

## American Leishmaniasis

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*The origin of leishmaniasis in the New World is discussed, and the numerous forms of the disease are briefly described. The epidemiological pattern of American leishmaniasis is clearly that of a zoonosis in various stages of development. Nine geographical types of cutaneous leishmaniasis are recognized, and probably others exist also; the visceral disease is of the well known Mediterranean type and of a uniform type throughout the Americas. The prevalence of human infection in the different regions is discussed with particular reference to the animal reservoirs. Disturbances of the terrain for agricultural development, road construction, etc., lead to epidemics and there is some evidence that the disease is now spreading in Latin America.*

The source of cutaneous leishmaniasis in the New World has been much debated and the subject has been discussed recently by Hoeppli (1969). It was thought at one time that characteristic deformities depicted on pre-Colombian pottery denoted the existence of indigenous leishmaniasis, but it was later pointed out that these facial scars could be better interpreted as syphilitic lesions or the results of some other infective process. Accordingly, it was considered probable that leishmaniasis had been taken to the Americas by the Spanish *conquistadores* and by inhabitants of the Mediterranean littoral. Now, however, the discovery of widespread leishmanial infection in wild rodents in vast uninhabited areas of South and Central America has again caused views on the origin of the infection to change. It is true that some zoonoses may be secondary, i.e., derived from a human source, like plague in California or South Africa, but the remoteness and extensiveness of leishmanial infections in wild South American rodents make such a hypothesis extremely unlikely. The source of leishmaniasis in Latin America is not entirely an academic speculation because the specificity of the causative organisms is involved, and the question arises whether the Old and New World species of *Leishmania* are the same or different. This point has been discussed elsewhere (Garnham, 1971) but, briefly, it seems that the cutaneous forms of leishmaniasis clearly have different etiologies, while the visceral form is identical throughout the world.

Two main types of the disease exist in the Americas, as in the Old World—namely, visceral leishmaniasis (kala azar) and cutaneous leishmaniasis. In South America, the latter is often called mucocutaneous leishmaniasis but it is increasingly evident that this disease (commonly known as *espundia*) is only one of many varieties of leishmaniasis occurring in the New World.

This article deals with epidemiological (i.e., relating to the natural focus) and clinical aspects of the disease but entomological factors are not considered. The cutaneous forms of the disease are described geographically (from north to south) because speciation appears to be related to special animal reservoirs and insect vectors of the different regions, though whether this is a true interpretation of the nosology is debatable; certainly, in the Amazonian region it is difficult to make specific identifications. Very little is known about the visceral disease, which has been recognized only comparatively recently and usually occurs sporadically; so far, no epidemics of kala azar have swept across wide tracts of the New World as they have so frequently done in the Old World. Perhaps the failure of epidemics to spread in the New World is due more to the habits of the vectors than to the sparseness of the population. Visceral leishmaniasis in Latin America was originally thought to be due to *Leishmania chagasi* but the causative agent is now considered to be indistinguishable in every respect except distribution from *L. donovani*, or from *L. infantum* if this is recognized as a valid species. The disease is certainly of the "Mediterranean" type (Alencar, 1958).

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## AMERICAN LEISHMANIASIS AS A ZOONOSIS

Human leishmaniasis should be thought of as a zoonosis, whatever evolutionary stage the local form of the disease may have entered. In Latin America, all stages may be observed from the pure zoonosis to the final anthroponosis, and various stages are manifested as specific diseases. The role of animals in maintaining this infection is fundamental but often puzzling. The two kinds of leishmaniasis, visceral and cutaneous, are associated with particular types of animal reservoir, kala azar with jackals and foxes or other wild canines, and cutaneous leishmaniasis with a variety of wild rodents. This distinction is not absolute and, in tropical Africa, rodents have been found infected with visceral strains. Curiously enough, the dog is later associated, as a liaison carrier, with both forms of infection.

The epidemiological pattern of American leishmaniasis is a progressive one on the same general lines as most zoonoses, at least those with a bacterial, viral, or protozoal etiology. At first, the infection is confined to the original wild animal host and its specific *phlebotomine* vector; man is outside this cycle but sooner or later intrudes into the feral environment, either sporadically to hunt or collect chicle, or, more permanently, to occupy the land. With sporadic intrusions the zoonosis continues its old course practically undisturbed, but when intrusion is permanent the environment becomes greatly changed; the wild animals are driven away and replaced by domestic animals and by vectors adapted to live commensally in houses. At this stage dogs may assume an important role in transmission, although the prevalence of canine leishmaniasis presents paradoxical features. In some highly endemic regions, such as the state of Ceará, Brazil, or Peru, dogs are commonly infected; in other, equally endemic, areas in Central America, dogs seem to play little or no part in transmission.

The animal reservoirs of *Leishmania* are usually ideal hosts in that they develop highly infective cutaneous lesions that contain organisms in the most superficial layers; these organisms are either harmless to the host or kill it only after many months.

## CUTANEOUS LEISHMANIASIS

The great interest and importance of American cutaneous leishmaniasis is its extreme variability. This is in contrast to the Old World disease where only two forms—the wet and the dry—are generally

recognized. Many of the American forms present such distinctive features that they form clinical entities and apparently represent infections by particular species. Nevertheless, the situation is not clear in some countries and the lines of differentiation between the forms of cutaneous leishmaniasis are blurred.

The cutaneous forms of the disease are as follows (in geographical sequence from north to south):

- (1) Chiclero's ulcer in Mexico, Guatemala and Honduras;
- (2) Costa Rican leishmaniasis;
- (3) Panamanian leishmaniasis;
- (4) *pian-bois* of French Guiana;
- (5) the "diffusa" form in Venezuela and Ceará, Brazil;
- (6) cutaneous leishmaniasis of Colombia;
- (7) Amazonian leishmaniasis;
- (8) the muco-cutaneous leishmaniasis (*espundia*) of Brazil; and
- (9) *uta* of Peru and Chile.

Each of these forms is associated with its own particular landscape epidemiology, but they all possess one feature in common—namely, close association with forests—that is in striking contrast to the semidesert or steppe conditions in which Borovsky's disease flourishes in the Old World. The only exception in the New World is the region where *uta* is prevalent (see p. 525). The disease becomes a problem mainly when the environment is disturbed, examples being outbreaks associated with the flight of revolutionary troops into the forest in Paraguay and the migration of famine-stricken Indians from the highlands around Lake Titicaca into the fertile Amazon basin below. Outbreaks are associated particularly with the deforestation of land, as in Brazil, Costa Rica, etc., for development or road-construction.<sup>1</sup> Thus any new project involving the disturbance of land in endemic areas should be accompanied by preventive measures against leishmaniasis.

## CHICLERO'S ULCER

This form of leishmaniasis caused by *L. mexicana* is an occupational disease, particularly associated with nomadic workers in the forest, who collect chicle gum and cut mahogany. It is confined to

<sup>1</sup> For further details about factors contributing to outbreaks the reader is referred to Garnham (1971).

forests of the Yucatan, Oaxaca, etc., in southern Mexico, Honduras, and the Petén (Guatemala). The human disease is entirely zoonotic in origin (Garnham & Lewis, 1959) and three species of sylvatic rodent are the reservoirs of infection. Lesions are present on 40% of *Ototylomys phyllotis*, 12% of *Nyctomys sumichrasti*, and 10% of *Heteromys desmarestianus* (Lainson & Strangeways-Dixon, 1964). These animals are largely arboreal in habit, but descend to the ground at night; there, they are readily bitten by the phlebotomine vectors. Other local rodents, such as the cotton rat, can easily be infected experimentally, and there is little doubt that the range of natural reservoirs extends beyond the three rodents named above. The presence of an infected animal indicates a focus of *L. mexicana*, and trapping is probably the most convenient way of locating an infected area; this method is easier than finding infected *Phlebotomus* and more certain than attempting to discover the origin of a human case. The epidemiology of the disease in Honduras has been thoroughly discussed by Williams et al. (1965) and by Disney (1968), and Biagi et al. (1965) have discussed transmission in Mexico.

The disease is normally contracted by people working in high forest but infected rodents have been found also in less primeval conditions, in second-growth forest for example, where people exposed to the night-biting vector may also become infected.

Chiclero's ulcer most commonly affects the ear, which, in the course of years, gradually becomes eroded away, the progress of the disease being very slow. Mucous membranes are never affected. The organism can only be found in the first two or three months after infection, as is usual with most forms of cutaneous leishmaniasis. The disease is, however, easily diagnosed by the positive Montenegro reaction.

The histopathology of chiclero's ulcer, which is almost pathognomonic of *L. mexicana*, was described by Garnham (1962). It need only be stated here that the organism produces, in hamsters and mice, large subcutaneous tumours that readily visceralize. The tumour is a histiocytoma with the parasites arranged in garlands around the periphery of the cells. Such a picture is only rarely seen in other forms of the disease.

#### COSTA RICAN LEISHMANIASIS

Leishmaniasis in Costa Rica is found particularly in new settlements where an immigrant population lives under rough conditions while clearing forest for agricultural or other purposes. Little is known

about the detailed epidemiology, but the clinical aspect of the disease is quite different from the northern form and, in general, resembles the leishmaniasis seen in many parts of South America, muco-cutaneous disease being occasionally found, though much less often than in Brazil. A few cases of a similar type of disease have also been seen in Honduras.

#### PANAMANIAN LEISHMANIASIS

Leishmaniasis has been extensively studied in Panama, revealing a complex situation. Hertig et al. (1958) reported the presence of a 10% infection rate in the heart blood of spiny rats (*Proechimys semispinosus* and *Hoplomys* sp.); parasites were absent from the tissues of the animals and from those of hamsters inoculated with extracts from these animals, but the extracts gave rise to lesions in human volunteers. In subsequent years, the infection has not been found in the rodents, but men entering the forests of Panama frequently contract leishmaniasis, and natural infections have been demonstrated in phlebotomines caught in the forests. The role of the spiny rat in the epidemiology of the disease in Panama was therefore difficult to understand, and it seemed likely that this animal was, like man, merely an accidental host, and that the true reservoir was some other animal, probably a rodent. Later work (Gorgas Memorial Laboratory, 1966, 1969) revealed natural infections in the kinkajou, opossum, porcupine and sloth, but these may be abnormal hosts and the natural host has perhaps not yet been discovered.

The clinical features of the disease in Panama follow the usual, milder course of South American leishmaniasis. Recent work on the immunology of different strains of the parasite isolated in Panama suggests that at least two types are present, which have not so far been linked with any special pathological features.

#### PIAN-BOIS OF FRENCH GUIANA

Although this disease due to *L. guyanensis* has been known for a long time, and its association with sylvatic conditions is well recognized, complete descriptions of the epidemiology and even the clinical features have still not been published. The condition undoubtedly merges into similar types of leishmaniasis prevalent in adjacent territories, such as the Orinoco-Amazon watershed.

The disease is manifested by the usual chronic ulcers on exposed parts of the body and in 5% of the cases metastasis to the nasal mucosa is said to occur.

#### LEISHMANIASIS TEGUMENTARIA DIFFUSA

This florid type of the disease caused by "*L. pifanoi*" occurs very occasionally in Venezuela (20 cases were reported, by Torrealba in 1967) and also on the north-west coast of Brazil and in Amazonas. It is characterized particularly by the invasion of the blood-stream by the parasite. Some of the clinical features are shared by cases of cutaneous leishmaniasis seen recently in Ethiopia. Large plaques form on the skin and are heavily infiltrated with infected macrophages. Such cells extend deeply into the subcutaneous tissue where they break down and the parasites escape and invade the blood-stream, perhaps via the lymph and thoracic duct. Positive blood cultures are obtained but, in spite of the systemic infection, "*L. pifanoi*" fails to become established in organs; the reason for this is unknown. Equally incomprehensible is the negative Montenegro reaction given by patients with this infection, and it is also strange that involvement of the nasal mucosa is rare in this form of the disease.

There is some evidence that the "diffuse" phenomenon is the result of a failure of cell-mediated immunity (Garnham & Humphrey, 1969) and it is now widely held that no particular species (such as "*L. pifanoi*") is responsible for this form of infection but that the factor lies in the host (Bryceson, 1969; Bryceson et al., 1969).

#### CUTANEOUS LEISHMANIASIS OF COLOMBIA

The disease is rather uncommon in Colombia although sporadic cases do occur, particularly in the Magdalena Valley. This region used to be heavily forested but it has undergone close agricultural settlement for nearly a century, and much of the forest has now disappeared. The infection has, however, managed to persist, though whether in rodents or other animals, or by interhuman transmission, is unknown. The disease is mild and mucous lesions are rare.

#### AMAZONIAN LEISHMANIASIS

In spite of the vast extent of the Amazonian sylvatic region, cutaneous leishmaniasis is not prominent among the human diseases, except when the environment is grossly disturbed, as in road-

making. Sporadic cases certainly occur and include the condition known as *espundia*. Nevertheless, the disease may be quite common on the borders of the region; for example, an epidemic broke out in 1963 among Indians who were driven by enemy tribes to take refuge in riverine forest of the Xingu, a tributary of the Amazon (de Carneri, 1963).

The situation has been studied by Guimarães & Azavedo (1964) and by a team from the Wellcome Foundation at Belém (Lainson & Shaw, 1968), where an intensive focus of infection has been found to exist in the wild rodent *Oryzomys*. As in foci further north, lesions are found at the base of the tail in these animals. A curious feature is that human cases of the disease are rare or absent in the vicinity of the Belém focus and, as in Panama and more southerly parts of Brazil, the strains may be undergoing, as suggested by Forattini (1960), a speciation that confines them to a particular host. It seems to be more probable, however, that the rodent-*Phlebotomus*-man chain is defective, so that human infections can rarely take place.

The latest work by Lainson & Shaw (1970) has demonstrated the existence of two strains of the parasite; one strain, growing with difficulty in cultures and in hamsters, affects a single rodent reservoir (*Orizomys concolor*) and produces *espundia* in man; the other strain, growing exuberantly in cultures, gives rise to large histiocytomata in laboratory animals, affects many species of wild animals and in man is confined to the skin.

#### MUCO-CUTANEOUS LEISHMANIASIS

This form of leishmaniasis, caused by *L. braziliensis*, is the classical form (*espundia*), which, until recently, was considered to be the only type of the disease in the New World, with the possible exception of *uta*. It is found typically in Brazil and in the adjoining forested territories east of the Andes in Peru, Ecuador, Chile, Bolivia, and Paraguay. The prevalence is unknown but is probably immense.

Nasal involvement occurs in 80% of infections with *L. brasiliensis*, although a proportion of these infections may be subclinical. Probably up to 30% of cases develop mucous lesions that end in terrible deformities of the nose and mouth, or the lesions may extend from the palate to the larynx and trachea, and cause death from septic bronchopneumonia. The mucous lesions may be extensions of a cutaneous ulcer, or, more frequently, are metastatic in origin, and can arise several years after the initial sore has

healed when it might be thought that the patient had acquired full immunity. Adler (1964) suggested that foci of infected macrophages persist in the cartilage of the nose or mouth and multiply in a site untouched by the immune mechanism. *Espundia* is the only fatal form of the cutaneous disease and is very resistant to treatment.

It is unwise to generalize about the epidemiology of *espundia* since the conditions are not uniform everywhere, but once again the forest environment constitutes the essential part of the natural focus. The disease is sporadic or uncommon until this environment is disturbed, but once settlement is attempted, involving widespread destruction of the forest, *espundia* may break out in the form of severe epidemics.

Brazilian workers minimize the importance of an animal reservoir, particularly when the disease is occurring in an almost epidemic fashion in newly developed regions, as in the states of São Paulo, Bahia, Matto Grosso, Goiás and Minas Gerais. However, it was in circumstances such as these that Pessoa (1967) stressed the potential danger of entry into a natural focus of the disease, e.g., the construction of the new capital or the North-South Highway. Dogs are rarely affected in Brazil; in the Matto Grosso, Forattini & Santos (1955) found only 1 infected dog out of 180 examined. *L. brasiliensis* is equally uncommon in wild animals, although Forattini (1960) noted rare infections in a paca, an aguti, and in *Kannabateomys amblyonyx*. Probably, a survey of wild rodents would reveal the existence of a sylvatic reservoir in the forests of southern Brazil, and recently Barbosa et al. (1970) demonstrated the infection in *O. eliurus* in forest in the state of Rio de Janeiro.

#### UTA

Cutaneous leishmaniasis (*uta*) caused by *L. peruana* has long been recognized in the high Andean valleys of Peru and Bolivia, and the fact that it was quite different from *espundia* was quickly appreciated since mucous lesions were practically absent. This form of the disease closely resembles the mild types seen in Colombia and Central America, or in the Old World.

Two remarkable features characterize *uta*—namely, its transmission at an altitude of 2 800 m in the barren Cordilleras, and the existence of an important reservoir of infection in the dog. The conditions prevailing on the Pacific slopes of the Andes are very different from those of the tropical

rain forest areas where cutaneous leishmaniasis is so common elsewhere in Latin America. The minor role played by the dog in the other leishmaniasis areas is also in great contrast to the situation in Peru, where infection rates as high as 50% have been reported in dogs. The dogs often lack visible ulcers, but the organisms can readily be found in the skin, especially in the nasal region. Herrer was able to reduce the infection rate to less than 2% by peridomestic spraying with DDT. On the other hand, the infection could not be found in a wide range of wild mammals.

#### VISCERAL LEISHMANIASIS

Kala azar was thought to be practically non-existent in the New World until the introduction in 1934 of the viscerotome for the diagnosis of yellow fever in cadavers in Brazil. When sections of the liver were examined it was found that visceral leishmaniasis was not uncommon (Pena, 1934), and the subsequent use of this technique elsewhere in Latin America (Colombia, for example) has disclosed a widespread prevalence of the disease, although cases are usually sporadic. Cases have been reported in Mexico, Guatemala, El Salvador, Colombia, Venezuela, Surinam, Brazil, Bolivia, and Paraguay. Although the epidemiology is not absolutely identical in all these countries, the infection follows a common pattern, unlike the diverse picture presented by the cutaneous varieties of the disease.

The disease is much more domestic than is cutaneous leishmaniasis and occurs principally in rural, non-forested areas and in small towns or settlements. It has been studied mostly by Deane and Alencar in Brazil, where it was noted that 80% of the cases occurred in children (compared, for instance, with the 100% of cases of chiclero's ulcer in adults).

The studies of Deane (1956) and Alencar (1958) clearly demonstrated that kala azar is a zoonosis, at least in some parts of Brazil (Ceará). Deane found a 12% infection rate and Alencar a 4% rate in the fox, *Lycalopex (Dusicyon) vetulus*. Dermal infection is intense in these animals, particularly around the muzzle, which is avidly attacked by the local vector (*Phlebotomus longipalpis*). The fox often comes close to human dwellings to raid chicken runs, *P. longipalpis* become infected, and the organism is transmitted to domestic dogs or, rarely, to cats or to man. The disease in the fox is quite severe, which is possibly an indication that this animal may not be a

true indigenous reservoir, and that the zoonotic picture may not be as clear as was at first thought. Thus, in Brazil, the zoonosis possibly evolves in the following way: the source is a wild canine (or even perhaps a sylvatic rodent); the infection infiltrates much later into the fox, *Lycalopex vetulus*, and at the same time into dogs; at the source, the infection in man is sporadic, but with the involvement of dogs and foxes it becomes, at times, epizootic and epidemic. The Brazilian investigators found that infection rates as high as 27% occurred in dogs in certain foci.

On the other hand, some workers think that *L. donovani* was introduced into South America by

early settlers, from whom it spread first to dogs and then to foxes; however, the distribution of the infection in remote parts of the continent seems to invalidate this hypothesis (see Lainson et al., 1969). Further evidence on reservoir hosts is needed before a conclusion can be reached.

Under certain conditions, kala azar could probably become an important disease in Latin America and, obviously, a close watch should be maintained on fluctuations in the incidence and for its appearance in new regions. Coelho (unpublished data) reported that a new focus exists in the State of Goiás, Brazil, where the infection appears to be spreading in recently colonized areas.

## RÉSUMÉ

### LA LEISHMANIOSE AMÉRICAINNE

Le présent article donne de brèves indications sur la leishmaniose dans le Nouveau Monde, notamment en ce qui concerne l'épidémiologie des diverses formes de la maladie et leur comportement en tant que zoonoses à divers stades d'évolution.

Il y a deux variétés principales de leishmaniose, l'une cutanée et l'autre viscérale. On pense que la première est indigène; l'origine de la seconde est plus discutable. Les formes cutanées sont extrêmement hétérogènes de nature. Il en existe actuellement au moins neuf que l'on distingue d'après divers critères: distribution géographique, réservoir animal, insecte vecteur, réactions d'immunité, comportement chez les animaux de laboratoire, réponse aux médicaments, etc. L'ancienne notion selon laquelle *Leishmania braziliensis* serait responsable de toutes ces formes a été désormais rejetée et cette dénomination est maintenant réservée à l'organisme responsable de la leishmaniose mucocutanée. La forme « diffuse » n'est plus

attribuée à une espèce spéciale (*L. pifanoi*); on pense qu'elle résulte d'une réponse anormale de l'hôte.

La forme viscérale (du type « *infantum* ») présente des caractéristiques homogènes et, bien qu'elle soit étendue, a une incidence sporadique sauf en pays sec, dans le nord-est et le centre du Brésil. Les formes cutanées s'observent en région forestière (formes sylvatiques) et proviennent d'un réservoir existant chez des rongeurs sauvages; la forme viscérale est en grande partie non sylvatique et dérive vraisemblablement d'espèces canines sauvages. Le chien ne joue généralement qu'un rôle négligeable dans la transmission de la leishmaniose cutanée, mais c'est un important réservoir intermédiaire de l'infection viscérale.

La maladie s'étend et c'est pourquoi des études continues de son épidémiologie sont nécessaires en tant que mesures de santé publique.

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