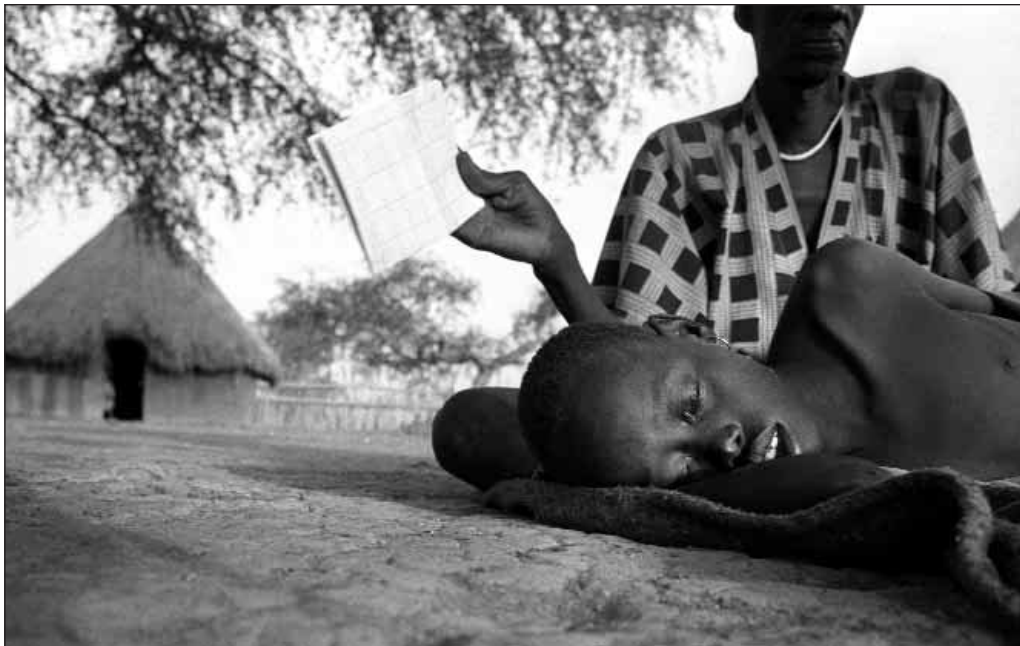


LEISHMANIASIS

Largely unknown in the developed world, leishmaniasis is a parasitic disease which threatens many poor countries. The disease principally affects poor communities in isolated regions, often as devastating epidemics. In Sudan, where civil war had caused a flood of internal refugees, an epidemic of visceral leishmaniasis lasted from 1984 to 1994 and claimed more than 100,000 in the Western Upper Nile province, a third of the population of the affected area.

Photo: © Sven Torfinn



Since 1988, Médecins Sans Frontières has treated more than 60,000 patients with leishmaniasis, principally in East African countries, including Sudan, Ethiopia and Uganda, but the best of efforts are dwarfed by the limitations of existing treatments and the world's lack of interest in this forgotten disease.

Transmission and symptoms

The disease is caused by one of over 20 varieties of parasitic protozoa called leishmania. The disease is endemic in 88 countries, infecting around two million people each year. It is estimated some 59,000 people died from the disease in 2001, mostly from its most severe form, visceral leishmaniasis^[1]. Over 90% of visceral leishmaniasis cases occur in five countries: Bangladesh, Brazil, India, Nepal and Sudan^[2].

The parasite is transmitted by the bite of certain types of sandflies, which live principally in forest areas in sub-tropical and tropical climates. Both animals and humans can act as the parasite's reservoir: the sandfly picks up the parasite by biting a host and then transmits it to another.

Leishmaniasis is prone to epidemics, especially when previously unexposed

populations are forced by war and famine to move into endemic areas. Unfortunately, there is presently little international cooperation on dealing with these epidemics.

There are three main types of leishmaniasis:

- Visceral leishmaniasis, also known as kala azar (Hindi for "black fever"), is the most severe form of the disease, where the parasite infects the immune system. Patients present with fever, wasting, anaemia and an enlarged spleen. If untreated, visceral leishmaniasis is fatal in almost 100% of cases, within one to four months.
- Mucocutaneous leishmaniasis begins with skin lesions which then spread, causing massive leprosy-like tissue destruction around the mouth and nose.
- Cutaneous leishmaniasis, the most common form, affects principally the skin, causing simple lesions which usually self-heal but leave scars.

Co-infection with leishmaniasis and HIV is emerging as a growing threat. Because both diseases attack the immune system, it means the body has even less chance of resisting the infections and treatment becomes less



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effective. In Ethiopia, 20% of visceral leishmaniasis patients appear to also suffer from HIV co-infection.

Treatment

Treatment of leishmaniasis has been hampered by the inadequacies and high prices of existing medicines and slow progress on research and development into new cures.

The most common treatment for visceral leishmaniasis was developed in the 1930s, using derivatives of antimony. Sodium stibogluconate (SSG) is taken as an intramuscular injection over 30 or more days. It is available under the brand name *Pentostam* from GlaxoSmithKline, as well as from generic producers. Another antimonial drug is meglumine antimoniate (brand name *Glucantime*).

SSG is still effective in many regions and can produce good cure rates. But resistance to the drug is a growing problem – especially in India, where as many as 65% of patients are resistant^[3]. Further, a course of treatment is long (30 days), painful and causes toxic reactions in some patients. Pentostam is also relatively expensive: \$273 per patient.

A generic version of SSG is being manufactured in India at considerably reduced price (around \$20). MSF uses it in a number of its projects, with good effect, but it is not yet widely registered for use in Africa.

Alternative treatments needed

Additional treatments are becoming available, including promising explorations of using two drugs together in combination, which could reduce the length of treatment and the chances of resistance developing. But there is little international interest in the disease. Available drugs were mostly developed for other diseases, and clinical research and development is under-funded and painstakingly slow.

Possibly the most effective drug available is liposomal amphotericin B (brand name *AmBisome*), first developed to fight various fungal infections. Its cure rate is very high, it is fast-acting (a few days) and it is very safe^[4]. MSF presently uses AmBisome for severely ill and

relapsed patients and is looking to expand usage. However, the drug is administered intravenously, making treatment in field conditions more difficult. The drug is also very expensive – as much as US\$3000 for a course of treatment, although MSF receives a discounted price from the manufacturer, Gilead. A combination of wider eligibility for this discounted price and financial support from international donors is needed.

Another promising drug is miltefosine, originally developed as a cancer treatment. It has been proved effective against visceral leishmaniasis and is in use in India^[5]. It is taken orally, so is easy to use. But its price is too high (\$102 from the manufacturer, Zentaris, but up to \$200 in private pharmacies in India) and its use is not advised for women of child-bearing age. Because the course of treatment is long (28 days) and because the body eliminates the drug very slowly, there is a strong risk of resistance developing quickly if it is not used in combination with other drugs. Further, its effectiveness needs to be tested against the strains of the disease prevalent outside India before it can be registered elsewhere.

Paromomycin, a broad-spectrum antibiotic, has also proved itself effective against leishmaniasis^[6]. It appears to work well in combination with other drugs, such as SSG. While its anti-leishmaniasis properties have been recognised for some time, until recently there has been little interest in the further development of paromomycin for leishmaniasis. The drug is now in final stage trials in India and trials are scheduled to begin soon in East Africa. Once these have been completed, the drug should be able to be registered for use against leishmaniasis.

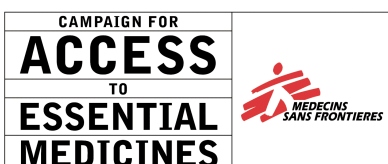
New diagnostic tools necessary

There are also considerable problems with existing diagnostic tests for leishmaniasis. Existing techniques are either invasive and potentially dangerous, require considerable laboratory facilities and trained specialists or involve lengthy delays as samples are sent to distant laboratories. Alternatives need to be developed which are both effective and easy-to-use in remote conditions.

MSF treats patients with leishmaniasis in many contexts and will continue to do so. To expand the numbers of people who benefit from treatment for this disease, MSF advocates:

- Lowering the prices for existing drugs.
- Speedy registration of generic SSG in East Africa.
- Finalised development, to the point of registration, of promising drugs such as paromomycin and miltefosine in endemic countries.
- More research and development of combinations of drugs, such as those involving AmBisome, paromomycin and miltefosine.
- More research into diagnostics suited to conditions in resource-poor countries, such as easy-to-use dipsticks.
- More effective and coordinated international responses to epidemics of the disease.

[1] C Davies, P Kaye, S Croft, S Sundar, "Leishmaniasis: new approaches to disease control", *British Medical Journal* 326 (February 15, 2003): 377-382. [2] World Health Organization/TDR, "Leishmaniasis: Disease Information", 2004 [Online]. Available: <http://www.who.int/tdr/diseases/leish/diseaseinfo.htm> [3] P Guerin, P Olliaro, S Sundar, M Boelaert, S Croft, P Desjeux, M Wasunna, and A Bryceson, "Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda", *The Lancet Infectious Diseases* 2 (August 2002): 494-501. [4] *ibid.* [5] A Burton, "Miltefosine – Oral Victory over Visceral Leishmaniasis", *The Lancet Infectious Diseases* 3 (February 2003): 64. [6] T.K. Jha, P. Olliaro, C.P.N. Thakur, T.P. Kanyok, B.L. Singhanian, I.J. Singh, N.K.P. Singh, S. Akhoury, S. Jha, "Randomised controlled trial of aminosidine (paromomycin) v sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India", *British Medical Journal* (April 18, 1998).



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