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# LEISHMANIASIS

by

Steven G. Reed, Ph.D.

September 1991

VBC Tropical Disease Paper No. 8

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Malaria
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**Life cycle illustrations:** Taina Litwak
**Cover design:** Anne Masters Design, Inc.

*The blue square shows a sand fly, the vector of leishmaniasis. The other symbols depict essential components of vector-borne disease control: the environment, communities and research.*

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## Executive Summary

The number of human cases of leishmaniasis is estimated to be 12 million, with 400,000 new cases a year. Most cases occur in tropical and subtropical countries.

Reliable epidemiological information on leishmaniasis is rarely available, but the incidence of the disease is believed to be increasing in many areas as forest clearing, resettlement programs and other planned and unplanned population movements expose more people to the risk of infection.

The various forms of human leishmaniasis are caused by protozoan parasites of the genus *Leishmania* that infect man and a variety of other vertebrates. The three main forms of leishmaniasis are visceral, cutaneous and mucosal.

Visceral leishmaniasis occurs when *Leishmania* multiply in the spleen, liver and bone marrow. An acute disease marked by fever and enlarged spleen and liver, it is the most deadly form of leishmaniasis and is usually fatal if left untreated. Cutaneous leishmaniasis occurs as one or more skin lesions that are usually self-healing but can be seriously disfiguring. The mucosal form occurs when *Leishmania* invade the mouth, nose and throat, causing severe destruction and permanent disfiguration of nose, lips and larynx.

The disease is transmitted by phlebotomine sand flies, a large group with more than 600 species. Most vector species are in the genera *Lutzomyia* and *Phlebotomus*. Domestic dogs serve as reservoirs for visceral leishmaniasis in North Africa, the Middle East, USSR, China and Brazil. Rodents and other wild animals are the primary reservoirs of the other two forms of the disease.

Successful vaccination programs have been achieved only for cutaneous leishmaniasis, using crude but often effective preparations. Several new vaccine preparations are being developed and the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR) is supporting field tests.

Treatment with pentavalent antimonials is used widely against visceral leishmaniasis, but its efficacy as a control method depends on the number of people treated, the animal reservoirs present and the sensitivity of the *Leishmania* species to the therapy. A variety of drugs that selectively interfere with the metabolic pathways of *Leishmania* are under investigation, including eflornithine, a drug that was recently approved for treating one form of late-stage sleeping

sickness. Cytokine therapies, such as interferon-gamma, are showing promise when used in combination with antimonials.

Developing superior chemotherapies, antigens for diagnostic tests, and vaccines should be the top priorities for leishmaniasis control because they will have the most long-lasting impact on disease transmission. Other priorities include basic research that will lead to better understanding of the parasites and their antigens and genes, training in surveillance and control, and operations research on alternatives to chemical control of the sand fly vectors.

# 1. Introduction

Human leishmaniasis is caused by a complex of protozoan parasites of the genus *Leishmania*. Unlike most other human parasitic diseases, leishmaniasis has no single dominant form of infection. The three main forms are visceral, cutaneous and mucosal.

Visceral leishmaniasis, also known as kala-azar, is caused by *Leishmania* multiplying in the spleen, liver and bone marrow. It is an acute disease, marked by fever, enlarged spleen and liver, and decreased white blood cell count.

Cutaneous leishmaniasis causes one or more skin lesions, which are usually self-healing. The lesions can be seriously disfiguring, particularly on the face.

Mucosal, or mucocutaneous, leishmaniasis occurs when *Leishmania* invade the mouth, nose and throat, causing severe destruction and permanent disfiguration. The nose, lips and larynx are often destroyed.

## a. Biogeography

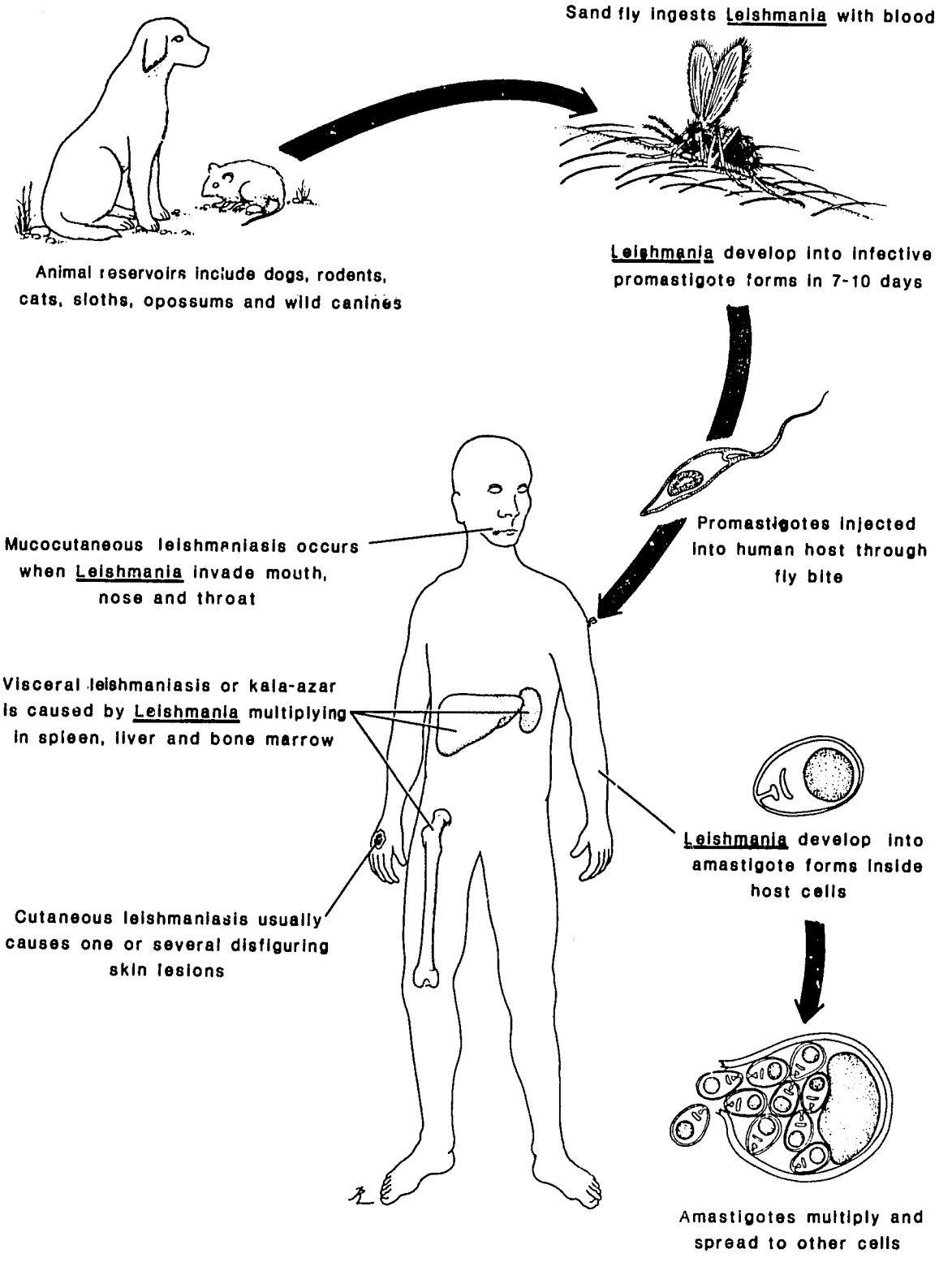
Leishmaniasis is distributed widely, occurring in Latin America, the Mediterranean, Africa, India and China and along the border between Texas and Mexico. The parasites have been reported on every continent except Australia and Antarctica, but the disease occurs predominately in tropical and subtropical regions.

## b. Agents

The *Leishmania* are a complex of protozoan parasites that infect man and a variety of other vertebrates. Human leishmaniasis is caused by at least 14 different species or subspecies of the genus *Leishmania*.

Traditionally a particular species of *Leishmania* has been associated primarily with one type of disease. *Leishmania donovani* and its subspecies cause visceral leishmaniasis and the rest of the species and subspecies cause various forms of cutaneous and mucosal disease. The use of refined taxonomic and diagnostic methods, however, has revealed that different types of

# Life Cycle of Leishmania



leishmaniasis can be caused by a single species. For example, *L. mexicana amazonensis*, generally associated with cutaneous leishmaniasis, recently has been isolated from cases of visceral or mucosal disease in Brazil.

The life cycle of *Leishmania* is relatively simple (Figure 1). The vector flies carry motile, flagellated forms called promastigotes, which are introduced into man when the fly bites. The promastigotes form flagellum-free amastigotes within the macrophages of the host's immune system, replicate and spread to other macrophages. If these amastigotes are ingested by the vector during a blood meal, they multiply and mature into the promastigote stage, completing the cycle.

## c. Vectors

The *Leishmania* of man are transmitted by phlebotomine sand flies, a large group of flies with over 600 known species. Most of the vectors of human disease are in the genera *Lutzomyia* (found in the New World) and *Phlebotomus* (found in the Old World). The flies are very small, fly poorly, and have short adult lives. They occupy a wide range of habitats that vary from semi-arid in the Old World to tropical rain forest in the New World.

Transmission occurs through the bite of the female sand fly, which requires a blood meal for egg development. Eggs are deposited in soil rich in organic matter. When the weather is very cold or very dry, eggs of some species may remain dormant for several months before hatching. The four larval stages of the sand fly develop in 30 to 60 days with four intermediate stages. After a seven- to eight-day pupal stage, the adult emerges.

## d. Reservoirs

There are many mammalian reservoirs, wild and domestic, of leishmaniasis. In India and some areas endemic for visceral leishmaniasis, there appears to be no reservoir other than man. Domestic dogs have been implicated as reservoirs of visceral leishmaniasis in North Africa, Brazil, China, the Middle East and the USSR. Wild canines, including foxes, also have been implicated as reservoirs in Brazil. Rodents and other wild animals, including hydraxes and sloths, are primary reservoirs of the other forms of leishmaniasis.

## 2. Distribution and Severity

Leishmanial diseases have a worldwide distribution, but most cases occur in tropical and subtropical countries (Maps 1-3). Reliable epidemiological data on the prevalence and incidence of leishmaniasis are not available for most endemic regions because of inadequate medical surveillance, confusion with other diseases, lack of specific diagnostic tests, and poor record keeping and reporting. The estimated number of human cases is 12 million, with approximately 400,000 new cases per year.

Both visceral and cutaneous leishmaniasis are endemic in Central America, with 50,000 to 100,000 cases reported annually, but incidence data are poor. An annual incidence of 3,000 cases is reported in Peru. The true incidence is thought to be much higher.

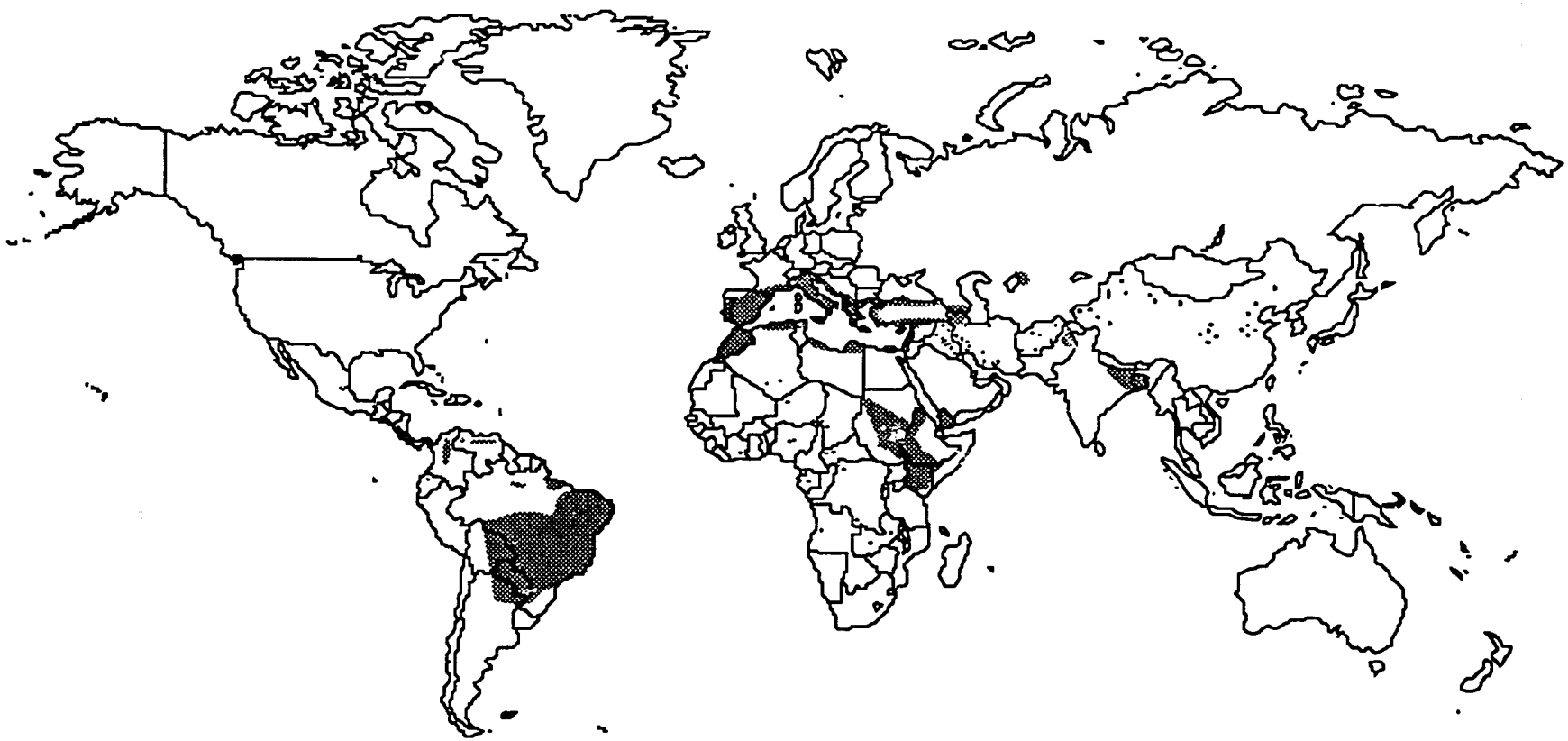
Large areas of the Middle East are highly endemic for cutaneous leishmaniasis. Epidemics, often associated with the sudden appearance of a group of individuals in a previously sparsely inhabited area, occur frequently. Visceral leishmaniasis is endemic in large regions of India, but epidemics have been frequent and devastating, particularly in the Bihar region of East India, where one outbreak reportedly killed 75,000 people in three years.

The leishmaniases occur largely in rural areas and in towns and villages. The number of leishmaniasis cases is rising in many countries, particularly in the New World, because forest clearing and cultivation projects, large water resource schemes, and colonization and resettlement programs are increasing contact between humans, vectors and reservoirs.

### a. Child survival

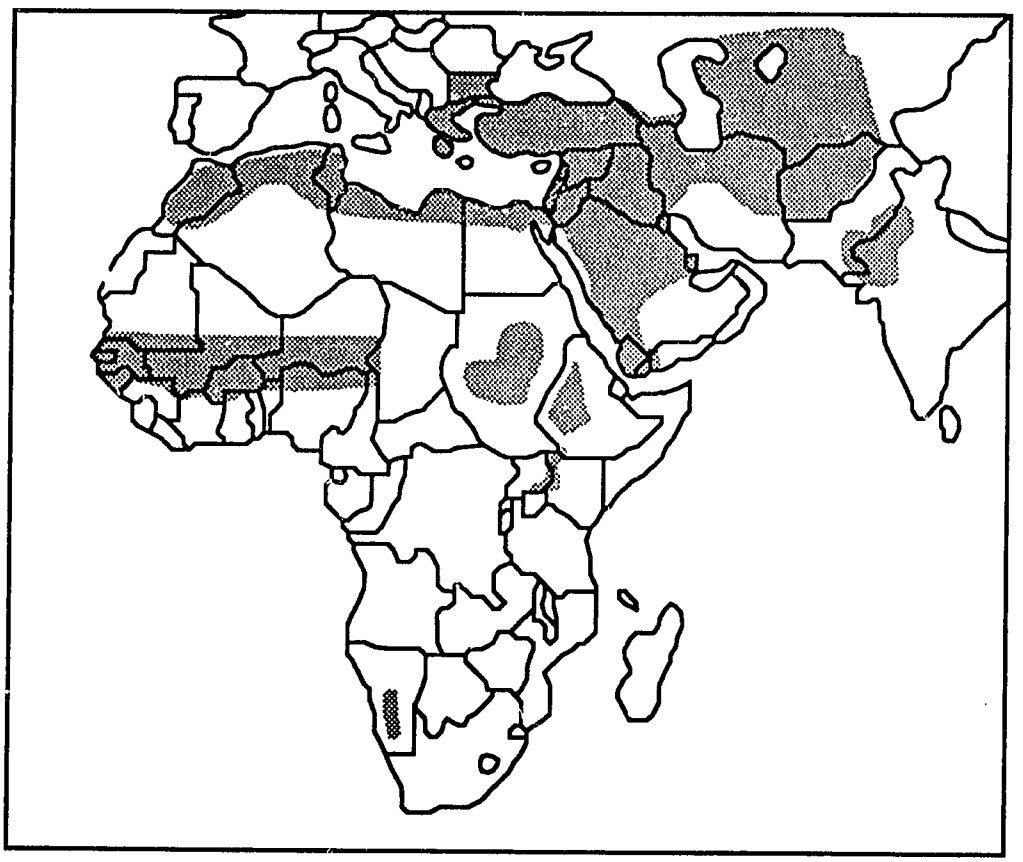
Visceral leishmaniasis is a significant threat to child survival. In some areas, leishmaniasis is predominately a disease of children. For example, the Mediterranean form of *L. donovani* primarily infects young children. More than 90 percent of the 3,000 to 10,000 cases seen annually in Iraq are in children younger than four. Most deaths from visceral leishmaniasis in Central America occur in children.

# Map 1. Global Distribution of Visceral Leishmaniasis



*Prepared by the Vector Biology and Control Project*
*Source map: World Health Organization, 1990*

## Map 2. Distribution of Cutaneous Leishmaniasis in the Old World



*Prepared by the Vector Biology and Control Project*
*Source map: World Health Organization, 1990*

## Map 3. Distribution of Cutaneous and Mucocutaneous Leishmaniasis in the New World

*Prepared by the Vector Biology and Control Project*
*Source map: World Health Organization, 1990*

## b. Economic Impact

There have been few efforts to measure the impact of leishmaniasis on economic productivity, but it is clear that the disability and disfigurement caused by the disease are impediments to development efforts. In addition, working or living near infected sand flies is a health hazard that people are not always willing to face. During the 1970s, sand flies and the cutaneous leishmaniasis they transmitted thwarted a Bolivian scheme to relocate people from overcrowded mountain areas. Many of the colonists abandoned their new land and 60 percent of them cited leishmaniasis as their reason for leaving. Oil exploration and road building also have been hampered by leishmaniasis in several Andean countries.

## 3. Control Measures

Successful control programs have used an approach that integrates the various control strategies: chemotherapy, vector control, vaccination and elimination of reservoirs. A high level of surveillance is necessary to gather the epidemiological data essential for effective treatment programs. Accurate surveillance, in turn, depends on sensitive and specific epidemiological tools, such as diagnostic antigens, to obtain information about subclinical as well as active disease.

### a. Diagnosis

Leishmaniasis diagnosis is based on clinical, serological and parasitological evaluations, and may require all three approaches. Definitive diagnosis is made by demonstrating *Leishmania* parasites in samples of spleen, bone marrow, lymph gland or skin lesion tissue for parasites.

Various antibody tests have been used for serological screening, including the complement fixation test, direct agglutination test (DAT), the indirect fluorescent antibody test (IFAT) the enzyme-linked immunoabsorbent assay (ELISA), and the dot ELISA. With the Montenegro intradermal delayed-hypersensitivity test, killed promastigotes or promastigote extract are injected under a patient's skin to detect previous exposure to *Leishmania*. This test can detect such exposure two to three months after infection. It is used for epidemiological studies because people who have been exposed to *Leishmania* will continue to have a positive reaction to the Montenegro skin test after recovery. Therefore, the test is also useful for evaluating the effectiveness of a therapeutic regimen or as a prognostic indicator.

#### Visceral leishmaniasis

The symptoms of visceral leishmaniasis are often not sufficiently specific to differentiate it from malaria or other infections, so it should treated only after the presence of the parasite has been demonstrated. Clinically suspect and seropositive individuals should be referred for examination to the nearest facility with parasitological laboratory capabilities.

Serological examination has become the easiest, most efficient screening procedure, but all of the methods available

have disadvantages for field use. Confirming diagnosis by demonstrating the parasite in the spleen, bone marrow or lymph glands is a prerequisite for treatment.

### Cutaneous leishmaniasis

Diagnosis of cutaneous leishmaniasis cannot be based on clinical characteristics alone. There are many atypical forms and the infection can easily be confused with mycobacterial, mycotic or bacterial infections. Parasitological diagnosis is made either by examining stained smears of material at the edge of the lesion or by *in vitro* cultivation.

### Mucocutaneous leishmaniasis

Demonstration of the parasite often is not possible because parasites are extremely scarce in mucosal lesions. The parasite can be difficult to maintain in the laboratory. The Montenegro skin test is usually positive in mucosal leishmaniasis. When 0.1 ml of an extract of killed promastigotes is inoculated into the skin of an infected person's forearm, an induration more than 5 mm in diameter often forms within 48 hours.

## b. Chemotherapy

Pentavalent antimonials administered for a minimum of 20 days are the most effective treatment available for leishmaniasis. Simple cutaneous leishmaniasis is usually self-healing, but multiple or disfiguring lesions require antimonial treatment. All cutaneous leishmaniasis patients in areas of Latin America where there is a risk of mucosal leishmaniasis should be treated with antimonials. Mucosal leishmaniasis is one of the most difficult forms of leishmaniasis to cure. Associated bacterial or fungal infections may have to be treated before chemotherapy with pentavalent antimonials can begin.

Treatment with pentavalent antimonials is widely used against visceral leishmaniasis. Before the introduction of antimonial treatment, acute visceral leishmaniasis caused death in 95 percent of all cases. Today, five to 10 percent of treated patients die from the disease. The efficacy of antimonial treatment as a control method depends on the number of people treated, the animal reservoirs present and the sensitivity of leishmanial species to the therapy. In India and China, for example, mass treatment is an

important part of control programs. Both countries manufacture their own pentavalent antimonials.

The pentavalent antimonials sodium stibogluconate and meglumine antimoniate are relatively safe if patients are monitored for reversible toxic effects. These drugs are rapidly excreted and do not accumulate appreciably. There is wide variation, however, in the dosing schedules used by health care workers. This has created some confusion about the efficacy of the drugs and controversy over current recommendations for treatment. In cases where patients are not cured by pentavalent antimony, a more toxic drug, amphotericin B, is often used.

## c. Vector control

House spraying with residual insecticides to reduce domestic transmission has probably been the most effective vector control measure. Various insecticides have been used to control sand flies, including DDT, BHC, dieldrin, malathion and chlorophos.

Insecticide spraying has been instrumental in eliminating epidemics of visceral leishmaniasis in the Indian subcontinent and China. A single spraying with DDT in China reportedly eliminated sand flies in the sprayed houses for several years. Spraying programs have also been used in Israel, Brazil, North Africa, the USSR and other areas with considerable success.

Successful control of sand flies has been an incidental bonus of insecticidal spraying to control malaria in several countries and to control cockroaches in Israel and locusts in Tunisia.

## d. Vaccination

Successful vaccination programs have been achieved only for Old World cutaneous leishmaniasis, using crude but often effective preparations. Historically, a thorn was used to introduce material from a lesion into the skin of the thigh or buttock of a child to protect against debilitating hand lesions or disfiguring facial lesions in later life. Even today, Bedouin mothers may swaddle infants with their buttocks exposed to sand fly bites. This leads to infection which, upon cure, confers immunity without subsequent disfigurement.

The most common vaccination procedure is inoculation with promastigotes of virulent strains of *L. major*. This practice is quite common in the USSR and areas of the Middle East. Inoculation leads to infection, but the lesion produced is relatively mild and self-healing, and infection results in lasting immunity to both *L. major* and *L. tropica*. Unfortunately, this pattern of consistently mild infections following inoculation and resulting cross-protection between species does not seem to occur with other species of *Leishmania*.

## e. Reservoir control

The most important reservoirs for visceral leishmaniasis are humans, canines and rodents. Mass chemotherapy programs in some areas have reduced the human reservoir. Large-scale killing of domestic dogs has been practiced in China and Brazil. In the USSR, gerbil burrows have been destroyed and the animals poisoned with zinc phosphide and anticoagulants to control cutaneous leishmaniasis. However, similar attacks on rodent populations do not seem to be widely practiced.

Reservoir control can be considered an important aspect of integrated leishmaniasis control, particularly if only one host species is the main parasite reservoir. It is important to remember, however, that different animals can act as reservoirs of the same parasite and the species that is eliminated may be replaced by another as the reservoir species.

## f. Alternative control methods

Although insecticides remain the most successful method of vector control, alternative methods need to be evaluated and, if successful, incorporated into control programs. For example, the use of bed nets impregnated with either insecticides or insect repellents should be evaluated as a method of personal protection against sand flies. Other methods, including reduction of breeding sites, vegetation clearing or improved housing, should be considered as a part of integrated vector control programs.

## g. Control among high-risk populations

In some regions, control efforts can be targeted at high risk populations. Examples include *L. chagasi* in children in Latin

America and *L. mexicana* infections (Chiclero's ulcer) in Central American workers. Studies in Brazil have shown that detecting infection before the onset of the disease greatly improves the effectiveness of the treatment for visceral leishmaniasis. Results from studies in Brazil also suggest that improving nutritional requirements in areas where a high percentage of the population tests positive for exposure to *Leishmania* could help reduce disease.

When occupational exposure is a problem, education on avoidance of sand fly bites is useful. Sand flies characteristically appear at dusk, but some species bite throughout the night. Knowledge of local biting patterns, coupled with the use of insecticides, repellents or protective clothing, can help prevent exposure.

## h. Constraints to control

The effectiveness of control measures often parallels the level of development of a country's health system infrastructure. Accurate epidemiological data are essential for any effective control effort, and countries capable of gathering, organizing, reporting and using such information usually can mount effective control programs within the limitations of the control measures available.

### Technical

There are several urgent problems affecting the control of leishmaniasis and most stem from a lack of understanding of the parasite and the vector. Recent improvements in biochemical and molecular methodologies have revealed that our understanding of the antigenic and genetic diversity of *Leishmania* is incomplete, although significant progress has been made in the past 10 years. The gaps in knowledge about the differences between various species and subspecies of *Leishmania* hamper efforts to develop vaccines, improved diagnostic tests and treatments.

There are no safe, effective vaccines for most forms of leishmaniasis. The only vaccines widely used are live parasites, which must induce active infection to be effective. Complications are rare, but treatment of vaccine-induced lesions has been necessary in a few subjects. Infection rates are never 100 percent, so there are cases in which the vaccine fails.

Another possible problem with vaccinating by live infection is that this procedure may induce immunosuppression. Russian scientists have observed a depressed response to diphtheria-pertussis-tetanus triple vaccine in children receiving the leishmanial vaccine.

Current diagnostic tests for leishmaniasis use crude antigens of *Leishmania*, which are frequently whole parasites. These antigens are difficult to standardize and often do not allow clear differentiation between *Leishmania* species or between *Leishmania* and other organisms. Rapid, efficient diagnostic assays that use specific *Leishmania* antigens are needed.

None of the *Leishmania* antigens in use can distinguish between different species, but studies using immunological techniques have revealed that such antigens exist. Ideally, and this is not at all an impractical expectation, genus-specific and species-specific diagnostic reagents would be available. In many areas, particularly in Latin America, species and subspecies distributions overlap and a correct, early diagnosis may influence disease outcome. For example, the lesions of *L. mexicana* and *L. braziliensis* are very similar when they first appear. *L. mexicana* is self-healing, but without treatment, *L. braziliensis* results in destruction of the nose and throat.

Pentavalent antimonials are an effective treatment, but they require daily injections for 10 to 20 days and monitoring for toxic effects. Such treatment is impractical for people who live in remote areas where close patient monitoring is difficult or impossible. In addition, cases of parasite recurrence after therapy are not uncommon. Resistance to antimonials appears to have developed in some cases.

Chemical control of sand flies is still one of the most important methods of leishmaniasis control, but DDT resistance has been reported from India and the USSR and is likely to develop in other countries.

## Human resources

The lack of adequate numbers of trained personnel to provide surveillance of large rural populations has undermined efforts to determine the prevalence of leishmaniasis in some countries. Drug distribution and house spraying also require significant human resources that often are not available.

In many countries, public health personnel and posts are already dispersed in remote areas to monitor malaria and other diseases. Unless an epidemic occurs, leishmaniasis is given low priority. Appropriate epidemiologic forms and a small amount of additional training would, in many cases, be adequate to expand surveillance for other diseases to include leishmaniasis.

## Economic

Major economic resources are required to mobilize the personnel necessary to implement control measures in vast regions. A complete therapeutic course of pentavalent antimonials used for treatment can easily exceed US $100. Hospitalization and treatment for mucosal leishmaniasis costs an estimated US $4,000 per patient. Insecticides also are a major expense when a large-scale application effort is needed. Vector control expenses include the cost of insecticides and equipment, and salaries for trained personnel to apply the insecticide.

# 4. Current Research

## a. Diagnosis

Field and laboratory research to identify *Leishmania* antigens useful in serology and in the intradermal skin test is a priority of some research programs. Scientists at several institutions are producing monoclonal antibodies and studying their possible application in leishmaniasis diagnosis. Monoclonal antibodies are being used to develop diagnostic technologies employing ELISA, Western blot and flow microfluorometric assays.

DNA probes have been used to diagnose leishmaniasis in patients from the Instituto de Medicina Tropical de Manaus in Brazil. These probes allow direct diagnosis from lesion material without isolation of the parasite.

A team of U.S., Brazilian and Sudanese researchers have developed a simple, rapid immunodot assay for serodiagnosis of active visceral leishmaniasis (AVL). The test uses protein A colloidal gold and can be interpreted visually. In laboratory trials, it clearly distinguished AVL from malaria, tuberculosis and Chagas's disease. The immunodot is a promising candidate for field diagnostic tests because it is easy to perform and does not require expensive instruments, it can be completed in two hours at a costs of about 25 cents, and it can be done with a tiny drop of blood or sera obtained from a finger prick. Field trials are needed for further evaluation of the immunodot assay for AVL.

## b. Chemotherapy

The development of chemotherapy for leishmaniasis has been slow, as evidenced by the continued use of antimonials, despite their drawbacks. A few laboratories are directing efforts towards understanding metabolic pathways of *Leishmania*, with an emphasis on chemotherapeutic intervention.

Eflornithine, used alone or in combination with other antiprotozoal drugs, has proved effective in experimental models. Several new compounds are being tested in humans and the use of topically applied drugs to treat cutaneous leishmaniasis is being investigated.

Improving drug delivery systems is a relatively new area of research on leishmanial chemotherapy. Liposome technology can take advantage of the fact that the *Leishmania* parasites inhabit only macrophages, which ingest and destroy liposomes. Researchers have greatly increased the effectiveness of antimonials in experimentally infected animals by encapsulating them in layers of synthetic lipids to form microscopic globules called liposomes. When the liposomes are destroyed, the drug is released inside the macrophages.

## c. Vaccine development

Since individuals who recover from natural or induced infection have lasting immunity to reinfection, developing a vaccine to prevent leishmaniasis is a reasonable goal. Several laboratories are characterizing vaccine models for leishmaniasis and a few are attempting to isolate parasite antigens with protective potential.

Monoclonal antibodies against some of the antigens under study can block parasite entry into the macrophage, its host cell. This may be an important consideration in the development of a molecularly defined vaccine.

Several candidate vaccines will be available shortly. TDR is supporting field tests of killed vaccines using the trypanosome *L. major* as antigen. These studies will be modeled on the protocol for the TDR-supported trial of a leprosy vaccine. While the field tests using crude antigen are underway, two molecular vaccines also will be tested.

## 5. Leishmaniasis from the A.I.D. Perspective

Leishmaniasis occurs in more than 35 A.I.D.-assisted countries. Accurate estimates of prevalence and incidence are rare, but the limited data available indicate that visceral leishmaniasis is a life-threatening disease in many of these countries. Attack and mortality rates are often highest among children. In some areas, visceral leishmaniasis represents a significant cause of child mortality. Cutaneous and mucocutaneous leishmaniasis are rarely fatal, but can cause gross disfigurement and have a great impact on the quality of life.

The social and economic importance of the leishmaniases are not fully understood, but it is clear that the disease can impede the success of development projects. Such development projects can also play a role in increasing leishmaniases in A.I.D.-assisted countries; therefore, measures to prevent or reduce their harmful effects should be part of original project plans.

TDR has targeted leishmaniasis as one of its six priority diseases. TDR-supported studies include epidemiological investigations, vaccine trials, drug screening, identification of reservoir hosts and vectors, and development of improved diagnostic tests. These efforts have yielded promising results and deserve continued support. A.I.D. supports leishmaniasis research through its contributions to TDR and directly through grants from the Office of the Science Advisor. Another area for consideration would be training personnel from established vector control programs to address the problem of leishmaniasis in areas where it represents a serious public health problem.

### a. The Horizon

During the next 10 years, the use of improved biochemical and molecular methodologies will lead to a better understanding of the *Leishmania* parasite. This, in turn, will lead to more effective drug treatments, improved diagnostic techniques and the possibility of a vaccine. Better understanding of the vector's biology and ecology will also result in improved control techniques. Social science methodologies will be employed to identify the role of social and economic factors in the spread of the disease and to develop alternative control methods.

## b. Priorities for future action

- Basic research that will lead to a better understanding of the parasite and its antigenic and genetic diversity, enabling scientists to develop more effective diagnostic tests, vaccines and treatments.

- Development of rapid, efficient diagnostic assays and intradermal skin tests that use specific *Leishmania* antigens.

- Evaluation of alternative means of vector control, including insecticide-impregnated bed nets, reduction of breeding sites, vegetation clearing and improved housing, for use in integrated vector control programs.

- Development of an inexpensive, non-toxic, orally administered drug to treat leishmaniasis.

- Operational research on the integration of leishmaniasis control with primary health care systems and the use of community participation to reduce leishmaniasis transmission.

- Training of local physicians to recognize leishmanial disease and of laboratory technicians and other health workers in the use of diagnostic tests for leishmaniasis.

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