTHEASTERN BRAZIL

In December 1936, Evandro Chagas and the young doctors he recruited in the capital of Pará made the first trip to Abaeté (today Abaetetuba) up the river of the same name, because its headwaters were the site of deaths identified through viscerotomies. In a village called Piratuba, the first cases of visceral leishmaniasis in the Amazon region were found. The disease would be located in three other

⁷ See also Gualandi (2013), Barreto (2012) and Deane, L. (1986).

municipalities in Pará: the coastal towns of Marapanim and Soure (indicated by viscerotomies), and Mojú (shown by clinical research).

The cases seen in these locations corroborated the idea that American visceral leishmaniasis did not occur in cities or in wetlands – that is, in areas with major waterways and flooded land – but rather on dry land with forest and a high concentration of wild mammals (Gualandi, 2013).

In Pará, a few naturally infected dogs and one cat were found. Granulations suggestive of *Leishmania* were seen in a wild rodent (the tree rat, *Phyllomys* sp.), but this remained only a suspicion. In addition to numerous inoculations in wild, domestic, and laboratory animals using materials derived from human patients, Evandro Chagas's team sought the vector insect. The main suspects were sandflies; the species most frequently found in the study areas (inside and outside homes) were *Phlebotomus longipalpis* and *Phlebotomus intermedius* (later reclassified as *Lutzomyia longipalpis* and *Nyssomyia [Lutzomyia] intermedia*). These insects were able to retain the protozoa in their digestive tracts, since both could be infected using animals with *Leishmania*, but their role in transmitting the disease was not proven conclusively (Ferreira et al., 1938; Paraense; Chagas, A., 1940; Chagas, A., 1939).

In mid-1938, Evandro Chagas returned to the northeast of Brazil, but was caught up by a very serious outbreak of malaria caused by the importation of a dangerous African vector, *Anopheles gambiae* (Anaya, 2016; Soper; Wilson, 2011).⁸ At the beginning of that year, the Commission for the Study of American Visceral Leishmaniasis (led by Evandro Chagas) was transformed into the Large Endemics Study Service (Serviço de Estudos de Grandes Endemias, SEGE), with a more comprehensive mission: to investigate not only visceral leishmaniasis, but also other rural endemics across the country, which became politically important targets for the government of Getúlio Vargas (Barreto, 2012).

In 1940, the Ministry of Education and Health charged Evandro Chagas with investigating malaria in the Amazon, since the campaign against *Anopheles gambiae* in the northeast had already managed to 'clean' extensive areas (Andrade; Hochman, 2007; Andrade, 2007). The Yellow Fever Service continued its campaign to eradicate *Aedes aegypti* in urban centers and to conduct mass vaccinations in rural and forest areas swept by sylvatic yellow fever (Benchimol, 2001). In 1941, other national services were created, including the National Malaria Service (SNM). Working in conjunction with the newly-created Federal Bureaus of Health and the state governments, they considerably increased the government's presence in the Brazilian territory (Hochman, 2001).

But Evandro Chagas did not live to see these changes. On November 8, 1940, at age 35, he died in a plane crash in Guanabara Bay, during one of his many trips to the field from Rio de Janeiro. The institute created in Belém was named the Evandro Chagas Institute, and the leadership of the SEGE was transferred to his younger brother, Carlos Chagas Filho, until this service closed in 1942.

LEISHMANIASES AND OTHER RURAL ENDEMIC DISEASES IN THE 1940S AND 1950S

World War II was underway, and after major duplicity the Brazilian government declared war on the Axis in August 1942. The Americans wanted to increase production of raw materials which were strategically important for the Allies, particularly rubber. That same year, the Brazil-United States Political-Military Agreement (May 1942) led to the creation of the Special Public Health Service (SESP). The Institute of Pathology of the North, now called the Evandro Chagas Institute, was incorporated into this Service, and despite its emphasis on malaria it conducted an extensive investigation into sandflies along the Amazon River (1944-1949). Many species which were thought to possibly be related to the transmission of *ferida brava* or cutaneous and

⁸ A good analysis of Evandro Chagas's performance in the campaign against *Anopheles gambiae* can be found in Barreto (2012).

mucocutaneous leishmaniasis (the dominant forms of the disease in the region) were found.⁹

Studies on visceral leishmaniasis slowed after the death of Evandro Chagas, but very substantial work was done on cutaneous and mucocutaneous leishmaniasis, especially after the first major epidemiological investigation of this disease began in 1939. This initiative by Samuel Barnsley Pessoa, director of the Department of Parasitology of the University of São Paulo Medical School, addressed São Paulo and the southern cone of South America. In 1948, Pessoa and his assistant Mauro Pereira Barreto published *Leishmaniose Tegumentar Americana* [*American Tegumentary Leishmaniasis*], which is still an essential reference on the subject (Pessoa; Barreto, 1948).

At that time, developmentalist nationalism was embraced by many teachers and researchers in the traditional medical schools and those which were being created in various parts of Brazil, as well as by sanitarians who found promising professional prospects in the new health services created at the federal, state, and municipal levels. A key character in this political-sanitarian-ideological scenario was Mário Pinotti, thanks to his ability to connect the aspirations of his generation to the political game which was underway in the country (Silva; Hochman, 2011). Pinotti led the National Malaria Service for 14 years, mostly during the post-war period, when the stage was set for the Cold War and also for great optimism about controlling diseases with new residual insecticides, antimalarial medications, sulfa drugs and antibiotics, new vaccines, and diagnostic technologies.

In 1945, the first homes in Brazil were treated with DDT, in the village of Breves, Pará. Chemical control of the malaria vectors was combined with therapeutic and prophylactic use of chloroquine, including distribution of cooking salt containing this substance, an idea inspired by adding iodine to salt to combat goiter.¹⁰

The Ministries of Education and Health, which had been united into a single entity in 1930, were separated in 1953 during Getúlio Vargas's second term. Mário Pinotti took over the Ministry of Health in July 1954, but the suicide of Vargas the following month and subsequent political upheavals did not allow him to accomplish much. Pinotti headed the team that produced the health program of Vargas' successor, Juscelino Kubitschek, whose developmentalist promises were well summarized in his campaign slogan: "50 years of progress in 5 years of government" (Hochman, 2009).

Living conditions for rural workers were expected to improve with the eradication or control of endemic diseases in the interior of the country, through specific strategies that varied according to the biological and social peculiarities of these diseases and the availability of medications, vaccines, and other control techniques. Also influential were the priorities established at a time when international health agencies played an increasingly important role in the decisions of the governments of Brazil and other countries.

Kubitschek took office in January 1956, and shortly thereafter Pinotti was appointed director of the National Department of Rural Endemic Diseases (DNERu), which replaced the national services with new structures that were also vertical. But they acted in a more integrated manner in 25 constituencies corresponding to states, territories, and the capital of the country (which had been the city of Rio de Janeiro but was moved to a new city built on the Central Plateau, Brasília).

LEISHMANIASES IN THE NORTHEAST OF BRAZIL

"Leishmaniasis, whether cutaneous or visceral, is a significant problem for the northeast, even if the number of cases is not high [...]" this statement came from the doctor responsible for

⁹ On the edges of the Amazon River, from Belém to the Brazil/Peru border, Reinaldo G. Damasceno, Ottis R. Causey, and Arouk identified 64 species, 21 of which were new to science.

¹⁰ The "Pinotti method" of medicating salt had considerable international repercussions and was incorporated into the arsenal of the malaria eradication program recommended by the World Health Organization in 1955 (Silva; Hochman, 2011).

reporting on “Endemic Diseases of the Brazilian Northeast” at the Medical Congress of the Brazilian Northeast held in Fortaleza in July 1953 (Alencar, 1953). Joaquim Eduardo Alencar was one of the group that founded the Ceará School of Medicine in 1947, and taught parasitology.

The congress and the topic under discussion reveal the growing density acquired by the medical field in the region and studies on its diseases conducted by local physicians, in increasingly close collaborations with researchers from São Paulo, Rio de Janeiro, and Minas Gerais. In his report, Joaquim Eduardo Alencar emphasized diseases caused by parasitic worms, yaws, trachoma, Chagas disease, and leishmaniasis. They were still the subject of sparse studies with little data from few sites. The exception were the helminthiases, which had been the focus of an extensive epidemiological study (the first with a national scope) coordinated by Amílcar Barca Pellon, director of the Division of Health Organization, and Isnard Teixeira, a sanitarian who worked in this agency of the Ministry of Education and Health. The Scholastic Helminthological Survey was completed in 1953. Among 615,000 Brazilian students between 7 and 14 years of age, it found an average prevalence of 7.26% for schistosomiasis and 46.1% for hookworm infection (Pellon; Teixeira, 1953).

And what did the rapporteur at the Medical Congress of the Northeast have to say about the leishmaniases? That these diseases had not been widely studied and that suitable elements to combat them were lacking because of uncertainties related to the epidemiology, the hosts and vectors, and the diagnosis and treatment of the visceral and cutaneous forms.

Cutaneous leishmaniasis, as we have seen, was better known. Since the 1910s, it had been found at railroad construction sites and in agricultural and extractive ventures

that penetrated forest areas. Physicians (particularly dermatologists) described hundreds of cases that came from rural areas to hospitals of larger cities. Health centers created in the interior of Brazil in the 1920s (and especially since the 1930s) played an important role in the increasing diagnoses of cutaneous leishmaniasis.¹¹

In stark contrast with these numbers, *in vivo* cases of visceral leishmaniasis were uncommon, which supported Evandro Chagas’s belief that the disease was sporadic. In four decades, only 34 cases of American visceral leishmaniasis had been recognized in live patients, most in Pará and Bahia (Deane, M.; Deane, L., 1955). The viscerotomies indicated 314 more widespread deaths from 1934 to 1950. The scene across the Americas was just as inconsistent, since only 35 cases had been described until that time.¹²

But in 1953 an epidemic broke out in northern Ceará, the first documented in the Americas, which drastically changed the representations of visceral leishmaniasis. In just five years (1953 to 1957), the total number of *in vivo* cases in the country soared from 34 to 1,832, most of them (81.38%) in Ceará. In the Americas, the total number of cases rose to 2,179 (1,840 living and 339 *post-mortem*), but more than 98% of the total (2,145 cases) were related to the Brazilian northeast (Deane, L., 1958).

THE CEARÁ EPIDEMICS: A NEW APPROACH TO VISCERAL LEISHMANIASIS IN BRAZIL

In the heart of the *caatinga* drylands, the city of Sobral was suffering from a devastating drought. Hundreds of families flocked to the suburbs of this city, which was known as the ‘Princess of the North,’ looking for work and food. Most continued on, looking for salvation in far-off places like Maranhão, the Amazon, São Paulo, or Rio de Janeiro. In the press and among doctors and the people, the term

¹¹ Valuable data can be found in Sousa (2009). Together with Richard Pearson, this physician and researcher from Ceará published an excellent article in which they analyze the circulation of smallpox and cutaneous leishmaniasis between northeastern and northern Brazil in association with the intense flows and returns of migrants driven by the rise and fall of the rubber economy in the Amazon (Sousa; Pearson, 2009).

¹² The total number of registered cases rises to 48 or perhaps 51, if we consider other studies reported by Deane, L. (1958). These data are found in Alencar (1959a, 1959b), Deane, L. (1956, 1958). The cases discovered in the United States were imported, except for one case of accidental laboratory contamination (Benedek, 1940, 1941).

calazar now appeared frequently; studies conducted during the outbreak in Sobral indicated that it had gone unnoticed for quite some time. Around 1935, inhabitants reported it wiped out almost the entire population of children under five years of age in several villages. Clinicians from the region confirmed that many years prior they had seen a sickness of an unknown nature, and only now knew what it was. Consequently, the low number of previous diagnoses did not express the rarity of visceral leishmaniasis, but rather the absence of medical assistance for the rural population and the lack of knowledge among doctors working in rural areas.

The records from the 1953 epidemic show the importance of the channels that connected these doctors with the structures that had recently been created in the area of health. A clinician in Sobral (Thomaz Corrêa Aragão) alerted the Federal Delegate for Children during one of his visits to the local Child Care Center. Physicians from this agency, the Federal Health Bureau, and the State Department for Children were then sent to Sobral. This commission examined 11 children diagnosed with leishmaniasis (all of whom were treated with Glucantime). Samuel Pessoa also traveled to Sobral, and consequently declared to the newspapers: "Never in Brazil has there been such a limited area with such a high concentration of patients" (Impressionado..., 1953, p. 2). The Campaign against Visceral Leishmaniasis in Ceará was then established under the leadership of Joaquim Eduardo de Alencar. When Samuel Pessoa returned to São Paulo, he sent two of his assistants to Ceará: Leônidas Deane

and his wife, Maria Paumgartten Deane, both former members of Evandro Chagas's team.

Leônidas made a first trip to Sobral, in October 1953, and asked rural dwellers there to capture wild animals. When the Deanes came to Sobral in December, a fox (*Lycalopex vetulus*) was waiting for them; when they examined it, they found that it was full of *Leishmania* (Deane, L.; Deane, M., 1954b).¹³ If the fox with *Leishmania* corroborated the wild reservoir that Evandro Chagas sought in order to substantiate the specificity and autochthony of American visceral leishmaniasis and its agent, *Leishmania chagasi*, the other observations made in the northeast undermined fundamental aspects of the theory Chagas proposed in the 1930s. Visceral leishmaniasis was now a disease that did not depend on forests, and could occur in urban areas; additionally, even in rural areas where it was predominant, it clearly had a focal character. Urban transmission was confirmed by human and especially dog infections acquired in the cities.

The studies on the disease ravaging Ceará concentrated in four municipalities where most of the cases originated: Sobral, Massapê, Viçosa do Ceará, and Tianguá. They covered two areas with diverse environmental characteristics: the *sertão*, a hot and dry plain with scarce vegetation, subject to seasonal droughts, and the mountainous *serras*, which featured a mild climate, rich vegetation, and abundant rainfall.¹⁴ There was a population of 150,782 inhabitants in the four municipalities. Three quarters lived in the rural area, and the remainder in villages or municipal centers, the most populous of which was Sobral, which had about 24,500 inhabitants at the time.

¹³ They believed they were the first to find a wild animal with visceral leishmaniasis, but soon learned that three Russians had just verified in Central Asia (Tajikistan) that the jackal (*Canis aureus*) also acted in this role (Latyshev et al., 1951). This and other articles about leishmaniasis were reviewed by the British parasitologist Hoare (1954).

¹⁴ The *sertão* drylands predominated in Sobral and Massapê, but the small Rosario and Meruoca mountains emerged; Viçosa do Ceará and Tianguá were largely in the mountainous area of Ibiapaba. The studies by Leônidas and Maria Deane addressed dogs naturally infected by *Leishmania donovani* (Deane, L.; Deane, M., 1954c); the biology of *Phlebotomus longipalpis* (mentioned in Deane, M.; Deane, L., 1955); urban visceral leishmaniasis (Deane, L.; Deane, M., 1955); experimental infection of *Phlebotomus longipalpis* (Deane, M.; Deane, L., 1954b, 1954a) and transmission of visceral leishmaniasis in Ceará (Deane, L.; Deane, M., 1955). The Deanes, in collaboration with Alencar presented a paper on the type of region in which visceral leishmaniasis occurred in Ceará (mentioned in Deane, L.; Deane, M., 1954a). Deane, L. (1956) presented a habilitation thesis (*tese de livre docência*) at the University of São Paulo in 1956 that described visceral leishmaniasis in Brazil, particularly the host and transmitters in Ceará. Alencar (1959b) also presented a habilitation thesis at the University of Ceará on canine *calazar*.

Most of the rural cases were concentrated in areas called *boqueirões* and *pé de serra*, narrow valleys between or at the foot of mountains. Although they were inhabited by about 10% of the rural population, these locations generated 63.5% of the cases, and they could be clearly connected to other prior cases or the presence of canine leishmaniasis. The Deanes always obtained “[...] information about the deaths of several people in each family, and sometimes found that all the children in a family had been struck down successively by the same disease” (Deane, M.; Deane, L., 1955). Meanwhile, in the *sertão* and the mountains, the frequency of infection was low, and cases were sparse and sporadic.

Children up to 9 years of age were most affected. The outbreaks appeared to be related to the cyclical increase in the susceptible non-immune population, especially children, and to the seasonal droughts that decreased the population's resistance.

Leônidas and Maria Deane no longer classified the parasite as *Leishmania chagasi*; they occasionally used the concept of American calazar, but they turned away from the idea of a disease originating in the Americas. Renowned protozoologists were skeptical about the existence of different species of *Leishmania*. For example, the English and Brazilian scientists Charles Morley Wenyon and Carlos Chagas believed that cutaneous leishmaniasis presented different forms in different regions, but these were due to the environmental characteristics of each region. The manifestations of visceral leishmaniasis also did not justify the existence of distinct species of *Leishmania*. The Mediterranean type mostly affected children and was related to canine leishmaniasis. In India, it mostly struck adults and seemed to be unrelated to dogs. Since the parasites could not be distinguished morphologically, Wenyon believed that there were only two species

pathogenic to man: *L. tropica* (cutaneous leishmaniasis) and *L. donovani* (kala-azar).

For the Deanes, the pronounced pathogenic action of *Leishmania* in foxes (which could die from this infection) did not fit together with secular parasitism, which would result in a relative balance between parasite and host. They therefore accepted the hypothesis that American leishmaniasis had been imported from the Old World through dogs or parasitized individuals.¹⁵

In Ceará, Leônidas and Maria P. Deane unsuccessfully attempted to infect cats or find cats infected with the disease. Three mammals (humans, dogs, and foxes) were known to be naturally infected and could serve as a source of infection for the insect vector. Dozens of species had been described in the northeast. Everywhere the disease occurred, the Deanes found *Phlebotomus longipalpis*, which the natives called *asas-duras* or *arrupados* (both names likely referring to the fact that the wings of these tiny flies stick up when they land). The Deanes quantified this coincidence through ingenious research methods, capturing large numbers of these insects within human dwellings, shelters for domestic animals, and also outdoors, using different baits at different times. They captured and identified 117,981 *Phlebotomus* of 12 different species: *P. longipalpis* accounted for 97%, and was seen to be much more abundant in areas where kala-azar was endemic/epidemic than where it was sporadic. *P. longipalpis* was often the only diptera biting inside the houses, but its anthropophilism was only relative, since outdoor captures yielded more flies than homes.

The endemic zone was soon extended to regions of the northeast with different environmental characteristics than those studied by the Deanes, through epidemiological investigations conducted by Joaquim Eduardo Alencar and other local physicians. The *boqueirões* and *pés de serra* were

¹⁵ The Deanes believed that other wild reservoirs of *L. donovani* probably existed in the Americas. The Central American spiny rat (*Proechimys semispinosus panamensis*) had been identified in Panama as a carrier of parasites which were morphologically indistinguishable from *L. brasiliensis*, the agent of tegumentary leishmaniasis. And in Kenya, where leishmaniasis was endemic, a hamster was infected by inoculating it with the emulsion of a ground squirrel spleen (*Xerus rutilus*).

replaced by humid river valleys, similar to those frequented by Evandro Chagas: initially, the Jaguaribe River Valley was investigated, followed by the banks of the Piancó River in Paraíba (Alencar et al., 1956; Alencar, 1962).

And how was the disease fought? In 1947, large-scale use of DDT against malaria began across nearly all of Rio de Janeiro state. As in India and other parts of the world, the campaign against visceral leishmaniasis adopted DDT in the northeast of Brazil. A study by the Deanes and Alencar was key in calibrating the use of this residual insecticide against *Phlebotomus longipalpis*: it was to be applied at least once a year on inner and outer walls of homes, up to 3 meters high, and in shelters for domestic animals (Deane, L. et al., 1955). After treatment, sandflies practically disappeared from the treated houses. In areas sheltering domestic animals, the action of the insecticide was less long-lasting, and in open areas the density of the insects was unaffected. The experiment showed that transmission of visceral leishmaniasis within homes could be significantly reduced, which was important considering that *P. longipalpis* fed more at night, when the human population (and especially more vulnerable children) were in their homes. But extradomiciliary transmission was the Achilles heel of the prophylactic strategy. Antilarval measures, which were so important in yellow fever and malaria, did not apply to visceral leishmaniasis. Larvae and pupae of *P. longipalpis* had been found in the wild, but not in aquatic environments. In fact, it was still not clear where they bred.

At least until 1960, the use of DDT in Ceará continued to be experimental in nature, since it was applied in one group of 14 municipalities but not in another group. During this period, 3,935 locations were treated with the insecticide. Kala-azar had been reported in 271; only 11 of these localities had the disease in 1960. It was completely wiped out in 4 municipalities. In the untreated areas, cases increased (Alencar, 1961).

DDT was sprayed by the National Malaria Service, which led to a contradiction that hindered the campaign against leishmaniasis. The staff of this agency acted according to the habits of *Anopheles* species (malaria vectors), which differed from the habits of *Phlebotomus longipalpis*. This led Alencar (1961, p. 178) to write: “[...] spraying was not done to the extent necessary, nor at the time advised, prior to the rainy season, after which the density of phlebotomus increases and with this the contagion intensifies.”

But DDT was only one aspect of the campaign, which was based on two other courses of action: discovering and treating human cases, and discovering and eliminating canine cases.

Considering present-day ethics with regard to animals, the number of dogs killed over the eight years of the campaign is shocking: 279,423 dogs were examined and 78,929 were slaughtered (28.24%), despite the fact that only 3,712 (1.32% of the total) tested positive (Alencar, 1961). The techniques for parasitological diagnosis were seen as uncertain. It should be noted that veterinarians would become as important to visceral leishmaniasis as dermatologists were in cutaneous leishmaniasis.

The work of the Deanes and other researchers highlighted the importance of an adjuvant factor (or for Samuel Pessoa, who was linked to the Communist Party, a determinant factor¹⁶) in the epidemiology of visceral leishmaniasis: the socioeconomic conditions and poverty of rural workers. A very meaningful statement is ascribed to Alencar: ‘Leishmaniasis is a disease of dogs and those who lead a dog’s life.’ Consequently, prophylaxis required improving the living conditions of the affected populations. There was no doubt that variations in morbidity and mortality were linked to “[...] social misfortunes [...]” (Alencar, 1959b, p. 19-20). In practice, however, actions related to the human populations were limited to systematic treatment with pentavalent antimonial

¹⁶ On Pessoa’s ideas about rural endemic diseases and his political militancy, see Hochman (2015).

drugs, which were provided to hospitals and clinics in the campaign at no charge.¹⁷

We saw earlier that by the end of 1957, 2,179 cases of leishmaniasis had been diagnosed in the Americas, 98% in the northeast of Brazil, without counting the deaths identified through the Yellow Fever Service's viscerotomies.¹⁸ After Ceará, the most affected states were Bahia and Piauí. Up to that time, the disease had been detected along the coast, from Pará to Bahia, and in the central states of Minas Gerais, Goiás, and Mato Grosso; it did not appear to occur in the southern states (an idea which later was refuted).

In July of 1958, Mário Pinotti took office as Juscelino Kubitschek's minister of Health, pledging that new generations would not suffer from five devastating endemic diseases: yaws, Chagas disease, goiter, trachoma, and leishmaniasis (Ministro..., 1958). That same year, the Fifteenth Pan-American Health Conference in Puerto Rico adopted a resolution declaring Brazil, the Panama Canal Zone, and nine other countries free of *Aedes aegypti*, the vector of urban yellow fever (Franco, 1969). Brazil also officially entered the global campaign to eradicate malaria in 1958.

At the same time that actions against leishmaniasis and other endemics were spreading across the country, the campaign formally constituted in Ceará in 1953 seems to have ceased to exist. In 1962, the DNERu signed an agreement with the Institute of Preventive Medicine (created by Alencar at the Federal University of Ceará) which encompassed visceral leishmaniasis research, hospital care for patients, and training for professionals to work with this endemic disease in the northeast (Seidl, 1962). Alencar led an investigation in Santarém, in the state of Pará (Alencar et al., 1962). It was the first time that leishmaniasis was found in that municipality, implying that the disease might penetrate the

state of Amazonas, where it had not yet been found. The investigation showed that emigration from the northeast to the north and to other regions of the country could be the source of new and unsuspected outbreaks.

The research by physicians in the northeast and north, by Samuel Pessoa and his assistants in São Paulo and the studies involving collaboration between the group in São Paulo and researchers in Bahia, Minas Gerais, Ceará, and Pará had shown that visceral leishmaniasis was a very significant health problem in the northeast and that emigration magnified its importance in other regions of Brazil. This had two important consequences: it increased the number of diagnoses made by doctors in rural areas as well as major cities where increasing numbers of rural workers from the northeast immigrated. It also boosted awareness of the fact that isolated cases should be investigated further, since they were likely to be connected to new endemic areas of visceral leishmaniasis.

Isolated clinical descriptions now gave way to epidemiological surveys, thanks to the reinforced public health apparatus at the federal and state levels and the strengthened institutional network capable of housing studies on the leishmaniasis. The departments of parasitology in the medical schools in São Paulo as well as Ribeirão Preto (also established in São Paulo state in 1947) and the Oswaldo Cruz Institute in Rio de Janeiro were the main hubs of this network, which included the Institute of Preventive Medicine at the University of Ceará, the Evandro Chagas Institute, the Special Public Health Service, and three research centers established in the late 1950s by an important arm of DNERu, the National Institute for Rural Endemic Diseases (INERu): the Bahia Research Center, in Salvador (later called the Gonçalves Moniz Research Center), the Belo Horizonte Research Center (which would later be called the René Rachou Research Center), and the Aggeu

¹⁷ The most commonly used substances were N-methyl glucamine, marketed as Glucantime (Rhône-Poulenc-Rohrer), and sodium antimony gluconate, commercially known as Solustibosan (Bayer). On these and other drugs used in leishmaniasis, see Rath et al. (2003).

¹⁸ Three hundred and thirty cases were diagnosed after examining approximately 470,000 postmortem liver samples to detect yellow fever, with visceral leishmaniasis accounting for 0.07% of this total (Deane, L., 1958).

Magalhães Research Center in Recife (which derived from Evandro Chagas's initiatives and had already conducted important research on schistosomiasis). Work in these institutions focused mainly on schistosomiasis, Chagas disease and malaria, but visceral leishmaniasis gained importance in studies involving cooperation from the universities of Pernambuco, Bahia, and Minas Gerais.

One event is a milestone in the establishment of this research network: the Kala-Azar Seminar, which was held in Salvador in November 1960 (Notas..., 1960a, 1960b, 1960c). Almost all the specialists dedicated to this disease (but who also worked with schistosomiasis and other endemic diseases) met at this event for the first time. In a session on November 12, the first day of the Seminar, they decided to found the Brazilian Society of Tropical Medicine (Notas..., 1960d). It is intriguing that visceral leishmaniasis was the lever for this important episode in the institutionalization – or even better, the revaluation – of tropical medicine, rather than malaria, Chagas disease, or schistosomiasis, which were priorities on the agendas of research institutions and public health agencies.

CONCLUSIONS

Visceral leishmaniasis was controlled in Brazil to a certain degree, but only momentarily. Today it has a high incidence and vast distribution, and assumes serious and lethal forms when associated with poor nutrition and concomitant infections such as AIDS.

Large undertakings in Brazil's hinterland after the 1964 military coup transformed cutaneous and mucocutaneous leishmaniasis into an equally serious problem in the Amazon region.¹⁹ In fact, because of environmental changes, human migrations, chaotic urban growth, and other economic processes affecting large portions of Brazil and many other countries at the end of the twentieth century, all forms of leishmaniasis which had seemed to be under control have re-emerged in rural and urban

zones and in areas that had been considered free from this disease complex. Since then an increase can be seen in international cooperation related to the leishmaniasis.

In Brazil, the growing urbanization of visceral leishmaniasis in recent decades has called into question the strategies for its control which were adopted during the optimistic period described above. Many uncertainties (new and old) surround the transmission, diagnostic techniques, treatment, and prevention of the leishmaniasis. They are classified as neglected tropical diseases (the only illnesses in this category which continue to grow), and although this disease complex is in fact neglected by public health policies and affect neglected populations, it mobilizes one of the strongest and most consolidated research communities in Brazil.

New paradigms, especially molecular biology, have changed the nature of studies on the leishmaniasis, and today they are far more complex than during the period we examined. The extreme specialization among the professionals who address these diseases today would appear to be counterbalanced (with rare exceptions) by an inability to perceive the problem holistically, in contrast with the multivalent generation of Samuel Pessoa, Leônidas Deane, and Joaquim Alencar, who were so sensitive to the social and environmental determinants of the leishmaniasis and other endemic diseases. This is because the leishmaniasis, like any other disease, are also a cultural event that depends on the categories of thought and verbal constructs which are specific to a generation, reflecting the history of the medical field and the surrounding society.

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¹⁹ On this, see Peixoto (2017) and Guerra et al. (2015).

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