ECOLOGY OF THE LEISHMANIA SPECIES IN THE GUIANAN ECOREGION COMPLEX

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Abstract. In the Guianan ecoregion complex, at least seven Leishmania species belonging to both the L. (Leishmania) Saf’ janova, 1982 and L. (Viannia) Lainson and Shaw, 1987 sub-genera are causative agents of American visceral leishmaniasis, mucocutaneous leishmaniasis, and cutaneous leishmaniasis, including localized and diffuse forms. They are mostly sylvatic species subjugated to their own specific Lutzomyia sand fly vectors and to particular wild mammalian reservoir hosts of the dense rain forest. Originally implicated strictly in wild zoonoses and developing in forested ecotopes, Leishmania show a particular adaptive plasticity to face environmental modifications following deforestation and anthropization. This review presents the different pathogenic complexes of these parasites, emphasizes their implication in human diseases, and considers the influence of humans on their ecology.

INTRODUCTION

The Guyanas are part of the biologically rich Guiana Shield, an ancient Precambrian rock formation situated in the northern part of South America. On this shield and alongside the Amazon River, the Guianan Ecoregion Complex (GEC) covers the Venezuela States of Delta Amacuro, Bolivar, and Amazonas, encompasses all of Guyana, Suriname, and French Guiana, and continues into the ecologically associated areas in the upper parts of the Brazilian States of Amazonas, Roraima, Pará, and Amapá (Figure 1). The GEC includes seven distinct ecoregions, some of them entirely unique: the Guayan highland moist forests, the Guianan moist forests, the Paramaribo freshwater swamp forests, the Guianan savannas, the Guianan tepuis, the Guianan freshwaters, and the Guianan-Amazon mangroves.1,2 As a cluster of particular ecologic areas, the GEC harbors a characteristic set of species, communities, dynamics, and environmental conditions. The equatorial tropical climate in this region is tempered by heavy rainfall and high relative humidity. There is a long rainy season from November to June followed by a short dry season from July to October. The animal biodiversity in the GEC is particularly diverse although the diversity of invertebrates is poorly known. The genus Leishmania (Protozoa: Kinetoplastida: Trypanosomatidae) in this region contains a wide variety of species.

In the GEC, leishmaniasis are basically zoonoses transmitted by the bite of small phlebotomine sand flies of the genus Lutzomyia (Diptera: Psychodidae: Phlebotomidae). Their major reservoir hosts are wild or domestic mammals, ranging from marsupials to monkeys, and occasionally include humans. These parasites benefit from numerous vectors and mammalian reservoir hosts that occupy various compartments of the biotope and form distinct pathogenic complexes. This review reports the different pathogenic complexes of Leishmania parasites in the GEC, emphasizes their implication in human disease, and considers the influence of humans on their ecology.

LEISHMANIA AND LEISHMANIASIS IN THE GEC

For 50 years, improvements in methods for the detection, isolation, and identification of Leishmania species have indicated a clearly marked speciation of this genus in the neotropics, which is probably due to the greater range of different sand fly and mammal species in the Americas. In this review, I will use the classification proposed by Rioux and others, based on an iso-enzymatic complexes analysis,3–5 and validating the Lainson and Shaw phylogenetic analysis on phenotypic characteristics,6 which divides the genus Leishmania Ross, 1903 into two sub-genera: L. (Leishmania) Saf’ janova, 1982 and L. (Viannia) Lainson and Shaw, 1987 (Table 1). In the GEC, at least seven species belonging to the genus Leishmania coexist, among which six are known to infect humans. The main Leishmania species responsible for human disease that have been isolated in the GEC are L. (L.) infantum, formerly called L. (L.) chagasi,7,8 which causes American visceral leishmaniasis (AVL); L. (V.) guyanensis, the main causative agent of localized cutaneous leishmaniasis (LCL); L. (V.) braziliensis, which causes mucocutaneous leishmaniasis (MCL), so-called “espundia”; and L. (L.) amazonensis, which is responsible for anergic diffuse cutaneous leishmaniasis (DCL) in persons with an abnormally weak immune response. Table 2 shows the Leishmania species that have been reported in the GEC. Many of these parasites are able to produce a spectrum of diseases rather than a single clinical form. For example, the typically dermotropic species L. (L.) amazonensis was reported in patients with visceral involvement,9 which is usually caused by L. (L.) infantum. Likewise, L. (L.) infantum has been associated with cutaneous lesions without visceral involvement.10,11 Host immunogenetic factors as well as parasite factors are likely play a role in determining some of the variations in the course of Leishmania infections.12,13 Overall, leishmaniasis have a wider geographic distribution than previously believed and are now being reported in areas that were previously non-endemic in the GEC, as in the rest of South America.14–18 The different Leishmania species isolated from human cases in the GEC will be referred to according to the clinical forms of disease they cause in each country.

American visceral leishmaniasis. American visceral leishmaniasis caused by L. (L.) infantum is endemic in many areas of Latin America.19–22 In the GEC, AVL is rural, sporadic or endemic, and domestic or peri-domestic. The disease is wide-
Leishmania (L.) infantum was isolated in the state of Pará, and L. (V.) guyanensis was also found in the northern Amazon region (states of Amazonas, Amapá, Pará, and Roraima). In Amazonas, cases are also caused in a lesser extent by L. (V.) braziliensis. Leishmania (V.) lainsoni was isolated in the state of Pará and L. (V.) naiffi in Amazonas and Pará. In French Guiana, L. (V.) braziliensis, L. (L.) amazonensis, L. (V.) naiffi, and L. (V.) lainsoni were also isolated, but most cases of LCL (96.7% in 1989 and 92.7% in 1999) were caused by L. (V.) guyanensis. Some disseminated CL were also recently reported in French Guiana in patients infected with L. (V.) guyanensis. In Venezuela, LCL is widely distributed throughout the country, but it is most abundant in rural and suburban areas and especially in new human forest settlements located mainly in the lowlands of the Amazon River basin. Leishmania (V.) guyanensis has been isolated in this region from numerous human cases. Leishmania (L.) mexicana, L. (V.) panamensis, L. (L.) colombiensis, and L. (L.) venezuelensis were also responsible for LCL in Venezuela but not strictly in the GEC. In Guyana, all cases reported are caused by L. (V.) guyanensis and L. (V.) braziliensis. In Suriname, both L. (V.) braziliensis and L. (V.) amazonensis were reported, but L. (V.) guyanensis is the most common parasite.

Diffuse cutaneous leishmaniasis. Diffuse cutaneous leishmaniasis is not common in the GEC. Cases caused by L. (L.) amazonensis have been reported in Brazil, mainly in the Amazon River basin (states of Pará, Amapá, and Amazonas), and in Venezuela. Leishmania (V.) colombiensis was also shown to be caused by L. (L.) venezuelensis but not strictly in the GEC.

Mucocutaneous leishmaniasis. Mucocutaneous leishmaniasis is also widespread in Brazil. Leishmania (V.) braziliensis is found in the states of Pará and Amazonas, where its habitat is the rain forest and occasionally the secondary vegetation of rural areas. One case of CL caused by a mixed infection with L. (V.) braziliensis and L. (L.) amazonensis was reported in Amazonia. In French Guiana, some cases of MCL caused by L. (V.) braziliensis were reported. In the Venezuelan part of the GEC, L. (V.) braziliensis was found in rural foci with peri-urban or jungle transmission.

**ECOLOGY OF LEISHMANIA SPECIES IN THE GEC**

**Vectors.** The degree of specificity of Leishmania species for their sand fly hosts in nature has not been extensively studied, especially in Suriname and Guyana, and results of laboratory transmission experiments should be interpreted cautiously. To incriminate any sand fly species as vector, anthropophilic feeding behavior must be demonstrated. It is also necessary to

**TABLE 1**

<table>
<thead>
<tr>
<th>Sub-genus</th>
<th>Phylogenic complex</th>
<th>Species</th>
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<tbody>
<tr>
<td><em>Leishmania</em> S. Janova, 1982</td>
<td>L. infantum</td>
<td>L. infantum Nicolle, 1908*</td>
</tr>
<tr>
<td></td>
<td>L. mexicana</td>
<td>L. amazonensis Lainson and Shaw, 1972</td>
</tr>
<tr>
<td></td>
<td>L. hertigi</td>
<td>L. deanei Lainson and Shaw, 1976</td>
</tr>
<tr>
<td><em>Viannia</em> Lainson and Shaw, 1987</td>
<td>L. braziliensis</td>
<td>L. braziliensis Vianna, 1911</td>
</tr>
<tr>
<td></td>
<td>L. guyanensis</td>
<td>L. guyanensis Floch, 1954</td>
</tr>
<tr>
<td></td>
<td>L. lainsoni</td>
<td>L. lainsoni Silveira and others, 1987</td>
</tr>
<tr>
<td></td>
<td>L. naiffi</td>
<td>L. naiffi Lainson and Shaw, 1989</td>
</tr>
</tbody>
</table>

* Synonymous with L. chagasi Cunha and Chagas, 1937.
show a similar distribution of the insect and the parasite, the completion of the parasite life cycle in the sand fly, and evidence of transmission by insect bite. Three phlebotomine sand flies genus are present in South America but only one, *Lutzomyia*, has been identified as a vector of *Leishmania*. In the GEC, vectors include at least 19 species in 6 sub-genera. *Lutzomyia* vectors of *Leishmania* species observed in the GEC are shown in Table 3. It is still unclear whether all incriminated sand flies are important vectors, or if some are merely incidental hosts.

*Lutzomyia* vectors are generally abundant year round in the GEC. Nevertheless, the period encompassing the end of the dry season and the beginning of the rainy season is more propitious for their development. During the day, sand flies remain hidden in dark and wet places, especially in cracks in rocks, walls, tree trunks, and stumps distributed from the ground level up to the forest canopy. Flying in the evening, the hematophageous females are particularly active at dusk. Several species also bite during the day when disturbed. This diurnal activity plays a very important role in infection of forest workers. Females seek blood to develop their oocytes. When a blood meal is taken from an infected animal reservoir host, amastigote parasites are taken up from the skin or the peripheral blood. Parasites then successively transform into several different promastigote forms during the first 72 hours in specific parts of the sand fly digestive tract. Parasites of the *L. (Leishmania)* subgenus were proved to develop mostly above the pylorus, whereas species of the *L. (Viannia)* subgenus develop in the peri-pylarian region of the digestive tract. The first promastigote forms, which are found in the blood meal phase, are multiplicative procyclic promastigotes. These differentiate into nectomonad promastigotes, which are a non-dividing migratory stage that moves from the posterior to the anterior midgut. When nectomonad promastigotes arrive at the anterior midgut they differentiate into leptomonad forms, a newly named life cycle stage that resumes replication. Leptomonad promastigotes are found in the anterior midgut and multiply there before spreading to the buccal structures. They are the precursors of the mammal-infective metacyclic promastigotes. Leptomonad forms also produce promastigote secretory gel, a substance that plays a key role in transmission by forming a physical obstruction in the gut, forcing the sand fly to regurgitate metacyclic promastigotes during blood feeding. The life

**Table 2**

<table>
<thead>
<tr>
<th>Sub-genus</th>
<th>Clinical forms in human</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><em>Leishmania</em> Saf’janova, 1982</td>
</tr>
<tr>
<td>L. infantum</td>
<td>B, FG, S, V</td>
</tr>
<tr>
<td>L. braziliensis</td>
<td>B, FG</td>
</tr>
<tr>
<td>L. deanei</td>
<td>B, FG, G, S, V</td>
</tr>
<tr>
<td>L. guyanensis</td>
<td>B, FG</td>
</tr>
<tr>
<td>L. lainsoni</td>
<td>B, FG</td>
</tr>
<tr>
<td>L. nautii</td>
<td>B, FG</td>
</tr>
</tbody>
</table>

* LCL = localized cutaneous leishmaniasis; B = Brazil; FG = French Guiana; S = Suriname; V = Venezuela; G = Guyana; DCL = diffuse cutaneous leishmaniasis; MCL = mucocutaneous leishmaniasis; AVL = American visceral leishmaniasis.

**Table 3**

<table>
<thead>
<tr>
<th>Sub-genus</th>
<th>Geographic distribution</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><em>Leishmania</em> Saf’janova, 1982</td>
</tr>
<tr>
<td>Nyssomyia</td>
<td>+ + +</td>
</tr>
<tr>
<td>flaviscutellata</td>
<td>+ + +</td>
</tr>
<tr>
<td>olmeca nociva</td>
<td>+</td>
</tr>
<tr>
<td>reducta</td>
<td>+</td>
</tr>
<tr>
<td>umbratilis</td>
<td>+ + +</td>
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<tr>
<td>whitmani</td>
<td>+</td>
</tr>
<tr>
<td>Nyssomyia longipalpis</td>
<td>+</td>
</tr>
<tr>
<td>spathiphora</td>
<td>+</td>
</tr>
<tr>
<td>Psychodopygus</td>
<td>+</td>
</tr>
<tr>
<td>aroycei</td>
<td>+</td>
</tr>
<tr>
<td>carreri carreri</td>
<td>+</td>
</tr>
<tr>
<td>complexes</td>
<td>+</td>
</tr>
<tr>
<td>panamensis</td>
<td>+</td>
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<tr>
<td>paraensis</td>
<td>+ + +</td>
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<td>squamiventris</td>
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<td>wellcomei</td>
<td>+</td>
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<tr>
<td>Trichophoromyia</td>
<td>+ +</td>
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<tr>
<td>ubiquitalis</td>
<td>+</td>
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<tr>
<td>Psathyromyia</td>
<td>+ +</td>
</tr>
<tr>
<td>dendra</td>
<td>+ +</td>
</tr>
<tr>
<td>shannoni</td>
<td>+ +</td>
</tr>
<tr>
<td>Viannamyia</td>
<td>+</td>
</tr>
<tr>
<td>farcata</td>
<td>+</td>
</tr>
</tbody>
</table>

*Main vector is in bold type and secondary vector is in normal type.*
cycle of the sand fly lasts 4–7 days depending on the temperature. The vector may then transmit the parasite to another animal during a narrow time frame.

There is a natural restriction of individual species of *Leishmania* to specific sand flies. As reported by Lainson and Shaw, it may be due to intimate vector or mammalian host contact in restricted ecologic foci. *Leishmania*-sand fly interactions have been recently reviewed. Leishmania have developed unique adaptive mechanisms to ensure their survival in the harsh environments faced throughout their life cycle. Cell surface and secreted phosphoglycans were shown to protect the parasite from the protolytic activities of the blood-fed midgut, to mediate attachment to the gut wall to maintain infection during excretion of the blood meal, and to contribute to the formation of a biologic plug in the anterior gut that may promote transmission by bite. The importance of vector saliva in modulating the host response to transmitted parasites has also been demonstrated.

The transmission risk to humans depends on the intrinsic anatomic, physiologic, and ethnologic capacities of the species (e.g., anthropophily, activity rhythm, and life expectancy). In contrast, since some sand flies feed on a variety of mammalian hosts, the *Leishmania* species harbored by a given sand fly species may be isolated from different animals sharing the same habitat, as observed for *L. (L.) amazonensis* in numerous terrestrial rodents and marsupials. The vector cycle has an annual profile that conditions the transmission of *Leishmania* parasites. Each vector species has its own specific time interval with the highest transmission potential at the end of the cycle when the number of females about to lay eggs peaks. Moreover, some well-delimited hot spots where transmission is high due to favorable conditions, such as a microclimate or a high density of adapted vectors, can be identified defined in the rain forests, whereas transmission risk can be null in some other forested areas. If the sand fly vectors are anthropophilic, humans may become infected by a variety of leishmanial parasites when they intrude into different enzootic areas. However, many phlebotomine vectors are not anthropophilic and most of their parasites rarely make contact with the human host due their remote habitats.

**Reservoir hosts.** A wild animal can only be incriminated as a reservoir if its roles in both maintaining the parasites population in nature and sand fly feeding are demonstrated. An important feature of infection in wild animals is their non-pathogenicity: infected wild mammals usually have no clinical symptoms but can maintain a prolonged infection. However, in equines, dogs, and unusual hosts such as humans, severe reactions against parasites may occur, resulting in skin lesions and/or pathologic changes in internal organs. In most cases, more than one mammalian species is infected with a given parasite. However, only a few of these species serve as the principal vertebrate reservoir, and the remainder are likely incidental hosts and do not play an important role in the natural transmission cycle. As reported by Shaw, a primary reservoir refers to the mammalian host of a parasite that is responsible for infection in the wild, whereas a secondary reservoir is an animal that is infected but unable to maintain the enzootic. The mammalian host is thus a key factor in the epidemiology of these zoonotic diseases. The wide variety of mammals able to harbor a large number of distinct *Leishmania* species shows the adaptability and plasticity of these parasites. The discovery of new accidental hosts sympatric with the main reservoir animals could be explained both by the genetic diversification of the parasites and immunogenetic resistance selected in their primary hosts. New accidental hosts living in the same biotope as primary hosts, which increases resistance against the parasites, can be considered as an ecologic trial and error process that could lead to new and more favorable reservoirs.

The primary source of infection for vectors in the GEC is usually a wild mammal, rarely a domestic animal, and originally not human. The reservoir hosts of *Leishmania* species in the GEC represent at least 20 species in 14 families in 6 orders of mammals: Marsupialia, Xenarthra, Primata, Carnivora, Perissodactyla, and Rodentia. Table 4 shows primary and secondary mammalian reservoir hosts of *Leishmania* species in the GEC. Since all of these species except Cerdocyon thous in French Guiana are present in each country in the GEC, this highlights the homogeneity of the fauna of the mammals in the GEC and raises the question of the dissemination possibilities. Since they are only present in South America, the importance of Xenarthra as reservoir hosts should be emphasized. An unusual fact is the quasi-absence of studies on bats. Since they represent 39% of the 560 mammal species reported in the neotropical rain forests, bats are doubtless the most common mammals both in terms of diversity and biomass. They are found in sylvatic, peri-domestic, and domestic habitats at all levels and colonize a wide range of ecotopes. Thus, they are likely to be in contact with a large number of potential vectors and reservoir hosts. However, few studies have been conducted to investigate their potential involvement in leishmanial pathogenic complexes (Rotureau B, unpublished data). In South America, *Lu. longipalpis* were proved to feed on at least four species of bats in a Venezuelan laboratory and bat wings were routinely used to feed sand flies in Brazil. Thus, the necessity for conducting further experiments on the potential role of Chiroteera in leishmaniases cycles should be emphasized.

**Diversity.** In certain *Leishmania* species, iso-enzymatic variations and genetic polymorphism in specific DNA segments induced by mutations or genetic exchange should be regarded as a capacity to adapt to new hosts. Some intraspecific adaptations of the parasites to some peculiar vector populations are also observed in the clonal population structures of several *Leishmania* species. However, isolates from different polymorphic species show plesiomorphic similarities in their enzymatic or genetic profiles, suggesting that they may have originated from one primary sylvatic enzootic form. Globally, although *L. (V.) braziliensis* and in a lesser extent *L. (V.) amazonensis* were shown to be highly polymorphic, *L. (V.) naiiffi* and *L. (V.) guyanensis* were shown to have less diversity. *Leishmania (V.) lainsoni* was shown to be more invariant. Several studies have discussed the polymorphism observed in natural populations of different *Leishmania* species. Until now, there has been little information available about the genetic variability of the parasites and its correlation with the eco-epidemiologic features of *leishmaniases* (Rotureau B, unpublished data).

**Pathogenic complexes in the GEC.**

*Sub-genus L. (Leishmania) Sajfjanova, 1982 Leishmania (L.) infantum.*

In 1911, Carlos Chagas reported AVL in the Amazon basin. Its causative agent, *L. chagasi*, was named in his honor in
1937. Some investigators have suggested that L. (L.) infantum may have been imported from Europe by conquistadors in dogs or rats on board ships. Experiments have suggested that L. chagasi is indistinguishable from L. (L.) infantum. However, this hypothesis is inconsistent with findings that support the autochthonous origin of this species, which suggest that it was maintained in neotropical canids since the separation of the American and African continents. Given this doubt, we will refer to this species as L. (L.) infantum.

**Vectors.** In Latin America, the principal vector of L. (L.) infantum is Lu. longipalpis. Its distribution coincides with that of leishmaniasis throughout Latin America, and experimental transmission to hamsters was demonstrated, even with an eight-year-old vector colony. This vector may exist as a species complex with different genetic profiles and biologic properties. **Lutzomyia longipalpis** is typically a peri-domestic phlebotome sand fly in dry regions. American visceral leishmaniasis has not been associated with forested regions. However, this sand fly has the capacity to invade new habitats after deforestation and the establishment of human settlements. It is known to concentrate in overcrowded towns with poor hygienic conditions and an abundance of domestic animals. In Para, Lu. longipalpis was the only sand fly species consistently present in and around the homes of patients with leishmaniasis and was consequently considered the principal or sole vector in the Amazon region of Brazil. This vector is abundantly found in houses, farm buildings and chicken coops, where it feeds on a wide variety of domestic animals, especially chickens and dogs. It appears to be the ideal vector for a synanthropic zooonathropo- 

**Reservoir hosts.** Domestic dogs are known to be the most important reservoir hosts of L. (L.) infantum chagasi, but they are not the primary reservoir because the primary source of infection of a dog population is a wild canid. Therefore, in Brazil, programs based on elimination of infected dogs have not curtailed the spread of AVL, showing that other reservoirs of infection exist. Persons with active AVL can infect the sand fly vectors, and in disease-endemic areas, persons with asymptomatic infections are more numerous and represent a larger reservoir of infection. Another factor in the L. (L.) infantum pathogenic complex in the GEC is the crab-eating fox, Cerdocyon thous. It was found naturally infected in Pará and experimental transmission was demonstrated. Rates of infection support the suggestion that this canid, which is commonly associated with forested or wooded areas, may represent the primitive natural host of L.
(L.) infantum in the GEC.\textsuperscript{81,113} Although foxes are shy animals, they often invade farms and houses of rural areas in search of food. Since no infections were detected in a large number of rodents and marsupials, it has been proposed that an enzootic may be maintained in foxes by a sylvatic population of Lu. longipalpis, from which periodic foci of canine and human AVL may arise in these sparsely populated rural areas.\textsuperscript{7} Thus, foxes are likely to be the primary reservoir hosts of L. (L.) infantum in the GEC, and dogs represent the principal secondary reservoir responsible for the amplification of the infection to peri-domestic sand flies. However, a study in the Brazilian Amazon showed that crab-eating fox populations did maintain the transmission cycle independently of domestic dogs and that they were also unlikely to introduce the parasite into Leishmania-free dogs populations.\textsuperscript{127,128} Some opossums commonly found in the GEC were naturally infected with L. (L.) infantum: Didelphis marsupialis in Columbia\textsuperscript{129–131} and D. albiventris in Bahia, although foxes and rodents were not infected.\textsuperscript{132,133} In Colombia, it was also suggested that the rodent Proechimys canicollis may be a reservoir host of this parasite,\textsuperscript{105} but no infection was observed in Proechimys guyanensis after inoculation with a strain from Amazonian Brazil.\textsuperscript{134} The status of these marsupial and rodent species as important reservoir hosts for L. (L.) infantum in some specific areas remains unclear.

**Diversity.** Different isolates from various cases in Pará and in the neighboring states of Maranhão, Ceará, and Bahia were shown to have similar enzymatic profiles, suggesting that the major endemics might have originated from a primary sylvatic enzootic form.\textsuperscript{80,81}

**Leishmania (L.) amazonensis.**

**Vectors.** In 1968 in the northern Amazon region of Brazil, L. (L.) amazonensis was found in Lu. flaviscutellata.\textsuperscript{135} Shaw and Lainson reported a correlation between the enzootic rodent leishmaniasis and the feeding habits of Lu. flaviscutellata.\textsuperscript{43} Their group observed its seasonal variations in different forest types and its biting habits at different heights, and showed its role as the quasi-specific vector of L. (L.) amazonensis in Brazil.\textsuperscript{20,61,136,137} Experimental transmission by the bite of Lu. flaviscutellata between hamsters was also demonstrated.\textsuperscript{110,138,139} The seasonal fluctuations in its populations was related to rainfall, with a peak at the beginning of the rainy season both in a degraded primary forest in French Guiana\textsuperscript{140} and in a dry secondary forest in Pará.\textsuperscript{61} In the states of Amazonas, Pará, Rondônia, and Acre, the infection rate in the Nyssomyia subgenus was approximately 7.5%, which emphasizes the crucial role of this sub-genus in the transmission of the parasite.\textsuperscript{51,141,142} In French Guiana, Lu. flaviscutellata, formerly known as Phlebotomus apicalis, was shown to be distributed throughout this country.\textsuperscript{143–146} and was also infected with L. (L.) amazonensis\textsuperscript{46,140} at a rate similar to that reported in Pará (approximately 0.5%).\textsuperscript{135,137} Transmission to humans was limited by the nocturnal feeding of this vector and its common occurrence in the low and wet forest rarely visited by humans. Although this vector may be poorly anthropophilic,\textsuperscript{43,135} it is likely that human cases occur occasionally in the GEC by intrusion into the forest.

In the Brazilian Amazon region, natural infection of Lu. reducta\textsuperscript{12} and Lu. olmeca nociva,\textsuperscript{12,142} which are taxonomically closely related to Lu. flaviscutellata, were also reported. Lutzomyia carreraei carreraei was observed to feed on a hamster lesion caused by L. (L.) amazonensis and to transmit this parasite to another hamster.\textsuperscript{122} However, in Pará, various field studies confirmed the quasi-exclusive parasite/vector relationship of L. (L.) amazonensis and Lu. flaviscutellata.\textsuperscript{51,147}

**Reservoir hosts.** This zoophilic sand fly is abundant in secondary forests soils. It is attracted to rodents, especially of the genus Proechimys,\textsuperscript{148} but rarely attracted to humans.\textsuperscript{43} The incidence of L. (L.) amazonensis may be as high as 20% in some forest rodents of Brazil,\textsuperscript{43} which suggests that they are the main reservoir hosts of this Leishmania species.\textsuperscript{20} Numerous species of rodents, marsupials, and carnivores have been reported as natural hosts in Brazil. Parasites have been isolated from the skin of D. marsupialis in the states of Amazonas, Amapá, and Pará,\textsuperscript{12,31,149,150} the skin of Marmosa cinerea in Amazonas,\textsuperscript{149,150} Philander opossum, Metachirus nudicaudatus, and Dasypus novemcinctus (probably D. leporina because of its location).\textsuperscript{31} Oryzomys megacephalus (formerly known as O. capito),\textsuperscript{31,151–153} Cercocyon thous,\textsuperscript{20,31,67,152} in Pará, Proechimys guyanensis in Amazonas,\textsuperscript{149} and skin of Proechimys cuvieri in French Guiana.\textsuperscript{140,154,155} Marmosa robinsoni (including M. miisi, M. fuscata, and Caluromys philander) were also reported infected in Trinidad.\textsuperscript{156} In guinea pig–baited traps, Lu. flaviscutellata was one of the dominant species observed in French Guiana.\textsuperscript{157} Leishmania (L.) amazonensis seemed to be restricted to P. cuvieri species.\textsuperscript{46} However, other investigators suggested that P. guyanensis was the principal host of this parasite in Pará.\textsuperscript{20,31} Proechimys cuvieri has been clearly distinguished from Proechimys guyanensis\textsuperscript{158} and the two species were demonstrated to be sympatric in French Guiana.\textsuperscript{159} Therefore, the main wild reservoir host status between these two species remains unclear in the GEC.

**Diversity.** Although the level of intra-specific variations of zymodemes in L. (L.) amazonensis is low,\textsuperscript{46} the observed genetic variability among some strains from different locations in Brazil (Pará and Parana States) supported the clonal population structure of Leishmania isolates and suggested that their distribution was closely related to both the origin of the gene pool, the present vector, and the reservoir movements.\textsuperscript{85}

Leishmania (L.) amazonensis is extremely common in the GEC, as in Amazonia, in a wide range of terrestrial mammals. It is noteworthy that infections in the wild rodent and marsupial hosts are always unapparent. Furthermore, it occurs in a large panel of woody ecotopes including primary high forest, swamp forest, and low dense secondary forest. Both its vector and reservoir hosts are able to thrive in all types of woodlands ranging from high primary forest to secondary and degraded forests resulting from deforestation, which increases the transmission risks to humans. The enzootic form has been shown to spread into plantations due to the adaptation of rodents, marsupials, and Lu. flaviscutellata to such habitats. The pathogenic complex of L. (L.) amazonensis thus shows a strong and worrisome adaptation potential.

**Leishmania (L.) deanei.**

**Reservoir hosts.** Deane and others first isolated L. (L.) deanei in Piauí.\textsuperscript{160} It has since been isolated in the GEC from the porcupines Coendou prehensilis and Coendou sp. in Pará.\textsuperscript{161} All infections reported were of an unapparent nature. To date, this unusual parasite, which has the largest amastigotes of the known Leishmania species, has not been found in other mammalian hosts other than Coendou.

**Vectors.** Leishmania (L.) deanei is likely to be highly host specific and vector-specific. Lainson suggested that based on
the arboreal habits of its known host Coendou, the vectors would be found on large tree trunks or in their resting places in hollow trees.\textsuperscript{162} However, although this parasite was isolated from the vector Lu. furcata that was collected in a hollow tree in which an infected porcupines was living,\textsuperscript{92} there are doubts regarding this host based on etho-ecologic and physiologic considerations of the role of primary vector for this parasite.\textsuperscript{8} Further studies are required to understand this parasite pathogenic complex.

**Diversity.** Some intra-specific variations were found by iso-enzymatic starch gel electrophoresis.\textsuperscript{82} However, there was no apparent relationship between these groups and their origin.

**Sub-genus L. (V.) Lainson and Shaw, 1987.**

**Leishmania (V.) braziliensis.**

**Vectors.** The quasi-exclusive parasite/vector relationship of L. (V.) braziliensis and Lu. wellcomei was first demonstrated in Brazil.\textsuperscript{147,163} This highly anthropophilic sylvatic phleboto-mines species, which is commonly found in the Amazon region, is said to attack humans both during the day and at night. In the Serra dos Carajá region in Pará, Lu. wellcomei was the most common human-biting sand fly during the rainy season in the primary forest greater than 300 meters above sea level, however, it was not observed after entering diapause during the dry season.\textsuperscript{147} This species displays no tendency to colonize human habitations in the primary forest. Defining the pathogenic complex of this parasite is quite difficult because the parasite is observed in many areas of South America with very distinct ecologies and different sand fly fauna. It is also noteworthy that Lu. wellcomei is absent in many lowland areas of Pará where L. (V.) braziliensis has been isolated from patients with MCL and LCL. Evidence suggests that the major vectors of L. (V.) braziliensis all belong to the sub-genus Psychodopygus, and in a primary forest in Amazonas, the second most frequent sub-genus was Psychodopygus (22.8%).\textsuperscript{62} However, natural resting sites of these vectors in the forest remain unclear.

**Lutzomyia gomezi** and Lu. ovallesi near the NEC in north-central Venezuela were the main anthropophilic species implicated as vectors of this parasite.\textsuperscript{164} Lutzomyia panamensis was also identified as a vector.\textsuperscript{165} In Pará, Lu. complexus was found naturally infected with L. (V.) braziliensis. It was also shown to be highly anthropophilic and have an extensive geographic distribution in the lower Amazon region, indicating its potential as an important secondary vector for this parasite.\textsuperscript{166} The sylvatic species Lu. whitmani, which is a known vector of this parasite in southern Brazil where it is able to invade peri-domestic areas, has never been found infected in the GEC. Moreover, in the Brazilian Amazon, it is infrequently observed on tree trunks and shows little inclination to bite humans and colonize human dwelling places.

**Reservoir hosts.** Domestic animals such as equines and dogs play an important role in disease-endemic areas. In Venezuela, donkeys (Equus asinus), dogs, and cats have been reported infected.\textsuperscript{167–170} The importance of dogs as a reservoir of this parasite has been reported.\textsuperscript{171} In Venezuela, the transmission seemed to occur peri-domestically by Lu. panamensis, and some investigators have suggested that infected equines with ulcers imported from disease-endemic areas are an important factor in parasite dissemination in a peri-domestic area where these sand flies are abundant.\textsuperscript{57,168} Conversely, wild reservoir hosts of L. (V.) braziliensis are not well known and the primary reservoir of this parasite in the GEC has not been determined because of the vast area of South America. Several pathogenic complexes and their corresponding epidemiologic cycles may be present. Since the main sand fly vector of this parasite flies at ground level, primary reservoir hosts of L. (V.) braziliensis are likely to be terrestrial mammals. In an area in Lara State outside the GEC that is endemic for CL, two rodents species were found to be naturally infected, one cotton rat (Sigmodon hirsutus) and two black rats (Rattus rattus).\textsuperscript{172} In Pará, isolates of Leishma-nia from the rodents Rhipidomys leucodactylus and Proechimys guyannensis were closely related to L. (V.) braziliens-s.\textsuperscript{31} Other isolates from areas of Brazil outside the GEC were obtained from R. rattus, D. marsupialis, Oryzomys sp., and Akodon sp.\textsuperscript{173} Globally, subspecies of the L. (V.) braziliensis phylogenetic complex are most commonly found in the viscera of their hosts.\textsuperscript{82} Several small forest rodents have been suspected as reservoir hosts in sylvatic ecotopes, and there is evidence that domestic animals (dogs and equines) may serve as reservoirs in urban cycles of this parasite.

**Diversity.** Strains of L. (V.) braziliensis isolated in Pará have greater genetic variability and are genetically different from those isolated in Minas Gerais in southeastern Brazil.\textsuperscript{84} Other isolates in Brazil were shown to have different origins; some Amazonian stocks were related to Psychodopygus sand flies and some Parana strains transmitted by Lutzomyia sand flies were considered secondary adaptations from the Lutzomyia leishmanial gene pool.\textsuperscript{85} The high genetic diversity of parasites in the Amazon River basin was related to the large number of sand fly vectors. The association of L. (V.) braziliensis genotypes with specific transmission cycles probably reflects an adaptation of different clones to some particular vector species.\textsuperscript{86} The distribution of this parasite seems to be related to the origin of the gene pool, as well as to vector and reservoir movements.\textsuperscript{85}

**Leishmania (V.) guyanensis.**

Leishmania (V.) guyanensis was first described in the GEC by Floch in 1954 as L. tropica guyanensis causing LCL in humans.\textsuperscript{174} Since 1978, the eco-epidemiology of this species has been studied in Pará (Lainson and Shaw), Amazonas (Arias), and French Guiana (Le Pont, Pajot and Dedet).

**Vectors.** In the GEC, L. (V.) guyanensis is transmitted mainly by Lu. umbratilis. It was first identified as Lu. anduzei in French Guiana\textsuperscript{144} and in Suriname.\textsuperscript{175} It has been isolated from this vector in the Brazilian states of Amazonas, Amapá, Pará, and Rondônia\textsuperscript{31,65,141,149,176–180} and in French Gui-ana.\textsuperscript{46,60,181,182} In a primary rain forest of French Guiana, Lu. umbratilis was the most common species found on tree trunks,\textsuperscript{182,183} as well as in Amapá on bases of trees.\textsuperscript{65} Lutzomyia umbratilis is found at all levels of vertical stratification from 1 to 20 meters above ground level.\textsuperscript{62} It is present at ground level year round with important seasonal and interannual fluctuations. Le Pont and Pajot reported that although it spends most of the year in the forest canopy,\textsuperscript{181} this sand fly was abundant at ground level for approximately two weeks at the beginning of the long rainy season in French Guiana, with an abundance of aggressive populations showing a correlation with rainfall.\textsuperscript{182,184} It is attracted by various species of mam-mals and was the most common species found on humans in French Guiana.\textsuperscript{141,182} It bites humans both day and night, particularly when disturbed from tree trunks.\textsuperscript{181} Forest workers clearing land for plantations or seeking gold are particu-
larly at risk. Infection with *L. (V.) guyanensis* was shown to be seasonal in French Guiana, unlike in Pará, with peaks during the wet period when vectors rest at the ground level. Similar infection rates were observed in both Brazilian (1.83% and French (1.76%) female vector populations collected. Conversely, populations of *Lu. umbratilis* from Venezuela and different areas in Brazil displayed morphologic disjunctions. Since the level of intra-specific variations of zymodemes in the *L. (V.) guyanensis* species is low, this might have epidemiologic implications that support a particular role for vectors populations. Peri-domestic transmission has only been observed in houses situated in the forest or its fringes. Infected sand flies flying from the forest to the village were presumably attracted to lights in houses. Until now, *Lu. umbratilis* has never been found colonizing human inhabitants in spite of the high prevalence of LCL associated with habitats in or close to primary forest.

*Leishmania* (*V.*) *guyanensis* was also isolated from other phlebotomine species of the sub-genus *Nyssomyia*, which indicated the importance of this group in transmission, particularly since these species are numerous and widespread in the GECs. This parasite was isolated from *Lu. whitmani* in Amapá and Pará and from *Lu. dendrophylla* in Amapá. Occasional infections have also been reported in Pará in *Lu. anduzei*, which is also a canopy and tree-trunk dweller and may have some role as a secondary vector in the GEC. Promastigotes in the salivary glands of *Lu. anduzei* and *Lu. spathotrichia* were also reported. In the Venezuelan state of Lara, which is near the GEC, *Lu. ovallesi* was infected with parasites that were hybrids between *L. (V.) braziliensis* and *L. (V.) guyanensis*. In the Brazilian Amazon region, *Lu. shannoni* was observed to feed predominantly on sloths (73.0%), the main reservoir hosts of this parasite; this shows their potential involvement in transmission to *Choleopus didactylus*. All of these vector species may act as secondary vector for *L. (V.) guyanensis*.

**Reservoir hosts.** In the GEC, *L. (V.) guyanensis* is typically a xenarthan parasite. Thus, the disease caused by this parasite is clearly a wild zoonoses that occurs in the canopy of the primary rain forest. The two-toed sloth, *Choleopus didactylus*, presented high level of intact skin and internal organs infections: 35.5% according to Dedet, 46.6% according to Gentile, and 45.7% according to Lainson in Pará. Moreover, in the Brazilian Amazon region, the incriminated vectors *Lu. umbratilis* and *Lu. anduzei* predominantly fed on *C. didactylus* (64.0% and 63.6%, respectively). In French Guiana, 100% of the *Lu. umbratilis* females in contact with *C. didactylus* were observed to feed rapidly and heavily. Therefore, *C. didactylus* appears to be the primary reservoir of *L. (V.) guyanensis* in the virgin primary rain forests of the GEC.

Two-toed sloths are quite common, have few predators, often stay for long periods individually in the same tree, and are responsible for infection of large part of the vector population resting on tree trunks. This observation of numerous infected sand flies present in the same confined zone shows a correlation with the high frequency of multiple lesions in patients with LCL in the GECs. This cycle is reminiscent of the close relationship between hosts in the pathogenic complex that occurs in the rain forest canopy in Panama with *L. (V.) panamensis* and involves *Lu. trapidoi* and *C. hoffmanni*. The anteater *Tamandua tetradactyla* was also infected (25%) with *L. (V.) guyanensis* in Pará. This species was described as an important secondary reservoir host potentially responsible for parasite propagation because of its high mobility compared with the two-toed sloth. However, in French Guiana, Dedet and others did not find parasites in *Tamandua tetradactyla* or *Myrmecophaga tridactyla*. *Leishmania* (*V.*) *guyanensis* was also isolated from the armadillo *Dasypus novemcinctus* in Pará. Marsupials were also infected in the GEC. In French Guiana, only 1.6% of the *D. marsupialis* collected from sylvatic ecotopes were infected, showing that the common opossum appears to be an occasional host, as reported by Lainson and others in Pará state.

In Amazonas, no infections were detected in opossums from an undisturbed forest, but 20% of the *D. marsupialis* captured in a biologic reserve affected by human activity were infected in the skin or viscera. In an urban area of Amazonas state, *D. marsupialis* showed a high infection rate (61.9%) and was assumed to be the primary reservoir host of this species. Opossums, especially *D. marsupialis*, may become a significant reservoir of infection where human activities have eliminated *C. didactylus*. Therefore, opossums may act as a primary reservoir of *L. (V.) guyanensis* in urban areas, although they may play only a minor role in virgin forest. Some rodents such as *Proechimys sp* (2.2%) in French Guiana and *Proechimys guyannensis* (in skin) in Pará were also found to harbor *L. (V.) guyanensis*. Moreover, rodents, and particularly porcupines (*Erethizonidae*), were the second most frequently mammal fed on by *Lu. umbratilis* (11.6%) and the *L. shannoni* group (8.5%) in the Brazilian Amazon region. Infections were also found in *Potos flavus* in French Guiana. These mammals may be occasional hosts for this parasite.

**Diversity.** The level of intra-specific variations of zymodemes in the *L. (V.) guyanensis* species is said to be low. *Leishmania* (*V.*) *naiffi*. *Reservoir hosts. Leishmania* (*V.*) *naiffi* has been isolated from the blood and internal organs (liver and spleen) of the nine-banded armadillo *Dasypus novemcinctus* in northern Pará and in Amazonas, Pará, and Rondônia (infection rate = 15.6%). Armadillos were assumed to be the main reservoir hosts of this *Leishmania* species in the Brazilian Amazon. It is noteworthy that the geographic distribution of *L. (V.) naiffi* was recently shown to be much larger than that initially reported, and now includes Peru, Ecuador, and Martínique.

**Vectors.** In Brazil, *Lu. ayrozai* is the presumptive vector of *L. (V.) naiffi* for armadillos, but it is not very anthropophilic. Heavy infections were detected in *Lu. squamiventris*, a common human-biting phlebotomine in Amazonas and Pará. *Leishmania* (*V.*) *naiffi* was also isolated from *Lu. paraensis* although it is not greatly attracted to armadillos. However, it is not known which of these sand flies is the principal vector for humans.

**Diversity.** An intra-specific polymorphism has been reported in *L. (V.) naiffi*. As suggested by Lainson and others, if one considers that *L. (V.) naiffi* rarely produces a discernable skin lesion in hamsters, some infections may have been missed when a lesion was the sole detection method. Nonetheless, considering its clinical features and its incidence in the GEC, this parasite does not appear to be an important pathogen of humans.
Leishmania (V.) lainsoni.

Reservoir hosts. Leishmania (V.) lainsoni was first isolated near a rubber plantation in Pará from a human case of LCL. and then on the Island of Tocantins from the skin of Agouti pacas. The asymptomatic nature of this infection led Silveira and others to suggest that this rodent might constitute a primary host of L. (V.) lainsoni in the Amazon region. Moreover, the monkey Cebus apella has been experimentally infected.

Vectors. In Serra dos Carajás in Pará state, Lu. ubiquitalis was found to be naturally infected with this parasite. However, this abundant sylvatic species (22% of the sand flies tested in the primary forest of northern Pará) had not been previously reported to bite humans in the forest. It was also shown that it would feed on humans in the laboratory, as well as in the field, even if it did not appear to be an anthropophilic species. Pathogenic complex of this parasite seems to develop at least in primary forests from northern Pará to French Guiana and it exists in other regions where the sand fly vectors and the reservoir hosts occur together.

Diversity. Leishmania (V.) lainsoni intergenic region typing profiles were shown to be invariant.

Other flagellates. Many other flagellates have been isolated from sand fly vectors and/or mammalian hosts in the GEC without being identified. Unidentified Leishmania strains were isolated in the Brazilian Amazon region from the viscosa of two Dasyus novemcinctus (peri-pylarian species biologically and biochemically different from L. (V.) braziliensis, L. (V.) guyanensis, L. (V.) amazonensis, L. (V.) donovani s.l., and L. (V.) deanei);210 from Lu. longipalpis and Lu. anunesi on Marajó island; from Lu. whitmani (L. (V.) braziliensis-like organisms);141 from Lu. shawi, Lu. ubiquitalis, Lu. whitmani, Lu. hirsutus, Lu. paraensis, and Lu. wellcomei;147 from Lu. maripaensis (parasites of the Viannia subgenus);177 and from Lu. clausin. Other parasites were isolated in French Guiana from Potos flavus,190 Lu. gozemi and Lu. yuelli pajoitl,40 and in Venezuela from a single Lu. ovallesi (coexistence of two Leishmania species belonging to the L. (V.) braziliensis and L. (L.) mexicana complexes).202 The life cycles of these species of unidentified, unknown, or uncertain taxonomic position have not been described and additional epidemiologic investigations are needed.

ROLE OF HUMANS IN THE PATHOGENIC COMPLEXES OF THE GEC

There have been few epidemiologic studies in certain areas of the GEC (especially in Suriname and Guyana) and in most of these foci, the natural vectors and reservoirs are uncertain or even unknown. In addition, transmission is not haphazard in natural primitive sylvatic habitats. Ecologic barriers maintain a relatively strict mammal-sand fly-parasite relationship among the different species of Leishmania within distinct ecotopes. It is the interaction of vector and reservoir ecologies that determines the epidemiologic pattern of the leishmanial diseases. Trypanosomatids are said to derive from monogenetic intestinal flagellates of arthropods. In that case, phlebotomine sand flies should be regarded as the primary hosts of Leishmania species and mammals may act as secondary hosts that provide a source of parasites for these insects. Humans may play a dual role in the GEC both by being part of the pathogenic complexes, mostly as occasional reservoir hosts, and by directly or indirectly transforming these cycles.

Transmission to humans. With regard to Leishmania sylvatic species, human contamination results in the intrusion of humans into forested pathogenic complexes and could occur during both short trips and long stays in the forest. In that case, most infected people are young adult males who enter the forest mostly for occupational activities and to a lesser extent for leisure activities. Individuals involved in recreational activities in the GEC rain forest such as seeking gold, forestry, military activities, construction of highways and hydroelectric dams, hunting, scientific research, and ecotourism are more exposed to infected sand fly bites. One important factor in the transmission of parasites is the establishment of human settlements in the forest. This has resulted in specific transmission processes with intra-domiciliary contamination that occurs by infected sand flies flying at night from the neighboring forests into human housing. Thus, increases in leishmaniasis are often associated with new agricultural activities or gold mining and the entry of new non-immunized persons in these areas with low demographic densities where infection is ordinarily a strict zoonosis. Another important factor in the GEC is the coexistence of several cycles in the same biotope that raises the question of the type of infection acquired by humans.

For example, both Proechimys cuvieri and Lu. flaviscutellata were found infected with L. (L.) amazonensis in a primary forest area of French Guiana where L. (V.) guyanensis was simultaneously isolated from Lu. umbratilis. Moreover, if one considers the high human migratory patterns in this area, special care should be taken in each country with regard to the distribution of each parasite, especially when new species are found. Intense migrations (legal or illegal) now observed in the GEC could lead to the isolation of species that are not endemic to specific areas.

Influence of humans on the ecology of the pathogenic complexes. If a geographically defined pathogenic complex is present in an area, the risk of humans being infected will be higher since commonly infected mammalian hosts are abundant and vectors are anthropophilic. Fluctuations in vector and reservoir populations may be natural, but can also be induced by human activity, either deliberately to control endemics or in indirect ways. Any modification of the environment may influence to various degrees the prevalence of leishmaniasis in a given region. Several general or more specialized reviews report and exemplify different risk factors linking leishmaniasis to environmental modifications.

Cutting down trees leads to immediate aggression by sand flies and diurnal contamination. However, damage to forests might play a more important role in the absolute multiplication and proliferation of specific vectors, and human activity may also increase the risk of infection. For example, in virgin primary rain forest devoid of human influence, the Psychodopygyus complex species were considered the main phlebotomine sand fly group of the Amazon region. In French Guiana, this group represented 62.7% of the sand flies caught at ground level. However, in the same type of forest that was affected by human activity, the same species complex became the minority, representing only 4% of the sand flies caught. The main species in this case belonged to the Nyssomyia complex, with most (35%) of the Lu. umbratilis
being two-fold more numerous on tree trunks than in pristine forest.\textsuperscript{183} At ground level of the forest affected by human activity, populations of \textit{Lu. umbratilis} were directly related to rainfall and did not increase only during a narrow time frame in the dry season, as was observed in the intact rain forest.\textsuperscript{181,182} This consequently increased the risks of contact with humans.

None of the mammal-sand fly-parasite combinations are likely to share exactly the same ecotope. Nevertheless, changes in the topography or in vegetation profiles could attenuate transmission, and subsequent growth of secondary vegetation could increase transmission risk by the creation of a new ecotope propitious to a different parasitic cycle.\textsuperscript{215} It is noteworthy that the vectors of the Guianan foci of LCL caused by \textit{L. (V.) guyanensis} occur principally in the anthropized rain forests. Destruction and subsequent regrowth of this area results in low and dense vegetation that is highly favorable to \textit{Lu. flaviscutellata} and may therefore increase the incidence of DCL due to \textit{L. (L.) amazonensis}.\textsuperscript{216} Moreover, some known mammal reservoirs such as rodents are very resilient and may rapidly adapt to completely different types of forests. For example, in the Brazilian Amazon region, \textit{Proechimys} has adapted to timber plantations for the production of paper pulp and \textit{Lu. flaviscutellata} populations have increased. This has resulted in the transmission of \textit{L. (L.) amazonensis} among these rodents.\textsuperscript{72} Forest degradation and deforestation followed by a subsequent regrowth of a wild secondary forest, as well as the development of agricultural plantations, appear to be favorable factors for the multiplication of sand flies, especially of the sub-genus \textit{Nyssomyia}, which includes many of the Amazonian vectors.\textsuperscript{213} Conversely, \textit{L. (V.) guyanensis} in primary forest is unlikely to survive in secondary forest or on new plantations, where there are few or no large trees. The microhabitat of plantations is unfavorable for the sand fly vector due to low humidity and the smooth surface of the small tree trunks. These trees also constitute an unfavorable environment for large and relatively heavy animals such as sloths. In addition, in most of the plantations in the GEC, this animal is deprived of its normal diet of foliage and fruits of native trees.

Alternatively, reducing forests and establishing open, dry terrain may create new areas favorable for \textit{Lu. longipalpis} and AVL. Human ecologic changes may result in modifications to the ecology of pathogenic complexes and transform the entire eco-epidemiologic patterns of leishmaniasis, leading to a reduction or more likely an increase in human disease.\textsuperscript{102}

Another important consideration should be the progressive urbanization of AVL in Brazil\textsuperscript{14} that is associated with human migrations to the periphery of large cities, where overcrowding and poor sanitation create an excellent habitat for insect vectors. In these peri-urban and urban areas, dogs seem to be the major reservoir of the parasite, and their migration could be responsible for the origin of new foci. In many towns, the infestation rate is maximal near the forest edge next to the sylvatic region. The transmission rate would then rapidly decrease with increasing distance from the center of the region because of short flight distances of the vectors. Vector-culling programs have already been tried in some Amazonian foci but results have been heterogeneous.\textsuperscript{187,217–220}

As reported by Lainson and others,\textsuperscript{173} the variety of leishmanial parasites observed in the Amazonian mammalian fauna compels us to believe that the predominantly sylvatic ecology of different \textit{Leishmania} species was present in the GEC before European colonization and the relentless impact it had on the virgin rain forests. However, the primitive source of the parasite is still likely to be present in the degraded forests. Today, some \textit{Leishmania} species can be maintained in both sylvatic and urban cycles that involve different vectors and hosts in their transmission.\textsuperscript{173} Some sand fly species survive by adapting to peri-domestic or even intra-domiciliary habitats in rural areas, and their reservoir of infection may also include some domestic animals such as dogs and equines. Complex evolutionary mechanisms such as adoption of new, secondary reservoir hosts, adoption of new vector species, and transport of infection in humans or domestic animals result in new pathogenic complexes that favor anthropozoonotic situations. Lainson and others reported that other \textit{Leishmania} species are doomed to extinction together with their sand fly vectors and/or, if ever, with their highly specific mammalian host.\textsuperscript{173} Therefore, deforestation results in increased open lands that may decrease the incidence of sylvatic CL, but increase the incidence of peri-urban and urban CL and visceral disease. Environment and leishmaniasis, as well as many other human tropical diseases, are linked together by human behavior, both personal activities and societal organization. Increasing risk factors related to natural and human-made environmental changes are making leishmaniasis a growing public health concern for many South American countries, especially in the GEC. It remains to see whether these processes will ultimately occur after the ongoing progressive devastation of the rain forest.

\section*{CONCLUSIONS}

Both geographic extension and numeric increase of leishmaniasis cases in the GEC, as in the rest of South America, are worrisome. Originally strict wild zoonoses, which developed in forested ecotopes, \textit{Leishmania} showed a peculiar plasticity of evolution to face environmental modifications following anthropization. If the explosive urbanization and clearance of forests for agricultural and other purposes reduced areas of certain endemic leishmaniasis, it should be realized that one form of leishmaniasis may be eliminated at the risk of encouraging another.\textsuperscript{71} A better understanding of all \textit{Leishmania} species life cycles, including a subtle grasp of their specific vectors and particular reservoir hosts ecologies, may help in future prevention and/or control of the diseases they cause.\textsuperscript{21} The study of the pathogenic complexes and their respective eco-epidemiology should be conducted in parallel with prophylactic and therapeutic studies.

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