The Six Diseases of WHO

Leishmaniasis

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Leishmaniasis is not a single disease; rather, it is a collection of diseases caused by several different species of *Leishmania*, each of which has its own potential to cause a characteristic set of symptoms in man. No reliable estimates of the incidence and prevalence of leishmaniasis exist. It has been estimated that there are 400 000 new cases of leishmaniasis every year,[1] but the importance to public health is perhaps better gauged from the estimates of the number of cases in the recent epidemic of visceral leishmaniasis in Bihar, when it was conservatively estimated that there were 18 000 cases in 1977 and 40 000 in 1978 (R W Ashford, personal communication).

Within the vertebrate host the protozoan parasite is restricted almost exclusively to cells of the mononuclear phagocyte (reticuloendothelial) system, in which they are present as amastigotes. Two main clinical manifestations of leishmaniasis exist—cutaneous and visceral—the distribution of which is shown in fig 1.

In the cutaneous disease the parasites are restricted to macrophages of the skin, whereas in the visceral manifestation, though amastigotes may be found in many tissues, the major centres of infection are within the phagocytic cells of the liver, spleen, and bone marrow. No convincing explanation of these different tissue tropisms has been presented. Arguments based on differences in temperature sensitivity or metabolic control[2] are difficult to reconcile with the observation that the same parasite may cause visceral leishmaniasis in one individual but a cutaneous manifestation in another.[3]

In both the cutaneous and visceral infections the organism is transmitted to man by an insect vector, phlebotomine sandflies. Within the alimentary canal of the sandfly the amastigotes that are ingested together with the blood meal transform to a spindle-shaped flagellated form—the promastigote. These are the infective form and are the stage of the life cycle that may be easily grown in vitro on blood-agar slopes. When an infective sandfly takes its next blood meal promastigotes are delivered from the anterior portion of the alimentary canal into the skin and thus a new infection begins.

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For many years progress on several aspects of leishmaniasis was handicapped by the difficulties of differentiating morphologically among the various species of *Leishmania*. Recent ultrastructural studies[4] have shown differences in the size of amastigotes, but the main advance in identifying parasites has been the introduction of the techniques of biochemical taxonomy.[5 6]

The subdivision of the genus is complicated and to some extent controversial. An oversimplified classification includes *L donovani*, the causative organism of visceral leishmaniasis throughout the world. In India and some parts of East Africa transmission of this parasite is from man to man, while in other areas dogs and wild canids act as an animal reservoir. In the Old World at least two organisms cause cutaneous leishmaniasis: *L major* is usually present in rural areas, with rodents acting as reservoirs, and is distributed from West Africa through the Middle East into the USSR, while *L tropica* is apparently more restricted in its distribution than *L major*, being present in North Africa, the Middle East, and the USSR. In the USSR in particular the parasite has an urban distribution and the transmission appears to be man to man. Recent studies indicate[3] that in a few cases *L tropica* may give rise to a visceral infection instead of a simple cutaneous lesion. In the New World *L mexicana* and *L braziliensis* are responsible for cutaneous leishmaniasis; both species have been subdivided into numerous subspecies.

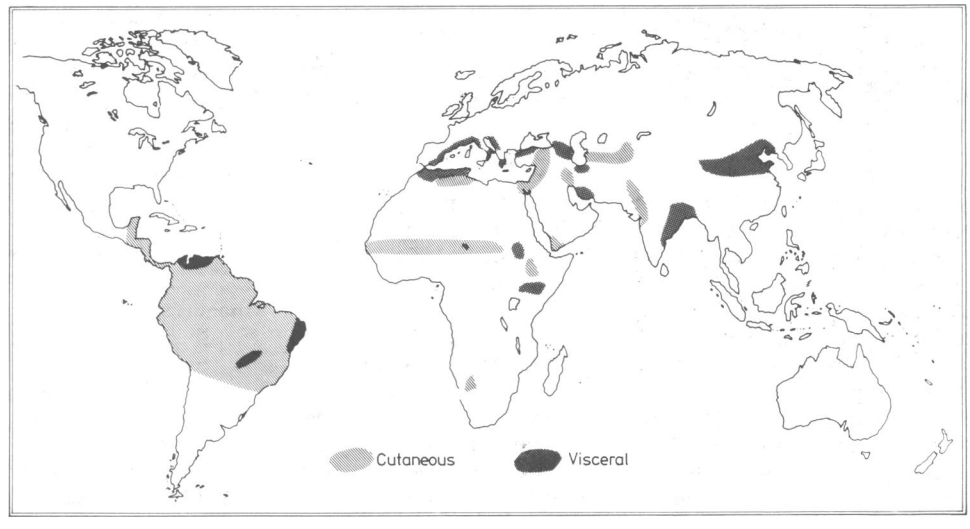

FIG 1—Geographical distribution of cutaneous and visceral leishmaniasis.

Though the basic outline of the life cycle is identical for all leishmanias infecting mammals, the details of the epidemiology

vary greatly, with many different species of vector and reservoir being involved with the various species of *Leishmania*.

The disease

The major symptoms of visceral leishmaniasis are intermittent fever, pronounced enlargement of the liver and spleen, anaemia, and leucopenia. Visceral leishmaniasis is sometimes known as kala-azar, a Hindu name for black fever that refers to the earth-grey pigmentation of the skin seen in some cases. Though it is difficult to obtain accurate figures, the infection is thought to be fatal in at least 70% of untreated cases.[7] Superinfection is an important cause of death.

In cutaneous leishmaniasis a nodule appears at the site exposed to the bite of infective sandflies. A shallow ulcer forms (fig 2), usually about 2·5 cm in diameter, though in some instances an area several centimetres across may be eroded.

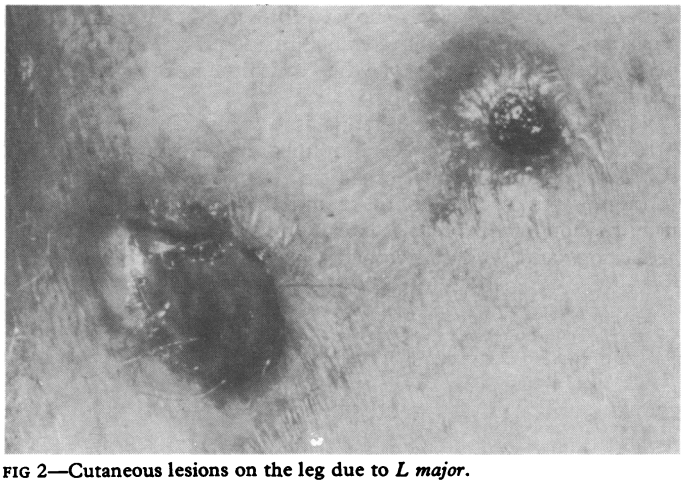

FIG 2—Cutaneous lesions on the leg due to *L major*.

Lesions may be single or multiple, with the multiple ulcers resulting either from several sandfly bites or from metastasis. Usually cutaneous lesions heal spontaneously, though the period required for healing varies from three to 18 months. A characteristic scar remains, and in most cases a solid immunity to further infection with the same parasite is established.

Leishmaniasis has other clinical manifestations in addition to the two forms described above. Diffuse cutaneous leishmaniasis is known in the New World, where *L mexicana* is the causative organism, and in Ethiopia. In this condition nodules 1 to 2 cm in size cover the whole surface of the body. The nodules that do not ulcerate contain a mass of infected macrophages but there is no cellular response; indeed, patients with diffuse cutaneous leishmaniasis appear to be incapable of responding to leishmanial antigen, though they respond normally to other antigenic stimuli.

Leishmaniasis recidivans usually associated with *L tropica* is a form of leishmaniasis in which an apparently healing lesion breaks down at the margin, giving rise to a spreading lesion that may persist for many years.

One or more of the subspecies of *L braziliensis* have a tendency (which may be up to 80% of cases, as in Paraguay) to develop metastatic lesions in the oral-nasopharyngeal tissues (muco-cutaneous leishmaniasis) that are extremely destructive and disfiguring. The delay between the primary infection with *L braziliensis* and the onset of mucocutaneous leishmaniasis may be considerable, 24 years having been recorded in one case.[8]

A condition known as post kala-azar dermal leishmanoid (PKDL) is sometimes seen as a sequel to a *L donovani* infection, particularly in India. Parasites are present in nodules covering the body, and it has been suggested that patients suffering from post kala-azar dermal leishmanoid act as a reservoir of the disease.

The response to chemotherapy of these less common conditions is often poor.

The diagnosis of leishmaniasis usually depends on finding Giemsa-stained amastigotes in biopsy material taken from bone marrow or the spleen. This material may also be cultured in blood-agar medium (known as NNN) at 26°C, when the presence of promastigotes in the culture confirms infection with leishmania. Serological methods of diagnosis, including indirect immunofluorescence (IFAT) and enzyme-linked immunosorbent assay (ELISA), have been extensively investigated,[9,10] but, though they have proved sensitive, they lack specificity, exhibiting in some cases extensive cross-reactivity with other common infectious organisms including mycobacteria and trypanosomes.[11,12] There is a great need for more specific serodiagnostic techniques for leishmaniasis.

Treatment and control

The first effective treatment of leishmaniasis was achieved with the antimonial tartar emetic. The present drugs of choice are still antimonials—the pentavalent antimonials sodium antimony gluconate (Pentostam) and antimony methyl glucantime (Glucantime). Amphotericin B and pentamidine are also used in antimony-resistant cases, which may be frequent in some geographical regions. There is an obvious need for a wider range of less toxic drugs for treating leishmaniasis.

The control of leishmaniasis by interrupting the transmission cycle can in many cases present almost insurmountable problems.[13] The control of cutaneous leishmaniasis in Central and South America would necessitate controlling sandflies and animal reservoirs in dense tropical forest—only the destruction of the forest would make this possible and even this ecologically dangerous process might merely lead to the replacement of one parasite by another.[14]

Major campaigns to control the rodent reservoirs of *L major* in the USSR have been successful. Control measures have included the use of poisoned bait, deep ploughing of burrows, and the construction of physical barriers to reinvasion, such as irrigation canals.

In circumstances in which leishmaniasis is transmitted from man to man, control has been achieved by eliminating the vector by spraying houses with insecticides. Urban cutaneous leishmaniasis has been virtually eliminated from the cities of the Southern USSR by this method, while the incidence of the vector of visceral leishmaniasis was considerably reduced in India by DDT spraying in the antimalarial campaigns.

The cessation of antimalarial spraying led to another epidemic of kala-azar just as had been predicted by Sen Gupta.[15] Personal prophylaxis is not possible, no suitable chemoprophylactic agent is available, and the use of insect repellents in hot humid environments is not feasible. For those places where an animal reservoir exists that cannot be easily controlled vaccination is the obvious method of preventing human infection. Natural live vaccines have been used successfully in the Middle East and in the USSR to prevent reinfection with *L major*, but in general the cross-immunity of one species of *Leishmania* against another is slight or non-existent. Obviously a live vaccine cannot be used to protect against a homologous parasite, when there may be a dangerous sequel to infection with that organism as is the case with *L braziliensis*. The immediate prospect of an effective multivalent vaccine is remote.

Recent advances

Though many problems of the control and treatment of leishmaniasis are unresolved, many advances have been made in the past 15 years after the renewed interest in the leishmania parasite. Some of the important advances are outlined below.

Though no new drugs have been developed for treating leishmaniasis, there has been an important development in the delivery of drugs. Though still used only in experimental systems, the use of liposomes (phospholipid dispersions) to encapsulate antileishmanial drugs has greatly increased, by several hundredfold, the efficacy of drugs administered in this manner.[16-18] The use of liposomes increases the efficacy of several drugs in both the cutaneous and visceral forms.[19] The rationale behind this method of administration is that intravenously administered liposomes are rapidly removed from the blood stream by the phagocytic cells of the liver and spleen. These are the very cells that in the visceral disease contain the parasites; thus high concentrations of drug are achieved in the vicinity of the parasite. Indeed, since lysosomal fusion occurs with the vacuole containing the parasite,[20] and since phagocytosed liposomes themselves will be present in lysosomes, there is the possibility of drug being delivered directly into the vacuole containing the amastigote.

We have also witnessed a tremendous increase in our knowledge of the epidemiology of leishmaniasis in many parts of the world. Thus, for example, the importance of rodents and carnivores as reservoirs of human visceral disease in the Sudan has been established,[21] while new facets of visceral leishmaniasis in the Mediterranean region are emerging.[22] In the New World the importance of the forest edentates, the sloth and tamandua (S American anteater),[23 24] as reservoirs of some subspecies of *L braziliensis* in Panama and Brazil has only recently been recognised.

Many advances have been made in handling the parasite in the laboratory. Though cultured promastigotes have always been readily available, it is only recently that defined and semidefined media have been used to grow this stage of the parasite.[25] It has not proved possible to culture amastigotes in cell-free culture but improved methods of isolation from animal tissue are available,[26] and the use of macrophage-like cell lines to grow intracellular amastigotes[27] allows large numbers of the mammalian stage of the parasite to be available for experimental studies. Unfortunately not all species of *Leishmania* can be easily handled in the laboratory and no convenient laboratory host has been found for *L braziliensis*, while the same parasite is also difficult to culture in vitro—which has serious implications, for example, in the preparation of antigens to be used in vaccination.

Problems relating to the identification of leishmania have been overcome by using the techniques of biochemical taxonomy, which include determining the buoyant density of DNA and the electrophoretic mobility of specific enzymes. The techniques have proved particularly useful in identifying parasites isolated from potential vectors and reservoirs.[28] A recent advance in the identification of New World leishmania has been the production of monoclonal antibodies specific for either *L mexicana* or *L braziliensis*.[29] These antibodies should prove useful for either the identification or the direct diagnosis of leishmaniasis. Clearly the areas in which the most rapid advances are being made are in investigations on the parasite itself rather than medical topics. Many of the studies on the parasite, particularly those on experimental chemotherapy and immunodiagnosis, could rapidly be translated into medical advances.

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Is sclerotherapy or surgery the most effective treatment for hydrocele?

Either sclerotherapy or surgery is effective in the treatment of hydrocele. On the other hand, it should be remembered that the thin-walled sac of a hydrocele that has been tapped infrequently in a younger patient will undergo considerable inflammation as a result of the action of the sclerosing agent. This can be exquisitely painful for the patient for several hours, or even one or two days. The older patient whose hydrocele has been tapped many times and may have had infection in the past will have a thicker-walled sac, and in this type the sclerosing agent causes minimal discomfort to the patient. Surgery may be done under local anaesthesia and through a relatively small incision if the hydrocele sac wall is thin. Bleeding and infection are the two commonest complications of excision of hydrocele and therefore every care should be taken to ensure complete haemostasis by oversewing the margin where the sac has been excised. Recurrence of hydrocele is distinctly more common after sclerotherapy than surgery because the sclerosing agent may not diffuse evenly throughout the whole of the sac.—J P MITCHELL, honorary professor of surgery (urology), Bristol.