

that there is already proof that DFMO is highly effective as a single agent against sleeping sickness with central nervous involvement.

Our actual words were "DFMO (BACCHI *et al.*, 1983), which has already undergone clinical trials as a therapy for sleeping sickness (VAN NEIUWENHOVE *et al.*, 1985), is active against trypanosomes in all three locations in the brain but is slow to clear the blood. It was difficult to evaluate this compound against others because of the very high dosage needed and because it was not possible to dose animals other than by mouth." We do not think we could have said more in a paper devoted to laboratory evaluation seeking only to advance for further study compounds which had not already received clinical trials for sleeping sickness therapy.

McCann and his colleagues have taken an important initiative in using an anti-cancer agent (DFMO) as a cure for sleeping sickness. Anti-cancer drugs which are already accepted for clinical use have an advantage in having undergone expensive toxicity trials that are such a barrier to the acceptance of a new drug for use in poor countries. We included three such drugs in our experiments: daunorubicin was inactive against the ependymal stage; DFMO was active but difficult to evaluate; bleomycin, however, was the most active single drug of our whole series. We did not recommend further studies with bleomycin because we were unaware, at the time, that it was already in extensive clinical use and is included in the British National Formulary.

Although DFMO has been highly successful in the cure of late sleeping sickness it is unlikely, because of the very high dose levels required, to become the first choice for sleeping sickness therapy and, even if it were, other new drugs would still be needed.

We think that our new test offers a cheap and easy means of assessing the ability of trypanocidal drugs to clear the brain and its appendages and we recommend its extensive use on all existing trypanosomicidal drugs, particularly those already in clinical use for other purposes. Suramin plus metronidazole was our first recommendation for clinical evaluation for sleeping sickness therapy, and we now add bleomycin, drugs that are accepted for clinical use. The undoubted success of DFMO in the field does not imply that the search for other effective cures for sleeping sickness should cease.

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#### Further comments on cutaneous leishmaniasis in Belize, Central America

In a letter to the editor (LAINSON, 1984: *Transactions*, 78, 851), I discussed the identity of the parasite causing cutaneous leishmaniasis in Belize, and defended the conclusion of LAINSON & STRANGWAYS-DIXON (1963: *Transactions*, 57, 242) that the parasite they isolated from patients (mostly chichleros) was *Leishmania mexicana*, based on its characteristic

development in hamster skin compared with the very different behaviour of *L. braziliensis* in the same animal. I find it particularly irritating, therefore, to read the editorial in the proceedings of the recent symposium "Leishmaniasis: the first Centenary 1885-1985" (1986: *Journal of the Royal Army Medical Corps*, 132, 123), which again casts doubt on the early identification of *L. mexicana* in Belize. I can but conclude that the writer has no practical experience regarding these fundamental biological differences, and that he is unfamiliar with the extensive literature on this subject, including my above-mentioned letter.

It is suggested, following the recent discovery of a parasite of the *L. braziliensis* complex causing cutaneous leishmaniasis in British servicemen stationed in Belize (EVANS *et al.*, 1985: *Transactions*, 78, 35), that "The lesson to be learnt from this... is that with the development of new investigative medical technology we should never stop questioning the dogma of our mentors lest we be responsible for the perpetuation of outdated ideas which could have serious adverse consequences", and that the significance of the new finding "...lies in the need to provide affected troops with the best possible treatment to prevent the possibility of late mucocutaneous extension of the disease...".

As I am sure many will agree, "...new investigative medical technology..." is hardly necessary to differentiate two parasites which are as strikingly different as *L. mexicana* and *L. braziliensis*, on both the morphology of their amastigotes and promastigotes and their behaviour in the hamster. I am not sure to which "dogma" or "outdated ideas" the editorial refers in its dire warning to the reader. Lainson & Strangways-Dixon certainly made no dogmatic statement to the effect that *L. mexicana* was the only leishmanial parasite in Belize, and they can hardly be blamed for the fact that all their isolates were of that parasite - a result probably reflecting differences in the epidemiological features involving the chichlero and other civilian forest-workers, and military personnel engaged in manoeuvres. Finally, as far as I am aware, mucocutaneous leishmaniasis has not been recorded in Belize.

By no means all text-books "...perpetuate the myth that *L.m.m.* infections are benign..." as suggested by the writer of the editorial. The disease "chichlero's ulcer" is surely infamous for its common production of highly mutilating and chronic lesions of the ear, a fact that has led to the alternative name of "chichlero's ear". Lainson & Strangways-Dixon illustrated some cases with a duration as long as 30-40 years.

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#### Dermal and visceral leishmaniasis and their causative agents

We read with interest Dr KILLICK-KENDRICK's answer (*Transactions*, 1986, 79, 737) to the suggestion of Dr SCHNUR *et al.* (*Transactions*, 1985, 79, 134) that Egyptian kala-azar might be due to *Leishmania major*, and Dr Schnur's recent news (*Transactions*, 1986, 80, 671) that the causative parasite is, in fact, *L. infantum*.

We join Dr Killick-Kendrick in his concern over the literary confusion that precipitous conjecture may cause: equally dangerous are misleading statements due to badly worded text, and the tendency of some to over-emphasize departures from the normal behaviour of parasites.

*L. chagasi* is the causative organism of American visceral leishmaniasis (AVL), in the epidemiological situation involving transmission by *Lutzomyia longipalpis*. OLIVEIRA NETO *et al.* (*Memórias do Instituto Oswaldo Cruz*, 1986, 81, 303), however, claim to have isolated this parasite from the skin ulcer of a patient in Brazil who was "...without any involvement of the various organs and systems...". Another isolate identified as *L. chagasi* was made from the ulcer on the ear of a dog in the same locality. From these results, the authors report "...for the first time, *L. donovani chagasi* inducing primary and active cutaneous leishmaniasis in both human and canine infections in the New World".

No attempt was made to locate parasites in the viscera or bone-marrow, however, and it remains impossible to be sure that either infection was confined to the skin: and, while skin ulcers are rarely recorded in human cases of AVL, such lesions surely are a *feature* of the canine disease. No comment is made on the positive Montenegro skin-test of the patient, which became negative 4 months after treatment: this is unusual, as positive tests do not normally become negative so quickly, and those of patients with visceral leishmaniasis are *negative* during the infection and (usually) become positive *after* treatment.

OLIVEIRA NETO *et al.* (*loc. cit.*) refer to a paper by LAINSON (*Transactions*, 1983, 77, 569) as an example indicating that "...current thinking is that the 'dermatotropic' *L. braziliensis*, *L. b. guyanensis* or *L. mexicana amazonensis* are the causative agents of American cutaneous leishmaniasis in Brazil, and the American visceral leishmaniasis is caused by 'viscerotropic' *L. d. chagasi*", and suggest that "Against this

established view there are recent reports demonstrating that kala-azar can be caused by 'dermatotropic' species of *Leishmania* in the Old World (SCHNUR *et al.*, 1981; 1985)..." (see, however, SCHNUR, *Transactions*, 1986, 80, 671).

Firstly, we cannot believe that the authors mean to suggest that the first 3 of these parasites are *not* causative agents of cutaneous leishmaniasis in Brazil, and that the last is *not* the cause of visceral leishmaniasis in the same country! Presumably, what they mean to say is that some parasites usually produce a visceral disease in man, but sometimes cause dermal lesions, and that others normally causing cutaneous leishmaniasis may occasionally visceralize.

Secondly, LAINSON (*loc. cit.*) did *not* suggest rigid dermatotropic or viscerotropic behaviour on the part of *Leishmania* species as implied. On the contrary, he has long warned of the "...misguiding illusion that there is a sharp division between parasites causing cutaneous and visceral leishmaniasis" (LAINSON & SHAW, in *Biology of the Kinetoplastida*, edited by Lumsden and Evans, 1979, Academic Press, London). Nevertheless, "one swallow does not make a summer" - nor, indeed, do 2 or 3. Clinical manifestations not normally associated with a given parasite may occur, but we should not lose our sense of perspective. In the Americas, cutaneous leishmaniasis of man is overwhelmingly due to parasites of the *L. braziliensis* and *L. mexicana* complexes, and visceral leishmaniasis to *L. chagasi*.

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## THE EPIDEMIOLOGY AND IMMUNOPATHOLOGY OF CUTANEOUS AND MUCOSAL AMERICAN LEISHMANIASIS

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