Tegumentary leishmaniasis in Brazil: a historical review related to the origin, expansion and etiology*

*Leishmaniose tegumentar no Brasil: revisão histórica da origem, expansão e etiologia**

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INTRODUCTION

In 1925, in the first and second issues of volume one of the *Annaes Brasileiros de Dermatologia e Syphilographia* [Brazilian Annals of Dermatology and Syphilography], Eduardo Rabello published, in the section named "Original Memories", a study called "Contributions to the study of tegumentary leishmaniasis in Brazil" (Figure 1), which covered the background and synonymy of the disease.[1]

In that revision, the author concluded that tegumentary leishmaniasis (TL) already existed in the country for many years and distinguished three stages in the historical development of the disease. The first one, of uncertain origin and based on vague references, extended until 1895, the year that was marked by the clinical observation of "Bahia button" and its relationship with the "Oriental button". The second stage extended until 1909, when the etiological agent of "Bauru ulcer" was identified and described. The third stage started in 1910, when the parasite was found in mucosal lesions, then added to the clinical picture of the disease, and went up to the publication of the article.

Archeological studies developed in Peruvian *huacos* - ceramic vases displaying reproduction of human images, both healthy and disease-mutilated ones - could assure the occurrence of *uta* and *espundia* - local names for the cutaneous and mucosal forms of TL, respectively - among the Incas, during the pre-Colombian era, although they were misinterpreted as syphilis in the beginning. On the other hand, studies of anthropomorphic ceramics produced by our Indian ancestors, due to their rudimentary characteristics, did not enable the same type of observation. The only safe and probably older indication of the disease in Brazil is found in a citation contained in the thesis by Tello, *Antiguedad de la syphilis en el Peru*, of 1908 and related to the written work *Pastoral Religioso-Político Geographico*, published in 1827 and reporting a missionary's trip in the Amazon region. The missionary observed individuals presenting ulcers in their arms and legs, related to insect bites, which resulted in destructive lesions in their mouth and nose. Since it had not been previously mentioned in Brazil, Rabello thought it was more reasonable to suppose that, being endemic in the Amazon region, but at the same time originated from Peru and Bolivia, the disease could have spread in the Northern states in Brazil by individuals who traveled to that area looking for work at the rubber tree exploitation sites and went back to their hometowns infected with the disease. As to the Central and Southern regions in Brazil, he found it was more likely that the disease could have been imported from Bolivia or from the Amazon, via the State of Mato Grosso, and also probably from Paraguay, via the states of Mato Grosso or Paraná, in view of its endemic form in those countries much earlier than the discovery. This long period of indemnity was probably determined by isolation due to poor transportation conditions at that time. The following were also considered strong evidence of the

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ANNAES BRAS. DE DERMATOLOGIA E SYPHILOGRAPHIA 3

MEMORIAS ORIGINAES

Contribuições ao estudo da leishmaniose tegumentar no Brasil

I — Historico e synonimia

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FIGURE 1: Reproduction of the title of an article by Rabello, published in the *Annaes*, in 1925

disease in the Central-Southern region in Brazil at the end of the 19th century: a) models found in the Museum of the *Faculdade de Medicina do Rio de Janeiro*, dated 1882 through 1884, which represent unquestionable cases of TL; b) cases diagnosed in Italian immigrants from Sao Paulo who had returned to their country, described by Breda (1884) in Italy, as *buba brasiliana* (Figure 2); c) reproduction of ulcerated nose disease in watercolor paintings presented to the Brazilian Society of Dermatology in 1912 (Figure 3), observed by Carneiro da Cunha, in 1906, in patients originally from Uberaba, State of Minas Gerais, who had

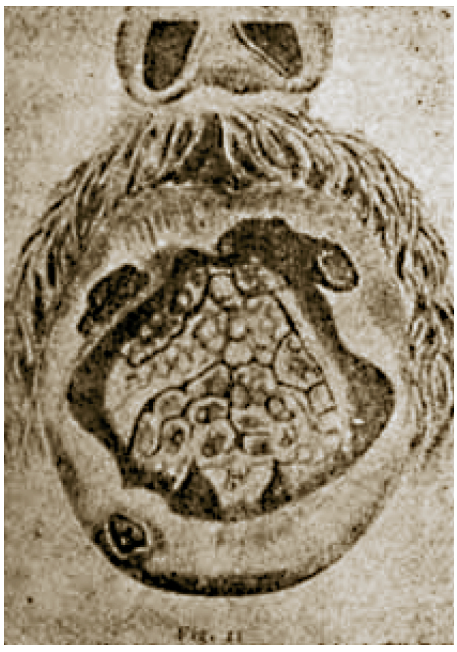

FIGURE 2: Reproduction of a picture by Breda (1884), illustrating a case of ATL which he called *buba brasiliana*

FIGURE 3: Reproduction of a watercolor painting presented by Carneiro da Cunha to the Brazilian Society of Dermatology, in 1912, illustrating a case of ATL he observed in 1906

lesions for 27 years, i.e., since 1879.

The second stage of TL in Brazil started with Juliano Moreira, who, while studying the so-called "Bahia button" in 1895, associated it for the first time with the "endemic button of warm countries". It was suggested that the disease would have been imported by Syrian emigration to the New World in ancient times, but this hypothesis was not shared at that time by observers in other areas of the country. Based on a doctorate thesis by Adeodato, presented to the *Faculdade de Medicina da Bahia*, in 1895, Rabello attributed this correlation to Moreira and not to Cerqueira, who, in fact, as of 1885, had observed patients with "Bahia button", however not establishing any association between the two lesions.

In 1903, Wright identified *Helcosoma tropicum* as the agent responsible for the "Oriental button", later on called *Leishmania furunculosa*, which allowed the association of various dermatoses with different names, usually designating the geographical areas affected, to leishmaniasis. The great epidemics of ulcerated cases accompanied by mucosal lesions, in the State of Sao Paulo, at the beginning of the 20th century, with the construction of the Northwestern Railroad, described as "Bauru ulcer", anticipated the end of the second stage, which culminated with the identification of the agent, almost simultaneously by Lindenberg and by Carini & Paranhos, in 1909.

The third stage is considered the most fruitful, according to Rabello, since identifying the agent led to confirmation of the disease in several areas of the country, such as Rio Doce Valley, in the State of Minas Gerais, the Amazon region and south

of Bahia, among others. Its beginning is marked by the finding of the causal agent in mucosal lesions by Splendore, in 1910. The most prominent fact in this stage was the discovery of the treatment with emetic tartar by Gaspar Vianna, in 1911, which was announced at the Dermatology Congress, in Belo Horizonte, in 1912.

At the end of the first part of his study, Rabello concluded that the presence of mucocutaneuous leishmaniasis had long been demonstrated in Brazil, and it had been named with regional expressions, such as "Bahia button" and "*buba brasiliana*", or had vague denominations, such as "*ferida brava*". Since leishmania was discovered as the etiological agent of the "Oriental button" and observed in the above-mentioned conditions, they were also included in the same nosographic criterion. In 1909, Lindenberg suggested the denomination "ulcerous leishmaniasis". Once the mucosal, infiltrative and vegetating lesions were recognized, in addition to ulcerous lesions, that denomination could no longer be used. Thus, Rabello proposed the expression "tegumentary leishmaniasis" which, including cutaneous and mucosal lesions of diverse morphology, allows to differentiate it from the visceral form of leishmaniasis. At that time the author found two inconveniences in the denomination "American leishmaniasis of the forests", as proposed by Brumpt & Pedroso, in 1913, both for the geographical delimitation of the disease and for providing an idea of a marked occurrence of the disease in the forests. He pointed to the fact that the disease existed and spread out of the areas of untouched forests, referring to several cases observed in the urban area of Rio de Janeiro at that time. Afterwards, he recognized that many cases of *gangosa* - mutilating rhinopharyngitis - were manifestations of TL. He also commented on the impossibility to distinguish, at that time, the leishmaniae found in tegumentary leishmaniasis in Brazil and those found in the "Oriental button", and therefore he considered as inadequate the denomination of '*L. brasiliensis*', given by Gaspar Vianna, in 1911, which made the author question the disease in Brazil as an autonomous entity. Later, he discussed other arguments in favor of a single nosological entity, including: a) attribution to the phagedemic characteristic of certain diseases in the tropics, probably due to interference of secondary microorganisms; b) predominance of benign cutaneous forms in Brazil, which sometimes presented self-resolution; c) occasional observation of aggressive and mutilating cutaneous forms of the "Oriental button", as well as demonstration of manifestations of severe mucosal leishmaniasis in Sudan, Egypt and India; d) similarity of the histopathological abnormalities of the disease in both areas; e) possibility, in the tropics, of associating with other diseases that could mask the original picture of TL. Rabello concluded that "consequently, the designation *American* could not be maintained for a disease which, without having a diverse etiology and an autonomous anatomical and clinical picture, has already being observed outside the American continent and whose zone of dissemination will be certainly wider in the future".

CHARACTERIZATION OF THE AMERICAN TEGUMENTARY LEISHMANIASIS IN BRAZIL

In the past, it was assumed that *Leishmania braziliensis* was the only agent causing the American tegumentary leishmaniasis (ATL) existing in the country. Up to the beginning of the 1960's, the classifications of parasites were based exclusively on clinical-evolutive behavior, with clinical forms of the disease in different geographical areas, since the parasite morphology, at optical microscopy, did not allow that kind of distinction.[2] In 1961, Pessoa proposed the subdivision of *L. braziliensis* into the varieties named *braziliensis, guyanensis, peruviana, mexicana* and *pifanoi*, which would be related to diverse clinical forms of the disease in different regions.[3]

From that time on, the classification of leishmaniae gained a new impulse with distinction of the two complexes, *mexicana* and *braziliensis*, based on more consistent criteria, such as the characteristics of the parasite behavior in culture media, experiment animals and vectors.[4]

Since then, the developments brought by electronic microscopy, molecular biology, biochemistry and immunology have opened new prospects in the taxonomy of leishmaniae.[5] The new methods that started to be employed in the characterization of leishmaniae include especially the study on the development of promastigotes in the phlebotomine vector intestine,[6] the morphometric study of amastigote and promastigote forms at electronic microscopy,[7-9] the electrophoretic motility of isoenzymes,[10] determination of the fluctuating density of nucleus and kinetoplast DNA,[11,12] analysis of DNA degradation products by restricting enzymes,[13] radiospirometry,[14] characterization of specific antigens of external membrane by monoclonal antibodies,[15] DNA/RNA hybridization techniques[16,17] and analysis of kinetoplast DNA by means of amplification technique using polymerase chain reaction.[12,18]

Currently, the most used classifications follow the taxonomic model proposed by Lainson & Shaw (1987),[19] which divides the leishmaniae in subgenera

Viannia and *Leishmania*. In Brazil, at least seven species of *Leishmania* responsible for the human disease have been identified, with the tegumentary form caused mainly by *L. (V.) braziliensis*, *L. (V.) guyanensis* and *L. (L.) amazonensis* and, more rarely, by *L. (V.) lainsoni, L. (V.) naiffi* and *L. (V.) shawi*, whereas *L. (L.) chagasi* is responsible for the visceral disease.[12] Each species presents particularities regarding the clinical manifestations, vectors, epidemiological patterns and reservoirs, geographical distribution and even the therapeutic response.

GEOGRAPHICAL DISTRIBUTION OF AMERICAN TEGUMENTARY LEISHAMANIASIS IN BRAZIL

Until the 1950's, ATL spread practically throughout the Brazilian territory, coinciding with the deforestation caused by road construction and new population settlements, with a higher incidence in the states of Sao Paulo, Paraná, Minas Gerais, Ceará and Pernambuco. From then until the 1960's, the disease seems to have entered a downturn with deforestation already completed in the most urbanized areas of the country in addition to the relative stability of rural populations.[2]

Since then, in areas of old colonization, new outbreaks have been reported in several states.[20] In Rio de Janeiro, they were particularly reported in Ilha Grande, Jacarepaguá, Campo Grande and Parati.[21] In Minas Gerais, in addition to the persistence of old endemic foci in the area of Atlantic forest of Rio Doce and Mucuri valleys,[22] numerous other cases have been reported outside these areas, with some foci in the metropolitan area of Belo Horizonte.[23] New foci have been described in Sao Paulo, in the Mogi-Guaçu valley and in the coastal area of Ribeira valley,[24] and a large focus was detected in the outskirts of the capital of Espírito Santo, in the towns of Viana and Cariacica.[25] In the Northeast, ATL also persists as an endemic disease in areas inhabited for a long time, especially in the mountainous areas of the states of Ceará, Paraíba and Bahia.[26]

In the past 20 years, an evident increase of the endemics has been observed, both in magnitude and in geographical expansion, with epidemic outbreaks in the Southern, Southeastern, Central-Western, Northeastern regions and, more recently, in the Northern region.[27] In areas of recent colonization, the expansion of the disease is associated with deforestation for construction of new roads, villages and enlargement of agricultural areas, with those being more common in the Amazon[28] and Central-Western regions, affecting mainly the migrant population and frequently sparing the native Indians.[2]

Between 1985 and 1999, a total of 388,155 cases of the disease were reported in Brazil. In 1999, the highest detection rates were observed in the Northern region (92/100000) and Central-Western region (50/100000), especially in the states of Mato Grosso, Amapá, Rondônia, Acre, Pará, Amazonas, Tocantins and Roraima, in addition to Maranhão, in the Northeastern region.[27]

THEORIES ABOUT THE ORIGIN AND EXPANSION OF AMERICAN TEGUMENTARY LEISHAMANIASIS IN BRAZIL

New developments in the biology and epidemiology of ATL enabled acquiring knowledge about the origin and expansion of the disease. In 2003, Altamirano-Enciso et al. carried out an interesting review of this theme, based on from historical pre- and post-Colombian sources.[29]

With the description of "Bahia button" and its association with the "Oriental button", the first theory about the "Mediterranean" origin of ATL was that it might have been imported during trips of Phoenicians or Syrians to the Northeastern region in Brazil, in Ancient times.[30,31] However, these trips have never been confirmed.

The second theory would be the "Andean" theory elaborated by Rabello, in 1925,[1] after the discoveries of the Peruvian *huacos*. Although not accepted by all the specialists in this subject,[32] Rabello's proposal about the origin of ATL in cold territories in Bolivia and Peru, predominates in the biomedical literature.[29]

The third theory, the "Amazonian" theory, was proposed by Marzochi & Marzochi, in 1994,[33] based on epidemiological studies and geographical distribution studies of *Leishmania (Viannia) braziliensis* in different ecosystems, involving different vectors and reservoirs. They suggested that the human disease might have emerged in the western Amazon area, mainly to the south of Marañon-Solimões-Amazonas River, where *L. (V.) braziliensis* is more prevalent. In conformity with the hypothesis of ATL dissemination suggested by Rabello, they also assumed that the process of spreading to other areas in Brazil was recent and occurred mainly during the rubber tree economic cycle, from 1880 to 1912, which attracted thousands of Northeastern region inhabitants. These populations, after the decline of this cycle, returned to their origins or were attracted by the coffee plantation expansion cycle in the Southeastern region, particularly in the states of Minas Gerais and Sao Paulo. This migration took place around 1930, when the major epidemics of ATL initiated.[34] Other further cycles that also implied some social mobility to the south of the Amazon, such as road cons-

tructions (1960-70), gold extraction (1970-80) and wood exploitation (1980-90), might have contributed to the expansion of ATL, which re-emerged in several states in the Central-Western and Southeastern regions, and the recent re-emergence in the Southern region, which coincides with the return of laborers to their home land. It should be also stressed the disease urbanization that took place in the metropolitan areas of Rio de Janeiro[35] and Belo Horizonte.[23]

This last model is supported by the comparison between the genetic heterogeneity of leishmania observed in the Amazon region and its genetic homogeneity found outside this region,[18,36] which is suggestive of its late introduction. Persistence of *L. (V.) braziliensis*, which can be confirmed in scars of ATL in patients involved with rural activities, many years after the clinical cure,[37] corroborates the possibility that human beings can be a source of infection and, therefore, be able to carry the parasite to other areas where transmitters exist, which possibly give origin to new foci of the disease.

An argument used to refute the Amazonian origin of ATL would be the fact that, in the past, the disease was not observed in the Indian populations - therefore considered unaffected by the disease -, what led to the idea that ATL did not exist in the forests until the end of the 19th century. Additionally, reports by Oswaldo Cruz and Carlos Chagas, in 1913, about the Amazonas valley described the occurrence of mucosal lesions only in the non-autochthonous population. Recent research has shown, with Montenegro hypersensitivity reaction, that the rate of leishmania infection in the subclinical form is high among native populations in the Brazilian Amazon, including children, and there are few cases of cutaneous disease with high tendency to spontaneous cure.[38]

The last theory, however, did lack historical confrontation. The ethnic-etiological study performed by Altamirano-Enciso et al.,[29] based on historical sources of the 16th century (Pizarro, 1571; Santillán, 1563; Loayza, 1586; Ávila, 1598), reinforced the theory of the Amazonian origin of ATL, especially it mucosal form, in the borders of Brazil and Bolivia and Peru. As a result of human migration between the Amazonian and Andean regions in archeological times, it gained the space occupied by high forests and later on the territories of warm inter-Andean lands. The investigation also suggested that during the Inca empire, some migrating groups (*mitmaq* or *mitimaes*) may have contributed to spreading ATL to different regions in the Northern Andes and that, even during the Spanish colonization, the disease continued to spread to new areas of mountainous inter-Andean lands and the central coast, where phlebotomes and dogs were close to agricultural communities, without losing the bond with the Amazon; therefore, ATL incidence increased in foreign groups.

Recently molecular studies also suggested that *uta*, a cutaneous form of ATL found in the Peruvian Andes and caused by *L. (V.) peruviana*, might have emerged in the Amazon about 500 to 1000 years ago and, after reaching the Andes as a zoonosis, by means of rodents, it spread to the Northern coast.[39] However, archeological studies have revealed that, in the formation period between the second and third millennium before our current Era, all this area was covered by lush vegetation, and it constituted one of the main human routes between the coast and the forest.[40] These biological studies, therefore, also corroborate the ethnic-historical data and they seem to confirm the Amazonian origin of the ATL.

Recently, Thomas-Soccol et al. designed the monophylogenetic theory of leishmaniae, based on studies of mitochondrial DNA of 20 different species of leishmaniae all over the world, considering the common origin of *Viannia* and *Leishmania* branches, which would date back to the Cretacean and Jurassic periods about 120 million years ago, when the continents were still united in a pangea.[41] Nevertheless, there is still much controversy regarding the origin of leishmania species, whether it is neotropical,[42,43] paleo-Arctic[44] or African.[45]

COMMENTS

Recent evidence based on the biological and ethnic-historical studies allow us to state that Rabello was right when he concluded that ATL was endemic in the Amazon region as of the beginning of the 19th century, and it spread to the Northern and Northeastern regions in Brazil by means of human migratory populations starting with the rubber tree cycle. However, he was wrong for supposing the disease was originally from the high Andes and that it further gained the low lands of the Amazon region. Recent studies have revealed that ATL emerged in the Amazon during archeological times, and had an opposite route towards the areas of high forests and later on the Andean region, with maintenance of the endemics during the Inca Empire and the period of the Spanish colonization due to the human flow in both ways.

Current researches also suggest that the disease might have spread to other regions in the country carried by the migrating population, who - after the decline of the rubber extraction in the Amazon - returned to their origins in the Northeastern region or those who traveled to the Southeastern region,

mainly to the states of Minas Gerais and São Paulo, attracted by the development generated by coffee plantations. However, this migratory flow to the Southern regions might have occurred after the observation of cases in the Southeastern region, at the end of the 19th century, and the occurrence of ATL epidemics in the Northwestern area of Sao Paulo state, during the first decade of the 20th century. Consequently, Rabello could be certain that the ATL in the Southeastern region was originally from the Amazon region or even from Bolivia and, in this case it might have arrived in the state of São Paulo via the state of Mato Grosso. Another possibility was importing the disease from Paraguay, via the states of Mato Grosso or Paraná. Even if it was originally imported from Bolivia or Paraguay, the disease would also have its origin in the Amazon, but in all possibilities, it might have been caused by older human migrations than those that occurred after the decline of the rubber tree cycle. Certainly, these last migrations could have been responsible for the major epidemics of ATL in the Southeastern region, as of the 1930's, and extending to the 1950's. Additionally, new human migrations to the south of the Amazon, generated by road constructions, mineral exploration and wood extraction in the 1960's, 1970's and 1980's, would have collaborated to the emergence of various epidemic outbreaks and the frank expansion of the endemics in various regions of the country, the last 20 years.

We should also comment on the impropriety of the restricted association between the disease and forests, already pointed out by Rabello, which was based on the observation of countless urban cases at that time. Later on, it was confirmed that the disease could manifest as one of the distinctive epidemiological patterns. A classical pattern, related to forestry activities and deforestation, with wild animals as reservoirs, and generally presenting as epidemic outbreaks with the colonization fronts. Another pattern, apparently not related to forests, that is generally observed in the outskirts of large urban areas, in old colonization areas, and that is possibly caused by the adaptation of parasites and vectors to environmental changes and to domestic animals as new reservoirs.

Once again, Rabello was mistaken when he emphasized the improper denomination of the etiological agent as *Leishmania braziliensis* and stated that "...the 'American' denomination could not subsist to an entity with no diverse etiology and an autonomous anatomical-clinical picture...", using some arguments, such as difficulty in differentiating it from the parasite that caused the "Oriental button" and inadequate geographical boundaries of the disease. With the resources available at that time it was really impossible to distinguish among the different leishmania species. They could be identified later on and even correlated with different patterns of epidemiology, geographical distribution, clinical manifestations and therapeutic response.

Since the brilliant historical revision by Rabello, in 1925, there have been considerable advances in knowledge of the leishmaniases, especially regarding the biological and immunological aspects of the disease. Diagnostic methods have improved as well as the therapeutic resources. Even with the progress attained, we are forced to acknowledge that 80 years later the situation of these diseases has changed very little. They continue to be present as an important public health problem in many parts of the world, coincidentally in developing countries, along with other infectious and parasitic diseases, which present a fundamentally social character, as a consequence of the marked inequalities that are still rampant in the world economy in the third millennium. ❑

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