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Endemic Leishmaniasis in Brazil: Future Implications

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Some predictions are made as to how work on leishmaniasis and its control will develop in Brazil in the future.

Key words: human leishmaniasis - Brazil - treatment - control

Unfortunately Gabriel Grimaldi could not be present to give his opening remarks. He must have new information on the distribution of *Leishmania* subspecies in Latin America. Such taxonomic work is a good example of how scientists and medical men can combine to try to unravel the complexities of this endemic infection. Gabriel can only examine the live organisms he receives and many braziliensis types infections are difficult to isolate, maintain and type. Also competence in isolation at the periphery using cultures or hamsters is very variable. I believe there is still an organism in mucosal leishmaniasis that we in Três Braços, State of Bahia, have never succeeded in isolating or typing. I also suspect there are many types of braziliensis infection. Dr Jackson Costa who has a large experience in Três Braços of Bahian. *Leishmania (viannia) braziliensis* (Lvb) is now working in an area of Maranhão where the clinical picture is very different yet the organism is typed Lvb. However host response must never be discounted as an important factor influencing clinical presentation. In Três Braços we see the whole clinical spectrum of cutaneous disease from diffuse cutaneous involvement (though not anergic) to *Leishmania* recidivans but recover just one subspecies Lvb. To complicate the picture further clones of one isolate show different properties.

The Núcleo Tropical in Brasília has field research concerned with the four endemic parasite diseases of Brazil and since its foundation in 1974 the order of priorities in terms of practical solutions has reversed. Today that order is malaria, leishmaniasis, Chagas' disease and schistosomiasis. Why? Because effective, cheap, oral drugs are available that kill over 90% of adult schistosome worms on a single dose and even, over time, reverse the signs and complications of hepatosplenic disease.

Leishmaniasis has a similar solution. The most practical answer for this sporadic endemic disease is a better drug than glucantime. An oral agent, cheap, easily given in the field and with few side effects would be ideal. We entered Três Braços in 1974 with great hopes for nifurtimox since favourable trials had been reported from Peru and Colombia. We have since tested numerous alternative substances without success and still have to rely on glucantime.

Rely however is hardly the correct word since like all pentavalent antimonials it is unstable, forms polymers and even degenerates to a trivalent compound. It must be protected from the light and is probably best kept in the refrigerator at 4°C and osmolarity and pH checked regularly to detect deterioration. For unresponsive patients aminoside in an option with which the Brasília group has had some success but application is parenteral and it has the side effects of the aminoglycosides namely eight cranial nerve damage and possible renal insufficiency. The standard second line drugs remain at the time of writing amphotericin B and pentamidine - both toxic and best given in hospital.

The future for new compounds rests with one hope. The American Army screen of 300,000 possible antimalarials has thrown up a number of substances with antileishmanial activity as well. One eight aminoquinoline has reached human trial in Kenya and will be tried in Brazil but it does not look promising. No commercial pharmaceutical company is interested. Bayer who produced commercial pentavalent antimonials (neostibosan, solustibosan) is not interested and sold their patent to Wellcome (pentostam) and Rhone Poulec (glucantime). Both the latter companies would like to stop producing a drug they can't standardise but the outcry from the clinicians keep them in production. The alternative, of course, is for Brazil to produce their own government sponsored pentavalent antimonial like India and China. Brazil has tried twice. I only have the experience of the second product which was so acid it produced intense venospasm on intravenous injection. I think the Brazilian Ministry of Health should enter in contact with Indian or Chinese colleagues to solve this problem because in this decade there will be nothing else for the field. Apart from the intricate

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laboratory screen *in vitro* and experimental animals, human trial protocols must start with kala azar, proceed to a limited skin leishmaniasis and only finally reach something like metastasising Lvb. Then an acceptable protocol must be completed in the hospital before it goes to the field.

Evidently in the future new amplified serological methods and DNA probes will facilitate diagnosis and aid the clinician particularly under difficult field conditions. I wish to enforce the view of the Núcleo de Medicina Tropical of the Universidade de Brasília. We believe to produce productive medical workers they must be not only competent at the bedside but also under field conditions. It is a great advantage to have the same man conducting the field therapeutic trial who was involved in the previous hospital evaluation.

I would like to comment briefly on the major forms of Brazilian leishmaniasis.

VISCERAL LEISHMANIASIS (VL)

No longer the exclusive province of *Leishmania donovani* and *L. mexicana* infections have been repeatedly recovered from kala azar patients in Bahia. We have recovered Lvb from marmoset liver and a human case presenting as kala azar in Brasília. Splenic puncture is essential for drug trial evaluation as detailed in a WHO Special Report (Anonymous 1984). An intact immune system is a condition for glucantime to work and reduction of cellular immunity promotes occult leishmaniasis. *Leishmania* like mycobacteria may live in the body for decades and the longest incubation period for VL I have seen is twenty years. Associated conditions like malnutrition, tuberculosis, hepatosplenic schistosomiasis can cause overt disease of subclinical infections.

Little can be said as to the control of VL especially in peri urban endemics, such as that in Teresina, Piauí. There are no cost effective studies either of insecticide use against *Lutzomyia longipalpis*, dog destruction or vaccination, or patient treatment but I speculate the last will be the cheapest. One has to throw the responsibility in part back to the family head. Informative repeated television programmes will alert even poorest parents at the periphery of a city to take their child to a community health centre. Basically the core of the whole problem is the scarcity of such centres. Brazilian medicine of the next century will be committed to funding such a service network as well as improving hospital services.

CUTANEOUS LEISHMANIASIS

We were just lucky that Três Braços transpired as a virtual monotransmission of one parasite, Lvb and since were early in the taxo-nomic field we have been able to define in detail the behavior of our type of Lvb in man. It is probably the worst since it is associated with a relatively high incidence of mucosal metastasis. We need analagous information as regards clinical features, diagnosis, histopathology and res-ponse to treatment in other forms of Lvb to formulate control plans. A mobile expert unit would be most suitable for this (bus and trailer containing adequate personnel and hamsters). The cause of the miniepidemics occuring in Três Braços is still not clear but probably an infected mammal (man, ungulate, dog) initiates perido-miciliary transmission. There is no hope for sandfly control.

Leishmania (Viannia) guyanensis (Lvg) is poorly documented clinically but apparently occurs only north of the Amazon river due to the distribution of its major mammalian vector the two toed sloth. Comparative data similar to that available for Lvb mentioned above is urgently needed. It is the author's impression based on attending outpatient clinics in Manaus, that Lvg lesions of man are more frequently multiple, ulcers shallow and response to treatment usually better than Lvb. Also amastigotes are more easily found in giemsa stained smears and histology with Lvg. Mucosal metastasis, if it occurs, is very rare.

Leishmania (Leishmania) amazonensis (La) is a rare human infection in Três Braços because the vector *Lu. flaviscutellata* rarely bites man but has an established cycle with rodents. Diffuse anergic cutaneous leishmaniasis (Convit's syndrome) is only caused by La in Brazil and is virtually incurable. Its incidence has been exaggerated by the Belém group who see a very selected patient group. It is actually very rare and after twenty years of work in the field and the hospital we saw our first case this year. Unfortunately as with most of these forms of human leishmaniasis there is no animal model. We do not know why only La causes this anergy. The absence of a good animal model for mucocutaneous leishmaniasis points to the importance of human host factors in the causation of disease.

So the bottom line (as the Americans say), the ultimate conclusion in 1993, is the well conducted therapy clinics serving personnel with leishmanial infections are the short term answer for the 1990's. With the degree of ignorance about human leishmanial infections the long term future control measures cannot be predicted. However I suspect, as I wrote elsewhere years ago, I will continue to use glucantime in my field clinics for the rest of my life (Marsden 1985). There is an urgent need in Brazil for a laboratory to screen *Leishmania* isolates for glucantime sensitivity.

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