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[Review Article]

Pathophysiology of *Leishmania*sis

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Abstract

SOME PARASITES are caused human-animal diseases, the pathogens carring from the animals to the people through the direct and indirect trance. The uncontrolled use of vaccinations and medications, as well as climate change and genetic engineering, have all contributed to the rise of novel diseases passed from animals to people. *Leishmania* is a parasitic organism that is transmitted by vectors and is capable of surviving exclusively within host cells. Belonging to the Trypanosomatidae family, this organism is accountable for causing many ailments, such as mucocutaneous, cutaneous, and visceral diseases, in both Old and the New World. *Leishmania*sis is a disease caused by subspecies that have different clinical manifestations, leading to experts' confusion Parasites cause inflammation, secrete poisonous compounds into tissues. Understanding the pathophysiology of parasites transmitted from animals to people aids in the development of efficient ways for eliminating these parasitic illnesses as well as the development of effective vaccinations for other bacterial infections.

Keywords: Pathophysiology, Zoonotic Parasitic Diseases, Animals.

Introduction

Leishmania is a parasitic organism that is transmitted by vectors and is capable of surviving exclusively within host cells [1]. Belonging to the Trypanosomatidae family, this organism is accountable for causing many ailments, such as mucocutaneous, cutaneous, and visceral diseases, in both Old and the New World [2]. *Leishmania*sis is a disease caused by subspecies that have different clinical manifestations, leading to experts' confusion [3].

*Leishmania*sis is a neglecting disease that effect underprivileged the people in over 90 countries spanning Asia, the Middle East, Africa, and South America [4]. The prevalence of cutaneous *Leishmania*sis (CL) is presently approximated to 700,000 \ 1.2 million cases, however it is probable that the true number of cases exceeds the documented figures [4]. About 95% of these instances are concentrated in the Americas, the Middle East, and Asia [5]. The latest annual projections for visceral *Leishmania*sis (VL) currently indicate a figure around 100,000, reflecting a significant decrease from earlier forecasts of 400,000. World Health Organize (WHO) reports that Brazil, China, Ethiopia [6], India, Kenya, Nepal, Somalia, and Sudan account for almost 95% of the recorded cases. *Leishmania*sis is more prevalent in those who are economically disadvantaged, endure frequent population movement, suffer from inadequate nutrition, practice poor hygiene, or have a compromised immune system [7].

Sand flies have a global distribution, and tropical species have the ability to complete their life cycle throughout the year [8]. Species inhabiting subtropical climates are restricted to completing their whole life cycles exclusively during the warmer months. Sand flies, which exhibit peak activity during nocturnal hours, possess a stealthy flight pattern and often go undiscovered or unobserved by their prey [9].

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Most cases of cutaneous *Leishmania*sis (CL) in the USA are a result of travel or immigration. Nevertheless, in 2015, the World Health Organization (WHO) categorized the USA as having endemic *Leishmania*sis [10]. Out of the 69 newly identified instances of *Leishmania*sis in Texas, a recent study found that 41 cases (59%) were classed as autochthonous cutaneous *Leishmania*sis (CL) [11]. This indicates that these cases were acquired locally within the USA and there was no history of travel outside the country. Climate change is expected to increase the occurrence and geographical expansion of *Leishmania*sis [12].

Etiology:

The female phlebotomine sand fly, which is most active at night, transmits the *Leishmania*sis parasite to humans' reservoirs or animals too [13]. The life cycle of *Leishmania* sp. comprises two distinct phases: amastigote as well as promastigote. The promastigote form is equipped with a flagellum, allowing it to migrate into the sand fly's intestines [14]. While feeding on blood, sand fly introduces promastigote form into skin of the mammalian host (15). Subsequently, the host's mononuclear cells engulf this form, transforming it into the amastigote form [16], often known as Leishman-Donovan body [17]. The amastigotes undergo replication and development inside reticulo-endothelial system of the host, leading to symptoms associated with the disease. The outcome depends on various factors connected to the host and the kind of parasite [18]. This infection elicits an amplified immune response via toll-like receptors [19], leading to the death of mucosal tissue and the dissemination of infection to other body regions. LRV2, a variant of LRV [20], was detected in L. major, a species belonging to the Viannia subspecies. The Amastigotes possess the capacity to disseminate through the circulatory system and the lymphatic system, resulting in the emergence of mucosal and visceral ailments. Recent studies have revealed that the *Leishmania* RNA Virus (LRV1) is capable of infecting both *L.V. braziliensis* species and *L. Viannia guyanensis* [20]. Nevertheless, there is no proven connection between the clinical phenotype and the level of severity [21; 22].

*Leishmania*sis, a disease of considerable epidemiological importance, has been designated by (WHO) as the neglected disease, receiving insufficient attention and funding from public and private entities involved in health development and research [24].

Types and Classification

The genus *Leishmania* consists of twenty-two species, which have been categorized into the subgenera *Leishmania* and Viannia based on their development in the digestive tract of Sand flies [25]. Each parasite species demonstrates specific preferences for geographic locations, host characteristics, and illness symptoms. *L. donovoni* primarily presents as visceral *Leishmania*sis (VL) in the South Asia and the East Africa [26]. This disease predominantly affects younger individuals, while older individuals typically have acquired immunity and are less susceptible. *L. infantum*, which is conspecific with *L. chagasi* in Latin America, can also present itself as VL [27]. Nevertheless, it is commonly found in the Mediterranean, Middle East, Pakistan, Iran [20], and Brazil. The etiology of all indigenous cases of *Leishmania*sis in Texas has been attributed to the parasite *L. mexicana CL* [28].

Life cycle

Life cycle duration in vector vary from 4 - 18 days, depending on the specific *Leishmania* species. It extended in cold conditions or reduced in the hot temperatures.

When an individual enters the forest and sustains a bite from an infected Phlebotomus, it breaks the biological cycle, which can be defined as "the wild animal reservoir to Phlebotomus-infecting female to the wild healthy animal" [30]. The interruption alters the sequence to "the wild animal's reservoir to Phlebotomus-infecting female to the human" [11].

Protozoan *Trypanosomatidae* and genus *Leishmania* undergoes a life cycle that has two clearly defined stages [31]. The initial phase, referred to as promastigote, is a flagellated structure with a size ranging from 12 - 20 μm. It is present in the arthropods, particularly diptera, it serves as the carrier and acquire the infection while feeding on blood of vertebrate host. Upon entering the digestive system of diptera [32], the parasite undergoes a subsequent phase referred to as an amastigote, which is characterized by the absence of flagella [33; 34]. This phase represents a type of parasite that is dependent on living within a host cell and has a size ranging from 2.5 to 3.5 micrometers [35]. The metamorphosis takes place within the phagocytic cells of the host, with a duration ranging from 4 to 25 days. When the female Phlebotomus mosquito, which consumes blood, punctures an infected animal, it ingests amastigote forms from reservoir's blood [36]. Inside insect's digestive tract, the parasite triggers a sequence of transformations in which the amastigotes transition into the procyclic promastigotes and into the metacyclic promastigotes [18]. The metacyclic promastigotes possess the ability to induce infection. When the insect bites a healthy animal, it spreads the infection by expelling these promastigotes through regurgitation [37].

Upon expulsion on epidermis, the parasite absorbed by the macrophages and the epidermal without involvement of the circulating monocytes. The occurrence of this process is limited to the skin to cause localized cutaneous *Leishmania*sis (LCL) [28].

Pathology

*Leishmania*sis is conventionally defined as an imbalance between TH1 which are the cytotoxic t cells and TH2 CD4+ helper cells which acting as presenting cells to antibodies to attack foreign antigens [38]. Individuals who display a dominant TH1 response are able to effectively control parasites, leading to very low levels of parasitemia. Nevertheless, the increased cellular activity and breakdown of their immune system renders them more vulnerable to mucocutaneous illnesses. Individuals with a TH2 response have increased levels of parasite burden because antibodies are unable to properly neutralize the intracellular pathogen [39] People who have an elevated TH2 immune response are more likely to develop disseminated illness. This disorder has the potential to cause visceral disease. In the New World, it presents itself as disseminated cutaneous *Leishmania*sis (DCL). DCL is distinguished by many lesions that are spread throughout the body [30].

Genus Lutzomyia includes almost 90% of pathogenic spp., many of possess the capability to infect humans. Lutzomyia is endemic to the tropical regions of the Americas [40]. Physically, they possess a conspicuous hump on their dorsal region and wings that are elongated ovals with pointy tips. Female species exclusively take nourishment from blood, mostly acquired from mammals but occasionally from less dominant terrestrial animals. Usually, they forage at night and take refuge in dark, moist areas during the day. Lutzomyia species absorb sugars that may have a pivotal impact on development of the Leishmania within vector [19].

Mexico, specific the rodent spp have been recognized as reservoir for parasites. To classified as the reservoir species, two conditions be met: firstly, it must host a significant number of parasites that can be efficiently transmitted during feeding, and secondly, the infection in these species must be relatively harmless or show no symptoms, in order to ensure survival of reservoir. Among mammals, blood and the skin and provide favorable circumstances for the parasite to multiply [41].

Study conducted in the Ethiopia have shown that the parasite load of at 20,000 \ mL of the blood is required to infection the sand fly spp., specifically *Phlebotomus orientalis*, with the *L. donovani* parasite [42]. Typically, over 50% of reservoirs exhibit no symptoms. Dogs can help maintain the peri-urban areas in border region of the Mexico, Belize, and in Guatemala. When dog go with the owners into woods, they acquire the ulcers that look like the clinical sores of *Leishmania*sis [43].

Direct human-to-human transmission of the disease, without the involvement of any other living creature, has been extensively documented in specific places where the sickness is prevalent [44]. Anthropozoonotic refers to the cycle in which a sand fly becomes infected by biting a human who is already infected, and then proceeds to transmit the infection to another human [45].

Moreover, the application of the molecular techniques such as PCR to identify parasites in the bloodstream of domestic animals has revealed that the animals possibly serve as the alternate source of the infection in India (12). Untreated reservoirs, such as pets or cattle, might facilitate the transmission of parasites, hence contributing to their proliferation. Moreover, the close closeness of sand flies to human owners can heighten the rate of transmission [39]. This is because human owners provide blood meals for sand flies and organic dung for their larval rearing and resting [37] bovine sources and 19% from humans. While it has been noticed that household animals can become diseased, there is currently inadequate data to confirm their role in transferring diseases to humans in India and the Indian subcontinent [33]. There are no existing records of this biological cycle occurring in the Yucatán Peninsula in the past. The occurrence of disease is impacted by various factors, such as the particular species of *Leishmania* responsible for causing the disease [46], the genetic susceptibility and level of immune competence of the host, insufficient nutrition, and the existence of other underlying conditions. Moreover, the environment also contributes to the development of diseases [47].

Possible factors contributing to these variations include 1- alterations in virulence of parasites, 2- variances in permeability of the skin, 3- individual disparities in genetic susceptibility of the host [31], and 4- differences in the attractiveness of various individuals to Phlebotomus [48]. The transmission of parasites from the sand fly to the host depends on the host's level of infectivity, the infectivity of sand fly with each bite, the average biting rate, and the population size of sand flies [45]. The biting rate was calculated to be 0.25 / day, which corresponds to inverse of feeding interval of 4 \days. Furthermore, it was shown that the sand fly has a latency period of 5 days [17].

Pathophysiology

After bite by the sand fly, promastigotes, are outside cells, are take in by host's macrophages. Inside macrophages, it changing into the amastigotes [41].

Parasites can either remain localized in a specific region of the skin or migrate to the mucous membrane of the nasopharynx. In addition, they have the ability to metastasize to bone marrow, the spleen, the liver, and other organs. As a result, three main clinical symptoms of *Leishmania*sis occur [49].

Cutaneous Leishmaniasis is known as the oriental or the tropical sore, Delhi, Baghdad, or Aleppo boil, uta or the chiclero ulcer, or the forest yaws [50]. Instances have been documented among US military personnel deployed in Afghanistan and Iraq, as well as among individuals going to places with a high occurrence of the disease in Central and South America, and other locations. Infrequently, *L. braziliensis* has the ability to widely spread within the skin, leading to the development of disseminated cutaneous *Leishmania*sis [9].

Mucosal *Leishmania*sis, or the espundia, is caused by *L. braziliensis*, however it can rarely be caused by onther *Leishmania* spp. parasites are thought to disseminate from primary skin lesion to the nasopharyngeal tissues via the lymphatic and circulatory systems. symptoms and the signs of the mucosal *Leishmania*sis appear several months to several years after initial development of skin disease [11].

Visceral *Leishmania*sis, referring to as kala-azar or Dumdum fever, is causing by *L. donovani* or *L. infantum* (formerly known as *L. chagasi* in Latin America). It is widespread in multiple regions, such as Africa (particularly Sudan), South and Central Americ, India, Central Asia, the Mediterranean basin and occasionally China [47]. The preponderance of cases is concentrated in northeastern India. Parasites disseminate from the site of sand fly bite to adjacent the lymph nodes, spleen, liver, and the bone marrow, leading to the systemic symptoms. The Subclinical infected are widespread; only the minority of infection persons developing progressive of the visceral disease (46). Children are more susceptible to symptomatic infection with L. infantum than to adults. Visceral *Leishmania*sis is a disease that exploits compromised immune systems, often found in persons with AIDS or other immunodeficiency illnesses [51].

The process by which the host machinery aids the uptake of amastigotes is not fully understood. Nevertheless, it is widely accepted that in human host [32],the amastigotes adhere to Fc receptors and mostly infiltrate macrophages through phagocytosis facilitated by immunoglobulins. Wetzel *et al*. shown that Abl2, a non-receptor tyrosine kinase, facilitates the uptake of *L. amazonensis* amastigotes by the macrophages [44]. Once inside the phagolysosomes, promastigotes transform into amastigotes and quickly multiply by binary fission, therefore evading immune response [16]. specified biological cycle is accomplished during a timeframe ranging from 53 to 100 days. Human pathogen species are classifying according to their molecular biology [35]. The prevalent complexes in America are *L. mexicana* and *L. braziliensis.* The disease in Old World is caused by *Leishmania* species: *L. tropica, L. major, L. aethiopica, L. donovani,* and *L. infantum*. The disease can be classified as the type of immune response it elicits, either as localized with a propensity for spontaneous recovery, or as generalized and advancing [9].

Nevertheless, it has been confirmed that there is a dynamic modification in immune response, marked by a shift from the Th1 to Th2 (39), along by heightened secretion of interleukin-4 as well as IL-6. This shift may also entail the inhibition of tumor necrosis factor alpha , IL-12, interferon gamma (IFN/γ), and the synthesis of nitric oxide [38].

Immunological response vary according to the particular clinical presentation. The LCL variations fail to stimulate humoral immunity [13]. Specific IgG antibody detecting in muco-cutaneous\ form [14]. Elevated levels of IgA are detected in individuals with the diffuse cutaneous type. IL-4 production has been observed in the early weeks after the disease begins [10]. CD8 T cells promote the expedited healing of wounds by the release of IFN/γ. Additionally, it has been observed that immune response referred to as "resistance" to infections caused by L. major is mostly facilitated by a Th1 response [26], which entails stimulation of macrophages. The primary feature of this response is the prominent generation of IFN/γ, which effectively inhibits the reappearance of infections and the development of long-term clinical symptoms [25].

In contrast, progression of disease has been associating by the Th2 immune response and heightened synthesis of the IL-5, transform growth factor beta IL-4, and IL-10. Prior studies have noted an elevation in the synthesis of IL-1α, IL-10, IL-6, TGFβ, TNF/α, and IFN/γ during the early phases of LCL. However, in the later stages, the levels of these cytokines are diminished [5]. Empirical evidence has demonstrated the natural killer cell has the role in beginning the development of T CD4 lymphocytes and regulating the first immune response in the cases of *Leishmania*sis causing by L. major [21]. Th1-mediated inflammation is responsible for controlling intracellular parasites during visceral *Leishmania*sis. IL-10 presence leads to T-cell fatigue by programmed death 1, resulting in a decrease in the severity of inflammation-induced illness [24]. The precise cellular subtypes involved for initiating IL-10 synthesis by T cells during VL remain unidentified [6]. Nevertheless, it has been noted that the population of IgD (hi) B cells undergoes a threefold rise as VL advances [52].

Both versions demonstrate a positive link between CD4 + Th1 cells and resistance, as well as a positive correlation between Th2 lymphocytes and vulnerability [27]. Nevertheless, it is apparent that both CD4 and CD8 lymphocyte is activate and indispensable in controlling disease [53].

These observations lead to the conclusion that "spectral" properties of the *Leishmania*sis are same to those of the leprosy [4]. More precisely, LCL denotes the hyperergic extreme, characterized by patients displaying a robust cellular reaction. At the opposite extreme is diffuse CL, which exhibits a gradual progression and frequently results in a deadly consequence [3].

Conclusion with Recommendations

The *Leishmania*sis is a contagious illness is spread by the vectors, which are the primarily kinetoplastid protozoans from *Leishmania* and *Endotrypanum* genera. The disease is widespread in tropical and subtropical regions and can pose considerable difficulties, particularly in communities with few resources. *Leishmania*sis can lead to a range of illnesses with varying degrees of severity, including harmless skin lesions as well as life-threatening visceral and disfiguring mucocutaneous conditions. Ensuring accurate and efficient diagnosis is crucial in order to provide appropriate clinical care for persons affected by this illness. The diagnosis and management of these illnesses are further complicated by the diverse array of species present in these two genera, as well as the inconsistent reliability of diagnostic testing. *Leishmania*sis is a multifaceted medical illness that poses challenges in terms of both diagnosis and treatment. The progress made in vaccine development, diagnosis, reporting, and therapy has the potential to significantly reduce the occurrence of illness and death related to this disease.

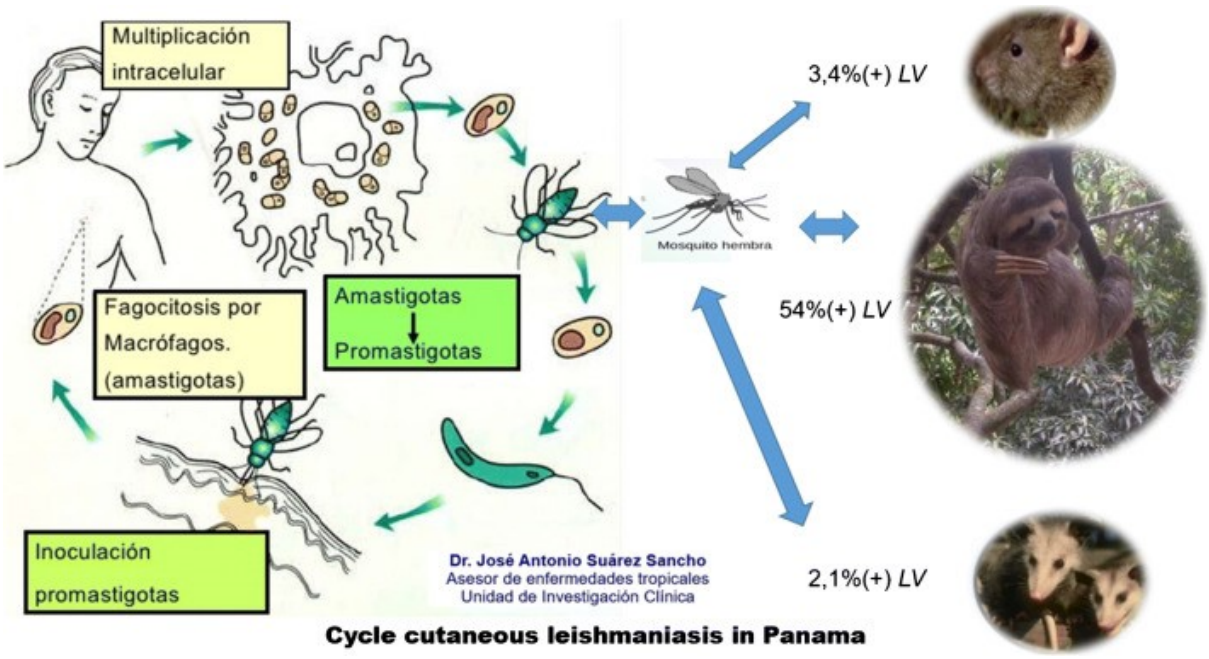

Fig. 1. Life cycle and etiology of Leishmaniasis (23).

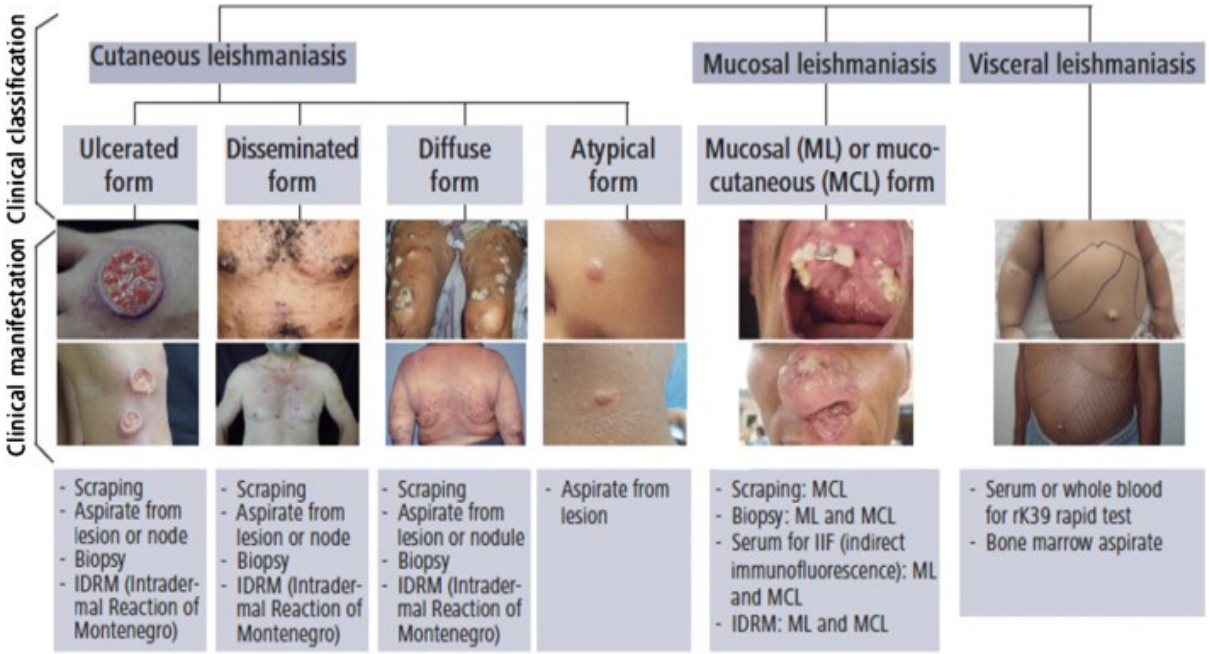

Fig. 2. Clinical Classification of Leishmaniasis (3).

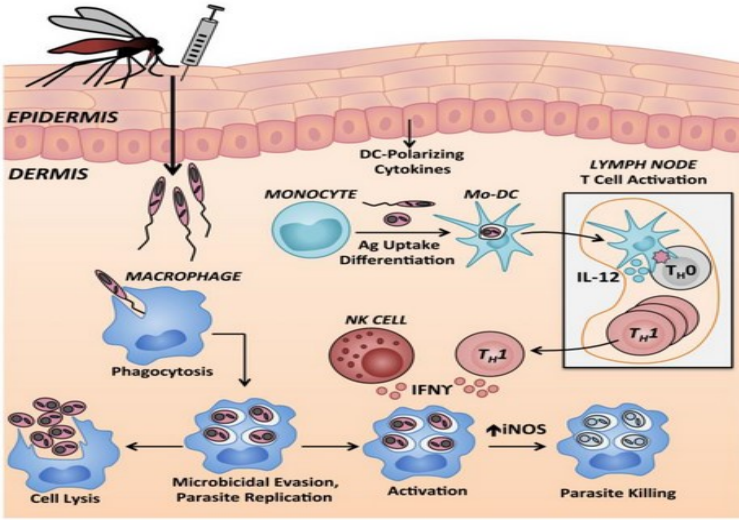

Fig. 3. Cutaneous Leishmaniasis pathophysiology [29].

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الفيزيولوجيا المرضية لداء الليشمانيات

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الخلاصة

تسبب طفيليات OME أمراضًا بين الإنسان والحيوان، حيث تنتقل مسببات الأمراض من الحيوانات إلى البشر من خلال الاتصال المباشر وغير المباشر. وقد ساهم الاستخدام غير المنضبط للقاحات والأدوية، فضلا عن تغير المناخ والهندسة الوراثية، في ظهور أمراض جديدة تنتقل من الحيوانات إلى البشر. الليشمانيا هي كائن طفيلي ينتقل عن طريق النواقل وهو قادر على البقاء على قيد الحياة حصريًا داخل الخلايا المضيفة. ينتمي هذا الكائن إلى عائلة المثقبيات، وهو مسؤول عن التسبب في العديد من الأمراض، مثل الأمراض الجلدية المخاطية والجلدية والحشوية، في كل من العالم القديم والعالم الجديد. داء الليشمانيات هو مرض تسببه سلالات لها مظاهر سريرية مختلفة، مما يؤدي إلى حيرة الخبراء. الطفيليات تسبب الالتهابات، وتفرز مركبات سامة في الأنسجة. إن فهم الفيزيولوجيا المرضية للطفيليات التي تنتقل من الحيوانات إلى البشر يساعد في تطوير طرق فعالة للقضاء على هذه الأمراض الطفيلية وكذلك تطوير لقاحات فعالة ضد الالتهابات البكتيرية الأخرى.

الكلمات المفتاحية: الفيزيولوجيا المرضية ، الأمراض الطفيلية حيوانية المصدر، الحيوانات.