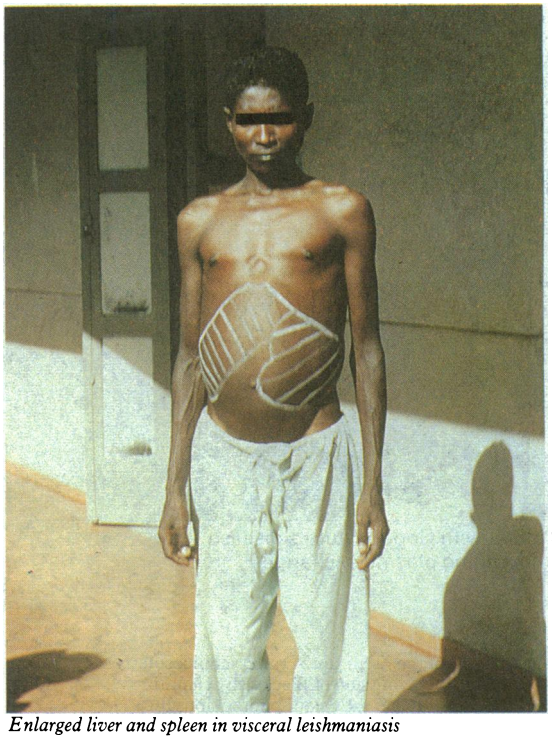
Leishmaniasis

P D Marsden

As well as Chagas' disease, malaria, and schistosomiasis our small unit also works on one other endemic infection—namely, leishmaniasis. Like malaria it occurs in virtually all warm climates, only Australia being spared. William Boog Leishman, the English army surgeon who gave his name (usually mispronounced) to the disease, first identified the parasite in liver sections from a soldier with fatal kala-azar caught in India.[1] We now know that there are 14 subspecies of leishmania, which produce a bewildering variety of clinical presentations. In leishmaniasis, unlike the three other infections mentioned above, we are still at the stage of defining the aetiological agents, epidemiology, and clinical picture. For this reason research into it is extremely active and involves various branches of science and medicine. I will therefore discuss visceral, cutaneous, and mucosal leishmaniasis separately in this and my next two communications.

The three principal differential diagnoses for patients with hepatosplenomegaly who live in or have recently visited the tropics are kala-azar, malaria, and schistosomiasis. Kala-azar, leukaemia, and the deposition disorders are the main cause of pronounced hepatosplenomegaly. Clinical clues will aid a diagnosis of kala-azar, especially if the disease is advanced. Patients will have a history of intermittent fever, sweating, and weight loss and be clinically anaemic, often with a tendency to bleeding. In the late stages the liver and spleen are equally enlarged. Patients always have pancytopenia and hypergammaglobulinaemia. The diagnosis is confirmed by identifying *Leishmania donovani* in bone marrow or splenic aspirates, either by examining smears stained with Giemsa or by cultivation in 10% rabbits' blood agar incubated at 26°C. The World Health Organisation's recent recommendations should be followed when performing splenic aspiration; inexperienced staff who push big needles into the spleen, restrict the needle's movement, or do not take precautions to minimise bleeding can cause haemorrhage. An intramuscular needle attached to a 10 ml syringe charged with sterile saline introduced rapidly into the immobile spleen should provide adequate material for diagnosis.



THE WELLCOME TRUST

Enlarged liver and spleen in visceral leishmaniasis

First hand experience of visceral leishmaniasis

I probably have more experience of visceral leishmaniasis than most of my colleagues. When I was a registrar at Dreadnought Seamen's Hospital in England and worked as a ship's surgeon for the Peninsular and Orient Steamship Company I saw many patients with kala-azar. It is called kala-azar (black fever) because of the skin pigmentation that occasionally develops. It is common among adults in India, and seamen visiting India would develop symptoms during the journey back to England, arriving home in a similar state to Leishman's English soldier. It was epidemics of kala-azar in the Indian army that led to English interest in the disease, and this resulted in the causative organism being identified and its life cycle elucidated, blood sucking sandflies being incriminated as vectors. Despite much research no animal reservoir has been identfied in India, although man seems to maintain the cycle, especially in the form of post-kala-azar dermal leishmaniasis. Colonel Short used to hire only technicians who could find amastigotes in white cells in the peripheral blood as these occur fairly commonly in Indian kala-azar. Fortunately, the condition responds well to treatment with antimonial drugs.

While I was a resident, and then assistant, at the London Hospital for Tropical Diseases I saw a number of English children who had acquired kala-azar while on holiday in the European Mediterranean littoral. They sometimes responded badly to antimonial drugs, and two of them had a splenectomy, the only time I have seen this used to treat the condition. While working in the tropics I found that kala-azar was uncommon in west Africa and unknown in New Guinea, but I saw many affected children and adults while working at Mulago Hospital, Uganda. Higher doses of pentavalent antimonial drugs were required than for Indian kala-azar, but the initial clinical response was usually good. We had no facilities for long term follow up as our hospital based services were overstrained. I have never seen a patient with either of the two types of Chinese kala-azar. I frequently see kala-azar in Brasilia now, especially in children, but fortunately it is almost as sensitive to pentavalent antimonial drugs as the Indian variety.

All these various types of kala-azar have been given subspecies names: *Leishmania donovani* (Indian), *L donovani infantum* (Mediterranean), *L donovani archbaldi* (east African), *L donovani chinensis* (Chinese), and *L donovani chagasi* (South American). Isoenzyme analysis does not, however, differentiate between them, and they may have a common origin. Of course, in historical terms it could have been the Portuguese who spread kala-azar around the world. European dogs have recently introduced kala-azar into communities in

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the United States. It is likely that *L donovani* was of animal origin, as were other members of the genus, and in Brazil, foxes are a significant animal reservoir. The sensitivity of the Brazilian disease to antimonial drugs does not fit with the resistance of the infantum subspecies found in Portugal. Today there are epidemics of kala-azar among poor children in *favelas* in cities of north eastern Brazil such as Teresina, São Lui and Santarém.

Subclinical infections

Recent work has shown that kala-azar is characterised in the acute phase by leishmania antigens inhibiting T cell function. T cell function is restored only after successful treatment, when the result of a skin test is positive. Longitudinal studies have shown that a proportion of the population in areas where leishmaniasis is endemic have a subclinical infection of *L donovani* and that malnutrition is an important factor determining whether the infection will become clinically manifest. Malnutrition could be at least partly responsible for the occurrence of kala-azar in adult Indians and east Africans.

It may be that leishmania is like *Mycobacterium tuberculosis* and never disappears completely once the amastigotes have established themselves in the body. Several patients who had never had any symptoms of the disease developed kala-azar after immunosuppression. I personally attended a man who developed kala-azar in England 14 years after he had left an area where it was endemic.

Brazil's control programme for kala-azar incorporates three measures: treating patients with the first line drug meglumine antimonate provided by the ministry, detecting and destroying infected dogs, and spraying homes and gardens with dicophane (DDT) to combat the vector *Lutzomyia longipalpis*. It has been suggested that under epidemic conditions most infected children should be treated at home rather than overstrain hospital services. This is logical as hospitals are full of bacterial pathogens to which patients with active kala-azar are very susceptible. Children tolerate antimonial drugs better than adults, but certain basic rules must be obeyed. For outpatient treatment the daily injection is best given at the end of the day so that the patients can rest afterwards, and it must be given slowly if administered intravenously. Patients with cardiac, renal, or hepatic dysfunction must be carefully screened before being given antimonial drugs and alcohol must be avoided during treatment. I shall have more to say about antimonial drugs in my next communication.

1 Leishman WB. On the possibility of the occurrence of trypanosomiasis in India. *Br Med J* 1903;i:1252-4.

New Drugs

Lipid lowering drugs

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Background

Atherosclerotic vascular disease, particularly of coronary arteries, is the leading cause of morbidity and mortality in the Western world. Considerable epidemiological data now establish a direct relation between increased total plasma cholesterol concentrations and the development of atherosclerosis. A similar link has been shown for raised concentrations of individual atherogenic lipoproteins, in particular the low density lipoprotein (LDL) fraction.[1,2] In contrast, a strong inverse relation has been found between high density lipoprotein (HDL) cholesterol concentrations and the risk of coronary heart disease.[3,4] Though it is not certain whether increased triglycerides are an independent risk factor,[5] high concentrations are usually accompanied by low concentrations of HDL, and this may be their link with coronary risk.

Many studies have shown convincingly that dietary and drug induced reductions in cholesterol concentrations are associated with a lower risk of developing coronary heart disease.[6] Evidence also exists of not only a decrease in the rate of progression of atherosclerosis in patients with established disease, especially of the coronary arteries, but also of regression when steps are taken to reduce plasma cholesterol concentrations.[7,8] Regression of xanthomas is commonly seen when patients with familial hypercholesterolaemia have their cholesterol concentrations lowered by drug treatment.[9]

Increasing awareness in doctors and the general population that high plasma cholesterol concentrations are a risk factor for developing coronary heart disease has led to screening for risk factors in the population at large, rather than focusing exclusively on people with established heart disease or a family history of hyperlipidaemia, diabetes, or other conditions related to atherosclerosis.

Hypercholesterolaemia is common and up to a quarter of the British population have total plasma cholesterol concentrations higher than 6·5 mmol/l.[10] British,[11] European,[12] and American[13] expert panels all agree on an ideal total plasma cholesterol concentration of 5·2 mmol/l or less and that people with consistently raised plasma cholesterol concentrations should be treated, especially if other risk factors exist; they have produced comprehensive management guidelines.[11-13]

Triglycerides have a more tenuous link with atherosclerosis. Recurrent acute pancreatitis, however, is a recognised complication of severe hypertriglyceridaemia (>10 mmol/l) associated with chylomicronaemia. Current recommendations are to maintain total triglyceride concentrations at 2·3 mmol/l or less.[12]

Secondary hyperlipidaemia should be excluded in all patients presenting with hyperlipidaemia. The more common causative conditions include diabetes, hypothyroidism, and kidney disease. Drug treatment with thiazides, β blockers, oestrogens, or retinoids may also have an adverse effect on serum lipids, and a heavy alcohol intake may raise plasma triglyceride concentrations.

Plasma lipids and lipoproteins

The main lipids are cholesterol, triglyceride, and phospholipids. They are rendered water soluble by their association in macromolecular complexes with proteins formed in the liver and intestine—apolipoproteins. These proteins are also important as markers for lipid particle recognition by specific receptors in

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