

Editorial

Leishmaniasis research - the challenges ahead

W.B. Leishman described stained parasite of *Leishmania* in 1903¹ the same time as L H Donovan described parasite of kala-azar². Widespread in 22 countries in the new World and in 66 nations in the old World, leishmaniasis is however, not found in south-east Asia. Human infections are reported from 16 countries in Europe, including France, Italy, Greece, Malta, Spain and Portugal³. Among the 88 countries endemic for the disease, 72 are developing countries, 13 of which are least developed.

Leishmaniasis is a group of diseases caused by protozoan parasite of genus *Leishmania* (*L. donovani* complex, *L. major* complex, *L. tropica* complex). Different clinical forms of leishmaniasis constitute severe public health problems: visceral leishmaniasis (VL) also known as kala-azar is the most serious form, usually fatal if left untreated; cutaneous leishmaniasis (CL), the most common form and is disabling when lesions are multiple; muco-cutaneous leishmaniasis (MCL) is a mutilating disease while diffuse CL (DCL) produces disseminated and chronic skin lesions resembling those of lepromatous leprosy and is also disabling. Most form of leishmaniasis are originally infections of small mammals (reservoir hosts), which play a major role in the epidemiology of the disease. Old World forms of *Leishmania* are transmitted by sandflies of the genus *Phlebotomus*, while New World forms mainly by flies of the genus *Lutzomyia*. Sandflies become infected by ingesting blood from infected reservoir hosts or from infected people.

Ninety per cent of VL cases occur in five countries namely Bangladesh, India, Nepal, Sudan and Brazil while 90% of CL cases occur in 7 countries: Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria. Annual incidence is estimated at 1-1.5 million cases of CL, 500 000 cases of VL. Overall prevalence is 12 million people and the population at risk is 350 million. The DALY burden is 860 000 for men and 1.2 million for women³.

In several areas of the world, there is a disturbing increase in the number of CL cases, e.g. in Brazil (21

800 cases in 1998 to 30 550 cases in 1999 and 35 000 in 2000), in Kabul, Afghanistan (14 200 cases in 1994 to 200 000 cases in 1999), and in Aleppo, Syria (3900 cases in 1998 to 4700 cases in 1999 and 5900 cases in 2000). This is related to economic development, and to behavioural and environmental changes which increase exposure to sandfly vectors⁴.

The epidemiology of the disease is extremely diverse: 20 *Leishmania* species are pathogenic for humans, and 30 sandfly species are proven vectors. There are two main epidemiological entities: zoonotic, where animal reservoir hosts are involved in the transmission cycle; and anthroponotic, where man is the sole reservoir and sole source of infection for the vector.

For treatment, first-line drugs are the pentavalent antimonials, and second-line drugs are amphotericin B and Ambisome (amphotericin B in liposomes), the latter available only in industrialized countries and are expensive. Newer drugs have also come in the market. Miltefosine, an oral tablet, and paromomycin that has just completed phase 3 trial in India and waiting for registration. Most available drugs are costly, require long treatment regimens and are becoming increasingly ineffective, necessitating the discovery of new drugs.

The Indian Council of Medical Research has contributed significantly in conducting clinical trials of antileishmanial drugs like miltefosine and paromomycin. An ICMR/WHO/TDR/Zentaris sponsored phase IV clinical trial of orally administered miltefosine was started in 13 clinical centres spread over 6 VL endemic districts in Bihar in 2003 and is ongoing. Another ICMR/WHO/TDR/iOWH sponsored randomized, control, open, clinical trial was also being done to assess the efficacy of injectable paromomycin vs. amphotericin B in VL patients.

More recently, the overlapping of VL and AIDS has led to an emerging new entity: *Leishmania*/HIV co-infection. In Europe, intravenous drug users have been

identified as the main population at risk. In east Africa and India, the problem is encountered in migrants, seasonal workers, refugees, sex workers and truck drivers. Individual risk factors such as malnutrition and immunosuppression play important roles.

The leishmaniasis, as a complex of diseases, are as yet impossible to control with a single approach or tool (a vaccine may prove a cost-effective exception). Control depends on early case detection and drug treatment where the reservoir is infected humans. The main control strategy is case finding and treatment plus, when feasible, vector control and, in zoonotic foci, animal reservoir control⁵.

Kala-azar is present in India for more than 100 years. The epidemic of febrile disease with splenomegaly was reported in about 1850 in Jessore district and in Bardwan in 1872. The disease with fever and enlarged spleen seen in Muzzafarpur and Dharbhanga districts in Bihar in late 18th century and early 19th century was given the name kala-azar. DDT spray under the malaria control programme had a secondary effect on sandflies, the vector of kala-azar. DDT spray for kala-azar was discontinued in 1964 and sporadic cases were reported from different parts of country in the early 1970s⁶. A big epidemic of kala-azar occurred in 1977 with 100,000 cases. It was suggested that presence of chronic cases of kala-azar and post kala-azar dermal leishmaniasis (PKDL) provided the reservoir infection⁷ and withdrawal of DDT spray led to rise in vector density. A big epidemic of kala-azar occurred again in 1991-1992 with 250,000 cases in Bihar⁸.

At present almost all districts of Bihar, 11 districts of West Bengal and five districts of Uttar Pradesh are affected in India. Elimination of kala-azar is feasible and possible. Early detection and treatment of cases of kala-azar and PKDL to eliminate reservoir of infection, and spray of insecticides for reduction of sandflies will add to rapid elimination of disease. Proper planning, firm political decision, effective implementation of the control programme are needed to eliminate the disease from India and other parts of the subcontinent.

This special issue of the Indian Journal of Medical Research (IJMR), features articles from many leading experts from India and abroad on various facets of the disease. Understandably, many of the articles are

from laboratories from those parts of India which are endemic for this disease. Significant progress has been made in the last few decades and a lot of effort has gone into R&D to develop new drugs and vaccine. This special issue includes a comprehensive collection of recent advances in the area covering from the epidemiology of the disease across the world to the basic biological aspects of parasite *Leishmania*, diagnostics including the challenges in the diagnosis of PKDL, clinical features, current therapeutic modalities including drug unresponsiveness, combination therapies and newer drugs available, and preventive strategies including vector control and vaccine development. Lacunae in the knowledge as well as areas for future research have been highlighted. I am sure the special issue should interest scientists engaged in leishmaniasis research, practicing physicians and policymakers.

Dr C. P. Thakur

Guest Editor

Chairman, Balaji Utthan Sansthan

Kala-azar Research Centre

Uma Complex, Fraser Road

Patna- 800 001, India.

e mail : cpthakur1@rediffmail.com

References

1. Leishman W B. On the possibility of the occurrence of trypanosomiasis in India. *Br Med J* 1903; *i* : 1252-4.
2. Donovan C H. On the possibility of the occurrence of trypanosomiasis in India. *Br Med J* 1903; *ii* : 79.
3. <http://www.who.int/tdr/diseases/leish/default.htm>, accessed on March 20, 2006.
4. <http://www.who.int/tdr/diseases/leish/direction.htm>, accessed on March 20, 2006.
5. <http://www.who.int/tdr/diseases/leish/diseaseinfo.htm>, accessed on March 20, 2006.
6. Thakur CP, Kumar M, Pathak PK. Kala-azar hits again. *J Trop Med Hyg* 1981; *84* :271-6.
7. Singh RP. Observations on dermal leishmaniasis in Bihar. *Indian J Dermatol* 1968; *3* : 1-5.
8. Report of the Expert Committee. Kala-azar in Bihar. New Delhi, Director-General of Health Services, Ministry of Health & Family Welfare, 1991.