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HUMAN INFECTION WITH *TRYPANOSOMA CRUZI* AND *LEISHMANIA VIANNIA BRAZILIENSIS* (Lvb) A CLINICAL PERSPECTIVE*

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These remarks are in English, the current language of science, as Chinese, Arabic, Greek and Latin were in the past. My qualification for making them is that, apart from my general clinical and teaching duties, I have spent 25 years doing research on *T. cruzi* and 15 years on Lvb. I am a clinician first and a parasitologist second so that my research is applied to aspects pertaining to diagnosis, treatment and prevention. This classification is used in this discussion and among these six topics there has only been one great advance during my time, the control of Chagas' disease in Brazil. Diagnostic techniques still lack sensitivity and precision and the drug companies have shown little interest in chemotherapy. For this reason I wanted to make some observations.

T. cruzi

Diagnosis. T. cruzi infection of man is analagous to the treponematoses in terms of the dependence of the clinician on reliable serology. Positive serology provides valuable background information for clinical management especially if immunosupressives are to be used. Yet my hospital in Brasília has no regulation regarding serological screening in what is a highly endemic area. A sensible regulation would be that all patients over 8 years of age coming from rural areas with a history of bugs in the house should have serology. The massive attack phase of the control programme in Goiás took place eight years ago. There are still no clear guide lines regarding serology. The insecurity of serologists is illustrated by the recommendation to use more than one test in more than one centre. For example in a current field study we are using IFÁ and Elisa in Belo Horizonte and Buenos Aires. There is a need for an uptodate authortative document standardising antigens and techniques. In terms of offering patients in the chronic indeterminate phase practical help we are hampered by the absence of an indicator of progressive myocarditis which might suggest the use of specific therapy.

Culture techniques have not replaced the more convenient xenodiagnosis as the most sensitive method of detecting circulating trypanosomes in the chronic phase. While xenodiagnosis cannot be used routinely in a hospital service it has great value in confirming serology, isolating strains, and evaluation of specific therapy. For years I dreamed of a superbug but the nearest we have got in terms of an efficient xenodiagnostic agent is first instar *Dipetalogaster maximus.* In the one experiment we have done to date insusceptibility of individuals in the colony to infection with a Bahian strain of *T. cruzi* was low but these observations should be extended. As shown years ago at the London School of Hygiene and Tropical Medicine insusceptibility to *T. cruzi* is a genetic trait and a uniform highly susceptible colony is feasible. Once produced this should be distributed since techniques of xenodiagnosis vary widely and are difficult to interpret.

Treatment. Specific treatment of Chagas' disease has not been a great success in financial terms for the companies who have invested in it. Bayer (the company in the parasitic field with the most significant contributions) and Roche producing respectively Lampit and Rochagan have rendered great service. However both drugs are unsatisfactory from the clinical view point being relatively toxic and requiring long schedules of application. Merck had a promising drug a few years ago but shelved it. You can't get companies interested in a patient problem where the subject is so poor he can't even get to see a doctor.

Clinical evaluation of the two drugs mentioned has relied heavily on repeated xenodiagnosis over years in some studies. In the acute phase definate benefit seems to acctive and all are agreed that one of these drugs should be used. The difficulty arises in trying to show benefit in the chronic phase which is the common situation. We only have speculations about what is the significance of a positive xenodiagnosis either parasitologically, immunologically or clinically in relation of prognosis. To what degree the pathology of the acute phase determines the subsequent development of chagasic cardiomyopathy and megasyndromes is still not clear. What of those rare patients with

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positive xenodiagnosis and negative serology? And the interesting finding from Uberaba of nests of amastigotes in the wall of the suprarenal vein which carries glucocorticoids. In a 1,000 serologically positive autopsies how many have amastigotes in their suprarenal vein muscle? This finding could answer that vexed question about where are the amastigotes producing the trypomastigotes infecting bugs in a positive xenodiagnosis. For me at the moment the evidence does not support the routine use of antitrypanosomal drugs in the chronic phase of infection, but the question arises can you define a special group of such patients where specific therapy would be of benefit? These are relevant questions for Brazilian medicine since 5 million people are infected.

Prevention: I am not ashamed to say that I cried the first night I passed in São Felipe, Bahia, where *Panstrongylus megistus* ruled in 1966. Only in Africa had I seen such a human predicament. How was it that after such brilliant work by the Instituto Oswaldo Cruz that such a situation could exist? I still don't fully understand the answer to that question. As someone formed in a school where a major preoccupation was the elusive tsetse fly, house dwelling triatominae seemed an easier target. The situation was urgent since insecticide resistance has been reported in *Rhodnius prolixus* in Venezuela. In 1982 the SUCAM administration under Dr. Fiusa Lima managed to arrange an additional 35 million dollars from the national development project of the Banco do Brasil to supplement an equal amount spent by their operating yearly budget on Chagas' disease control. This far sighted measure will undoubtedly result in a great economy in health expenditure over time although due to the long incubation period between *T. cruzi* infection in man and the appearance of Chagas' disease the benefits are not yet evident. We have calculated and published the heavy financial drain placed on a national health service by patients with chronic Chagasic cardiomyopathy and megasyndromes. Such patients are the commonest cause of admission to our hospital beds. It is lamentable that currently the vigilance phase of the national control programme is short of funds apparently due to the funds being deviated to cope with other priorities such as malaria, dengue and yellow fever. The estimated cost of the programme is relative chicken feed – it might buy one sophisticated American war plane. In our hospital in Brasília an immediate effect of this programme was evident. We have not seen a case of acute Chagas' disease acquired by natural transmission on our service for several years and we used to see such cases frequently especially from the Barreiras area of Bahia.

The Brazilian Chagas' disease control programme is a justifiable source of pride for every Brazilian interested in Chagas' disease. To effect such a programme on a national scale required an organisation capable of getting to the most remote rural areas where transmission is worst and SUCAM has that capacity. Certainly without SUCAM Brazil could not have entered the vigilance phase and the absence of similar effective organisations in other Latin American countries makes control harder and more expensive. The Brazilian Ministry of Health has already been approached to try and help some such countries. The vigilance phase is costly and I would like to make a plea for more emphasis on community participation. Our research shows that with the right orientation and methodology the great majority of householders will inform a central reference point when triatomine bugs are seen again in the house after the attack phase. Sending SUCAM personnel round in transport at this stage is expensive although obviously supervision of community vigilance is essential. Unfortunately space does not permit a discussion of new insecticides (pyrethroids), methods of their application nor the many possibilities of house improvement. Also changes in the area under study such as road construction and agricultural projects undoubtedly affect Chagas' disease transmission in a variety of ways that are almost impossible to measure.

An important aspect of this vigilance phase in the capacity of secondary vectors to colonise houses and effect transmission. For example in our study area of Mambaí, Goiás, we have identified 4 of the 12 bug species captured in the area that invade the peridomicile after *Triatoma infestans* control in 1980. These are (in order of importance) *Triatoma sordida, Rhodnius neglectus, Triatoma pseudomaculata* and *P. megistus. T. sordida* has registered more invasion than the other species and may actually have effected transmission in a few cases. However compared to the previous situation when *T. infestans* was transmitting the risk is small. Why *T. infestans* is such a good vector is not well investigated. In fact the whole biology of behavior of triatominae under *field* conditions is poorly understood. At Caxambu, a significant venue for Chagas' disease research, it is well to ponder why this should be so especially as the answer to the problem is domiciliated bug control. In part the answer is that medical entomology is not attractive to young Brazilian graduates. Not because they lack competent teachers but because of poor career prospects. Coming from a school where this discipline was one of the strongest departments it is difficult for me to understand this situation.

Leishmania viannia braziliensis (Lvb)

Lainson changed the name again but Lvb is more acceptable than the repetitious *Leishmania bra-*

ziliensis braziliensis (Lbb) and comemorates the important contributions of the parense Gaspar Vianna. Some years ago I agreed to write an article on the control of leishmaniasis. It proved virtually impossible because, in contrast to Chagas' disease, it is global in distribution and we know so little about the epidemiology. This is particularly the case in human Lvb infections. The wild animal reservoir still eludes us, little is known of vector behavior and the parasite behaves in man in an unpredictable manner. As I tell my patients it is difficult to formulate a prognosis.

It was obvious from the begining of our work that we would never understand mucocutaneous leishmaniasis sitting in a hospital in Brasília and this led to Air Barreto, Cesar Cuba Cuba and myself working in Três Braços, Bahia, an area that Air knew was highly endemic. Initially our difficulties were very great but they cannot be detailed here. Suffice it to say that although we began work in 1974 our first paper did not appear until six years later. Eventually we found that >95% of our patients were infected with Lvb. Because of the long genesis of this infection in man our work is still in its preliminary phases. Severe clinical patient problems are transfered to Brasília where the hospital team led by Raimunda Nonata Sampaio takes care of them. We wish to acknowledge the unfailing support of the Department of International Medicine Cornell Medical Center in this endeavour. Especially their success in obtaining operating funds from the National Institutes of Health.

Diagnosis. The main problem is the difficulty isolating Lvb from skin ulcers and especially from mucosal lesions. Adlers introduction of the hamster into leishmaniasis research was key. However using direct smears, multiple NNN cultures and hamster innoculation we cannot better a 50% isolation from primary skin lesions. Mucosal isolation is more difficult due to contamination problems in culture and the difficulty of obtaining adequate biopsies in some cases. Histology shows amastigotes to be extremely scanty in the tissues yet immune responses are more marked than other types of leishmaniasis. We continue work on better isolation methods.

Because of the difficulty in finding the organism immunodiagnostic aids assume a special importance. Leishmanin skin tests are strongly positive within a month of lesion appearance and particularly so in mucosal involvement. We await a standardised antigen with interest since we are still making our own antigen in the laboratory. The indirect immunofluorescent test has been extremely valuable in our experience for Três Braços does not have Chagas' disease transmission. Elisa shows promise as a more sensitive test but such sensitivity is of doubtful value to the clinician and at the moment we run both tests in tandem.

Antigens are a key factor in such tests. For years we used as a source our Josefa strain of *Leishmania mexicana amazonensis* because Lvb grows so poorly but with more specific antigens better tests seem possible. Better antigens mean better antibodies. Grogl in Washington has already identified amastigotes in some of our mucosal biopsies using monoclonal antibodies where light microscopy found no parasites. Using such techniques perhaps specific Lvb circulating antibodies or antigens can be identified. Would a skin test antigen using an Lvb fraction be more sensitive? The questions are endless.

Of course having isolated a Leishmania you still have to characterise this isolate. I need not detail to this audience how this is done but acknowledge tremendous advances from the scientific community in terms of isoenzyme, monoclonal antibody and kinetoplastic DNA analysis. Unfortunately by the time such results reach the clinician the patient has gone. Therefore the scheme we have adopted is recommended. Since the nature of the organism determines clinical management find out what are the dominant causative organisms of leishmaniasis in the area of your practice and modify treatment schedules accordingly.

Treatment. Leishmania clinicans are one of the few groups of doctors left currently using that mainstay of 19th Century medicine heavy metal therapy. Others are colleagues treating third stage African sleeping sickness (arsenicals) and rheumatologists using gold. I have written elsewhere how this sad state of affairs has come about. The only concerted activity on drug development for leishmaniasis occurred when as a result of a few American soldiers getting leishmaniasis in Panamá the Walter Reed Army Institute of Medical Research began to examine some of the 300,000 compounds they have screened for antimalarial activity for anti-leishmanial effect. A number of compounds seem promising but alas not for Lvb. I am resigned to using antimonials for the rest of my active clinical life for the following reason. Certainly any new compound of promise coming to human trial should be tried in kala azar first because there are so many good parameters of cure to measure. Then in a form of limited skin leishmaniasis in the Old or New World. Only then would it get to Lvb in a hospital study and drug trials with this species are fraught with difficulties such as adequate control groups to compensate for self healing, evaluation criteria especially in mucosal disease and prolonged follow up. If such a hospital trial of a candidate drug were successful in Lvb it could be taken to the field. Clinicians dream of an oral cheap effective drug with few side effects but thats all they can do dream. No drug company is interested. Our situation in Brasília is that we have so many mucosal patients waiting for beds that we could not think of

mounting a hospital trial in cutaneous Lvb infection.

To return to the antimonials. It is correct that pentavelent antimonials have a bad name in part because of the elevated toxicity of trivalent compounds. I can vouch for this having treated many patients with tartar emetic and related compounds. Such compounds have different pharmokinetics being bound to erythrocytes. However it is wrong to say that pentavalent antimonials have negligible side effects. Side effects are common, dose related and we have detailed them in a series of publications. Particular care should be taken in the use of pentavalent antimonials in patients with impaired renal function. At the field clinic level treatment with Glucantime is very difficult. A parental drug given over a long period with cumulative toxicity has obvious problems. The very application implies a net work of applicators in remote rural communities and we have attempted to meet this need. Since this is currently the best practical measure for control it is further considered under prophylaxis. There is a pathetic lack of information in the literature on the pharmacokinetics of pentavalent antimonials and really we still don't know how it acts. The little advance in this field has led to modifying treatment schedules to give more drug than the traditional recommendation for a longer period of uninterrupted treatment. For example in mucosal disease which is unpredictable in its response we begin with an initial course of 20mg Sb^v/kilo body weight daily for 30 days and there is a recommendation that such a dose should be given twice daily. Nobody knows just what is the concentration of antimony reached in the nasal septum with such doses. Radioactive labelled antimony has never been available to us to find out. Until we fully understand how pentavalent antimony is handled in man how can we formulate rational treatment?

Prevention. Our work area in the Bahian littoral forest is subject to periodic epidemics of human Lvb infection that we do not understand. This is a major research interest at the moment. In a recent epidemic residual insecticide spraying of houses with DDT appeared to have little effect. Ecological studies of the vector *Lutzomyia whitmani* suggest infection occurs mainly in the peridomicile but spraying that is rather like controlling *Lutzomyia umbratilis* by spraying tree trunks. There are such a lot of trees in Amazonas! The sylvatic animal reservoirs of Lvb in Três Braços are largely unknown but to attempt to control them is a bit fanciful. Dogs and donkeys show relatively high infection rates and could initiate an epidemic. We are contemplating a programme of treatment for those infected animals that cannot be destroyed. No recommendation is possible for Lvb control at the present time apart from efficient field treatment clinics.

We have two such clinics in Três Braços and Corte de Pedra, Bahia. The latter is accessible by bus along the road BR-101 and receives many patients. We have reported the incidence up to 1987 but in 1988, 588 people were treated with Glucantime by UnB and SUCAM personnel. Training such personnel should be a Ministry of Health priority since this ministry is spending much money on furnishing Glucantime. The Rhodia Specia profit from this is not known to me. Attempts by the government to make their own Glucantime have not been successful but India and China make their own pentavalent antimonial. My suggestion to import someone from there to show us how was not acted on. There is no evidence that one pentavalent antimony is better than another in equivalent dosages. A well conducted clinic with adequate patient instruction works and we will be reactivating our field treatment posts which are supervised by these clinics. The difficulty of course is getting a resident doctor to handle not only this aspect but the host of medical problems that such a clinic attracts. Medicine in Brazil has a flavour of that in Tanzania where at one time 80% of the doctors in the country were in the capital Dar Es Salaam. The concept that doctors should serve the people is not common here and some form of government legislation to ensure a national health service inevitable.

Finally the vexed question of a possible vaccine. When I look at the history of vaccination in infectious disease I am not optimistic. Its not that I don't believe the immunologists can make it but its application will be the problem. After all Jenners' discovery was not effected for almost twp centuries and the present vaccine application programme in Brazil is far from perfect.

Closing remarks. I am working on a new course in Tropical Medicine for the Cornell Medical students entitled The Conquest of Infectious Disease. It opens with Pasteur and closes with aids. You have to be careful with history for undergraduate medical students. They have so much to learn. But it is a noble tale.

An interest in entomology teaches one many biological lessons. The naked ape has a different sort of intelligence to insects but he has not been a great success and like the carboniferous age dragonflies is doomed to extinction by some ecological catastrophe. Let us pray that the final phases of the conquest of human infectious disease are enacted in time.

Note: These remarks are dedicated to my wife Mariinha Reis who brought me back to Caxambu after a near fatal car accident.