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Review Article

Vector-Host-Parasite inter-relationships in Leishmaniasis: A New Concept

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ABSTRACT

This manuscript proposes a new hypothesis and a new concept in Leishmaniasis transmission, that points to a "vector-host-parasite" specificity. This concept will open a new approach for analysis of *Leishmania*/sandfly problems in transmission. Indeed, it will help to answer the following questions: 1-Why transmission doesn't occur from accidental hosts at all, but transmission occurs from reservoir host to either reservoir or accidental host? 2-Why transmission in nature is much more efficient than it would seem to be from experiments in the laboratory? 3- Why Leishmaniasis usually occur as an endemic disease and not epidemic one?

KEYWORDS: vector, *Leishmania* parasite, accidental host, reservoir host, transmission, differentiation.

INTRODUCTION

The transmission of *Leishmania* depends on the intimate biological association of three different types of organisms, commonly a mammalian vertebrate host (humans, dogs, rats, etc.), an hexapod invertebrate vector (sand flies) and the pathogen (leishmanial parasites). Each pair of associations (vector-parasite, vector-host and parasite-host) interacts with each other to generate the precise epidemiological patterns observed in nature. The development of parasites in their invertebrate vectors has been one of the most challenging problems facing parasitologists (Jacobson & Doyle 1996). This is because investigators have always been met with problems in studying the transmission of *Leishmania* parasites, particularly, the transmission of infantile kala-azar in the Mediterranean basin. There were many attempts for transmissions, which made by Johnson & Hertig (1970) with few successes and many failures. They found that the parasites tended to persist throughout the life of the sand fly but the transmission failed. Then, they were not able to find out the reasons for these failures.

Knowledge of the development of *Leishmania* in sand flies and its transmission to vertebrate host(s) has been based on observations on infected flies maintained in the laboratory under conditions, which differ from those, experienced by vector species in nature. It is most likely that transmission in nature is much more efficient than it would seem to be from experiments in the laboratory (Adler *et al.* 1938). In addition, the use of laboratory hosts gives answers that may be less relevant for the natural epidemiology of the disease (Randolph & Nuttall 1994). This manuscript is the first that reviews the inter-relationships between "vector-parasite", "vector-host" and "parasite-host" interactions in the light of studies that were carried out by previous authors.

Insect vectors for leishmaniasis ("Vector-Parasite" relationship): Vector is taken to mean an insect, which transmits the parasite in nature. While it is often very difficult to prove this, it is possible to accumulate evidence, through experimental infection, naturally caught infected sand flies, data on feeding habits ...etc., which makes incrimination of a vector highly probable (Ashford & Bettini 1987). The cycle of *Leishmania* in the vector involves a complicated system of interactions at different stages (Molyneux & Killick-Kendrick 1987). Many authors referred to several hypotheses to explain "vector-parasite" specificity, but the relationship between the life cycle of the parasite and vector physiology has remained ambiguous.

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The early hypothesis introduced to explain "vector-parasite" specificity was based around the digestive processes of the insect (i.e. vector - specific) that determine which parasites develop inside it (Borovsky & Schlein 1987). Borovsky & Schlein (1987) studied the effect of *Leishmania major* and *Leishmania donovani* on the digestive enzymes of *Phlebotomus papatasi* in the presence of rabbit blood. They suggested that low levels enabled *L. major* to thrive but high levels inhibited the growth of *L. donovani*. However, Walters *et al.* (1992) reported that there was no evidence of parasite susceptibility to gut proteolytic enzymes of sand flies.

Daba (1994) found that there are two factors affecting proteolytic enzyme activity in the gut of *Phlebotomus langeroni*. The first one is the kind of blood meal that *P. langeroni* feed upon. This finding might relate to the variation in the inhibition capacity among the vertebrate bloods (Huang 1971). The inhibitory factor(s) combines with the insect midgut protease to neutralize it, thereby inactivating it (Fisk 1950); several authors (Kiekens *et al*. 1965) considered this phenomenon. The second factor affecting the proteolytic enzyme activity in *P. langeroni* gut is the leishmanial species. Mixing the blood meal with *Leishmania* of different species (*L. infantum* or *L. major*) induced changes in the level of protease activity from normal in the gut of *P. langeroni*. This suggests that parasite nutrition and their metabolic products influence the protease activity of the insect.

Additionally, Daba (1994) revealed that there is an absence of vector-specificity in the *Leishmania* / sand fly relationship, since the reduction or increase in the proteolytic activity of *P. langeroni* has no effect on the survival of either *L. infantum* or *L. major* inside the *P. langeroni* gut. Both parasite species tended to persist throughout the life of the sand fly despite changes in the proteolytic activity.

The authors believe that the hypothesis based around the digestive processes of insect is real only when the comparison is made between haematophagous insects with different sizes, but for members of the same genus (like sand fly species) having approximately the same size, secrete approximately the same amount of the proteolytic enzymes in their guts that can be tolerated by *Leishmania* parasites.

The absence of vector - specificity in *"Leishmania* / sand fly" relationship has also been reported by several other authors. Bernett & Suyemoto (1961) suggested that virulence of leishmanias might be influenced by the species of sand fly, but they offered no supporting experimental evidence for this proposal (Killick-Kendrick 1979). Belding (1965) found natural infections with *L. donovani* in several species of sand flies. Moreover, there is no vector specificity in the New World species (Coelho 1966) as indicated by the Old World species of *Leishmania* (*L. tropica*) that could be easily established in New World flies, *Lutzomyia longipalpis* and *Lutzomyia renei* (Coelho *et al.* 1967). Meanwhile, all Panamanian strains of *Leishmania braziliensis* produced infections in both sand fly species *Lutzomyia sanguinaria* and *Lutzomyia gomezi* and two strains of *Leishmania mexicana* caused infections in either *Lu. sanguinaria* and *Lu. gomezi* (Johnson & Hertig 1970). In addition, it was found that *L. mexicana* produced infections in *Lutzyomayia abonnenci* (Walters *et al.* 1987), *Lutzomayia diabolica* and *Lutzomayia shannoni* (Lawyer *et al.* 1987). The patterns of development of *L.mexicana,* in either *Lu.diabolica* or *Lu.Shannoni,* were virtually identical, and the sand flies of both species usually were infected for life (Lawyer *et al.* 1987). *Leishmania chagazi* caused infections in both P.papatasi (Adler & Theodor 1939) and *Lu. longipalpis* (Walters *et al.* 1989 b). Furthermore, *Leishmania panamensis* could survive in both *Lu. gomezi* (Walters *et al.* 1989 a) and *P. papatasi* (Walters *et al.* 1992). In Italy, there is evidence that only *Phlebotomus perniciosus* transmit *L. infantum*, whereas *Phlebotomus perfiliewi* is the sole vector of *Leishmania tropica* (Adler & Theodor 1930), but Maroli & Bettini (1977) suggested that in some parts, *P. perfiliewi* may transmit *L. infantum.* Some sand flies may be infected with mammalian species of Leishmania like *L. hertigi,* which are not infective to man (Lainson & Shaw 1979). *L. major* developed in the New World sand fly *Lu. longipalpis* (unnatural vector for *L. major*) suggesting that *Lu. longipalpis* was a

successful biological vector for *L. major* (Walters *et al.* 1993). Killick-Kendrick (1990) reviewed that in Latin America, there are 15 proven or suspected vectors of *L. b. braziliensis* and nine suspected vectors of *L. b. panamensis.* He mentioned that the degrees of certainty of the vector status are subjective and it is important to take into account that the evidence that one particular species of sand fly transmits a given parasite is never exactly the same for any other pair. Previously published lists of known and suspected vectors of the leishmaniases have not given assessment of the strength of certainty (Lewis 1971; Young & Lawyer 1987). Their suggestions will not be universally accepted and may have to be changed in the light of new observations (Killick-Kendrick 1990). Meanwhile, Killick-Kendrick (1990) expects that in future lists, the names of vectors suspected on totally inadequate evidence could be omitted.

The second hypothesis introduced to explain "vector-parasite" specificity was suggested by Schlein *et al.* (1990). They reported that the proteolytic enzymes of the insects are naturally modulated by specific glycoconjugates excreted by *Leishmania* in their vectors (i.e. parasite-specific) and the absence of the appropriate glycoconjugate by *Leishmania* in unnatural hosts is due to the early mortality of parasites in the blood meal. They also mentioned that if this is true, then glycoconjugates released by *Leishmania* parasites were able to protect the species of *Leishmania* in the gut of sand fly vector, indicating that these substances may not be completely vector-specific.

Daba *et al.* (1997) found that there is no early mortality of either leishmanial species (*L. infantum* or *L. major*) in the gut of the sand fly species, *P. langeroni*. This means that both glycoconjugates released by either *Leishmania* species were able to protect their parasite species from the proteolytic enzymes of one sand fly species.

The absence of parasite-specificity in "*Leishmania* - sand fly" relationship has also been reported by several authors. *P. papatasi* has been infected with *L. tropica, L. braziliensis* and two strains of *L. infantum* (Adler & Theodor 1927 a), *L. chagasi* (Adler & Theodor 1939) and *L. donovani* (Adler 1947). On the other hand, *Lu.longipalpis* is susceptible to several species of *Leishmania* for which it does not serve as a natural vector in the New World (Walters *et al.* 1993).

The third hypothesis introduced to explain "vector-parasite" specificity was the attachment of *Leishmania* to the mid gut epithelium of an appropriate vector (Molyneux & Killick-Kendrick 1987). Studies on several combinations of *Leishmania* and sand flies demonstrated that hemidesmosomes form on the inner surface of the flagellar membrane that act as the method of attachment in the hind gut and fore gut (except the proboscis). This successful attachment to the insect cuticle appears to be a prerequisite for successful establishment and colonization of the parasites in the vector (Molyneux & Killick-Kendrick 1987). In view of the specificity of these associations, specific receptor molecules act between the flagellar membrane and the insect cuticle (Molyneux & Killick-Kendrick 1987). Studies in a number of laboratories have shown *in vitro* plant lectin mediated parasite-parasite, parasite-flagella and flagella-flagella attachment in many *Leishmania* (Dwyer 1974). Therefore, it was suggested that the insect lectins perhaps play a role as determinants of sites of establishment in the vector (Pereira *et al.* 1981). Carbohydrates are inhibitors of lectin-mediated agglutination reactions of leishmanial promastigotes (Dwyer 1974). The presence of molecules inhibiting agglutination or attachment, such as carbohydrates in the foregut of the sand fly, could increase the number of free-swimming promastigotes able to colonize the proboscis (Molyneux & Killick-Kendrick 1987). Therefore, carbohydrates might enhance transmission by their effects on lectin-mediated "parasite-vector" attachments in the sand fly foregut as they are taken into the midgut (Molyneux & Killick-Kendrick 1987). Thus the presence of lectins in various sugar solutions of plant origin may affect the distribution and association of flagellates in the foregut of sand flies (Molyneux & Killick-Kendrick 1987).

On the other hand, Warburg *et al.* (1989) devised an *in vitro* assay to investigate attachment of *L. major* and *L. panamensis* to the midgut epithelium of *P. papatasi*. Both

parasites exhibited a much stronger affinity for the internal surface of the midgut than to other sand fly tissues. Tests with 13 sugars to see if the attachment was lectin-mediated gave negative or inconsistent results. A monoclonal antibody to a protein, which occurs on the tip and localized patches along the length of leishmanial flagella substantially, inhibited adhesion. The above authors concluded that the recognition of the microvilli was probably mediated biochemically and that the recognition of cuticle was probably by a different means. Furthermore, Svobodova *et al.* (1996) found that the midgut lectins from seven different species of phlebotomine sand flies, all agglutinated promastigotes of various *Leishmania* species. They pointed out that there is little information about the nature of the attachment sites and the mechanisms involved in sand fly - promastigote interactions, since, the role of the sand fly agglutinin(s) *in vivo* still remains unclear.

In other words, several previous studies have mentioned that there was little consistency in the attachment of parasites inside their vectors during their investigations. For example, *L. donovani* flagellates were found attached and developed in *P. argentipes*, but transmission experiments were not successful (Adler & Theodor 1927 b). Although unattached promastigotes were observed in the pharynges of all the transmitting flies, they were also seen in many non-transmitting ones (Warburg & Schlein 1986). Walters *et al.* (1989 a) suggested that , because the parasites moved quickly from the hindgut to the anterior of the thoracic midgut, they perhaps had no need to stabilize themselves in the midgut by association with the microvilli.

Several authors have also reported the absence of vector-parasite specificity. Hertig & McConnel (1963) found that the behaviour of promastigotes from nine Panamanian humans and two spiny rat strains in five species of sand flies was essentially similar. These infections tended to persist throughout the life of the sand fly. Many species of sand flies have been shown experimentally, to be susceptible to infection with almost any species of *Leishmania* parasite and many sand flies species have been found naturally infected (Johnson & Hertig 1970). In Colombia, no vector species of *Leishmania* has been identified (Werner & Barreto 1981). The known epidemiology of the infection in other parts of the world has implicated only sand flies of the subfamily Phlebotominae as responsible for the transmission of the disease, and several *Lutzomyia* species have been confirmed as vectors in neighboring Brazil, Venezuela and Panama (Werner & Barreto 1981).

Finally, from all the above mentioned, it is cleared that the rigid adherence to the assumption that the role of a sand fly as a vector of one particular parasite is immutable may be misleading. Therefore, the present authors consider that all the members of genus *Phlebotomus* are the chief vectors for all leishmanial infections, since; their gut environment is favourable for the survival of *Leishmania* parasites.

The natural hosts of sand flies ("Vector-Host" relationship).

Sand flies often have a wide choice of hosts and the available sources of blood meal may change seasonally. Similarly, host availability and/or host preferences may vary from area to another as with *Lutzomyia trapidoi* in Panama (Tesh *et al.* 1972).

In a visceral leishmaniasis (VL) focus at El Agamy, Egypt, it was found that *P. langeroni* feed on several kinds of vertebrate host bloods including avian blood to survive and lay eggs (El Sawaf *et al.* 1989). It was reported that the blood of turkeys or chicken is lethal to *L. major* in *P. papatasi* (Schlein & Jacobson 1994). Schlein & Jacobson (1996) assumed that the Kenyan and Turkemenistani *L. major* parasites fail to develop in their respective vectors when ingested with human blood. Their experiments showed that human blood causes substantial mortality of *L. major* promastigotes in cultures; while in *P. papatasi* it decreased significantly the number of parasites in individual flies. These slight infections were seldom sufficient for transmission by bite. They, therefore suggested that when *P. papatasi* ingest *L. major* parasites from man, and not from the natural rodent reservoir, their potential for transmission is decreased. However, they suggested that even in the specific vector, the success of infections can depend on the source of the sand fly blood meals.

Daba *et al.* (1997) studied the relationship between sand fly and host blood (human, dog, rat and avian) in the presence of either *Leishmania* species (*L. infantum* and *L. major*) (i.e. "vector-host" relationship in presence of *Leishmania* parasites). The results of this investigation revealed that these host blood types, fed upon by *P. langeroni*, may be suitable for the survival of *Leishmania* parasites (either *L. infantum* or *L. major*) e.g. human, dog and rat blood or it may be unsuitable for that purpose, e.g. turkey blood that is lethal to either parasites in *P. langeroni* gut.

From the above, it is clear that the nutritional requirements for insect survival differ from those required for parasite survival. This leads to a new hypothesis that not all the hosts of sand flies can be considered hosts for *Leishmania* parasites.

Vertebrate hosts for leishmaniasis ("Host-Parasite" relationship).

In leishmaniasis there are direct and indirect relationships between hosts and parasites. The direct relationship between "host-parasite" interactions: The direct relationship is the interaction between the parasites and the macrophages of the vertebrate host (transmission and infection). This relationship is summarized as: When the sand fly takes a blood meal, the infective stages are transmitted to the vertebrate hosts, where they are phagocytosed by resident skin macrophages (Alexander & Vickerman 1975). This infective stage (flagellated form) is converted to an amastigote (aflagellated form), which replicate by binary fission until the macrophage is lysed. They are then released to infect other macrophages, or to be taken up by a sand fly where they differentiate back to a procyclic promastigote (non-infective stage) (Dell & Engel 1994).

When a vertebrate host acquires the disease, the degree of disease severity depends, in our view, on two factors. The first is the immune response of the infected individual, since the response of the immune system may vary among different species of vertebrates or even among individuals of the same species. The second factor is the percentage of the virulent clones (infective forms) to the avirulent ones (non-infective forms).

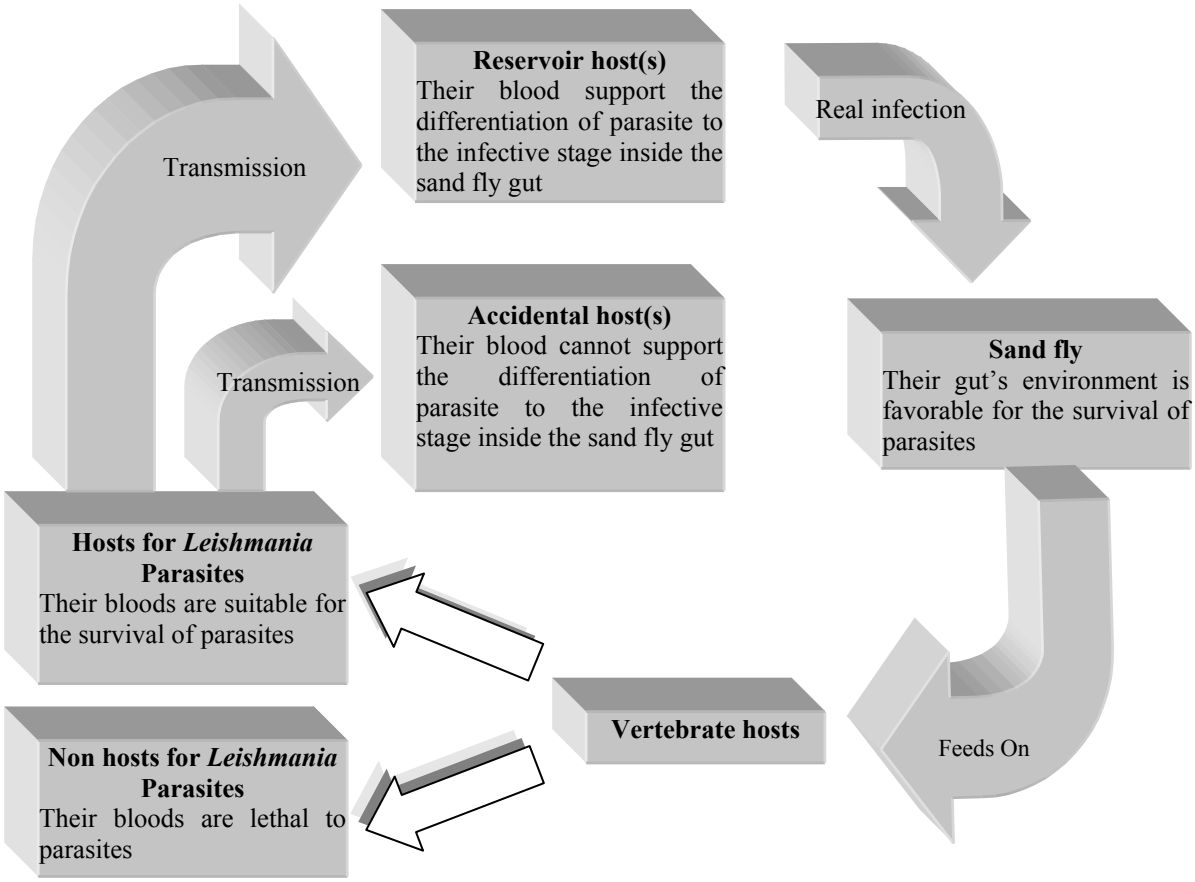
The indirect relationship between "host-parasite" interactions: The indirect relationship is the interaction between the parasites and the digested host's blood that affect the differentiation of *Leishmania* stages inside the sand fly gut (Daba *et al.* 1997, 1999, 2000).

Previous reports mentioned that there is sequential differentiation of promastigotes from a non-infective to an infective stage within the digestive tract of their sand fly vector, prior to inoculation into the mammalian host (Sacks & Perkins 1985; Franke *et al.* 1985). Other reports have recorded changes in size as well as in shape of *L. major* promastigotes during culture *in vitro* in different culture conditions (Greenblatt *et al.* 1985) or during development of either *L. major* or *L. infantum, in vivo*, inside the *P. langeroni* guts that contained certain kinds of blood (Daba *et al.* 1997). These two investigations point to the importance of the surrounding feeding medium as a factor affecting parasite differentiation.

This finding leads to a new hypothesis, which proposes that some kinds of blood may possess inhibitory factor(s) or may lack some essential components needed for the differentiation of parasites to the infective stage.

This hypothesis leads to a new concept that the natural host of *Leishmania* includes the reservoir host(s) and the accidental host(s). The reservoir hosts are those whose blood can support the development of the parasites to the infective stage in the sand fly. While the accidental hosts are those blood cannot support the development of the parasites to the infective stage in the sand fly. So, the sand fly cannot transmit the disease. Thus, the accidental hosts do not play an important role in the natural transmission and are not essential for parasite maintenance. In other words, the natural reservoir host's blood is the key factor for the differentiation of *Leishmania* parasites to the infective stage. They play an important role in disease transmission and they are essential for parasite maintenance.

Schematic representation of the life-cycle of *Leishmania* parasites in nature
["Vector - Host - Parasite" interactions]



From the above explanation, it is clear that the failure of many laboratory trials to transmit some *Leishmania* species by laboratory infected sand flies could be attributed to the absence of the "vector-host-parasite" specificity due to the use of laboratory animal bloods or other culture media that do not affect the parasite survival but affect the parasite differentiation. More studies are needed to confirm this new concept.

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الملخص العربى

العلاقة التداخلية بين العائل الوسيط والعائل الخازن والطفيل لمرض الليشمانيا: مفهوم جديد

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هذا البحث يوضح العلاقة بين كل من :- العائل الوسيط – طفيل الليشمانيا / العائل الوسيط – العائل الخازن / العائل الخازن – طفيل الليشمانيا0 هذه العلاقات الثلاثة تكشف لنا عن نظرية جديدة ومفهوم جديد يشير إلى تداخل جـ وهرى بين كل من العائل الوسيط – العائل الخازن – الطفيل 0

هذا المفهوم سوف يفتح المجال لتحليل المشاكل التى تواجه الباحثين والتى تتسبب فى عدم نجاح نقل العدوى معمليا حتى فى وجود الطفيل داخل العائل الوسيط الخاص به ؛ ويجيب على بعض الأسئلة والصعوبات التى قد تواجه الباحثين فـى هذا المجال ومنها على سبيل المثال: لماذا لم يحدث عدوى من عائل عرضى نهائياً وإنما تحدث العدوى فقط من العائل الخازن إلى عائل خازن أو إلى عائل عرضى؟ / لماذا تتم العدوى بكفاءة فى الطبيعة و تفشل فى التجارب المعملية ؟ / لماذا يعتبر مرض الليشمانيا مرضآ مستوطنآ وليس مرضآ وبائياً ؟