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REVISÃO

PENTAVALENT ANTIMONIALS: OLD DRUGS FOR NEW DISEASES

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INTRODUCTION

Clinicians like myself feel a sense of pressure because things change so slowly for the patient in spite of the volume of current research. This is currently the case in the chemotherapy of leishmaniasis where the drug formulations used in the first line treatment have not changed for four decades. Neither is a practical alternative on the horizon. There is no money to be made in treating the poor people of rural areas suffering from this disease. The small efforts that have been extended in this direction have not met with success. Therefore we must try to use antimonials more efficiently for the benefit of the patient and this is the chief purpose of this review.

HISTORY

We are indebted to Dr. Edgard de Cerqueira Falcão[23] for a monograph summarising the contributions of Gaspar Vianna with a collection of his scientific papers. The original communication on the use of tartar emetic in cutaneous and mucosal leishmaniasis is reproduced[72]. Also, in a less well known paper, Vianna illustrates a very good result in a patient with severe mucosal disease[73]. He used a 1% solution of tartar emetic although the origin of the drug is not stated. Early preparations of tartar emetic were made by allowing antimony goblets to stand with white wine and extracting the supernatant. Confirmation of Vianna's favourable results followed in several Brazilian publications[6 22 69]. In 1915 the effectiveness of tartar emetic in the treatment of infantile kala-azar in Italy was reported[19]. The drug was then widely used during the epidemic of kala-azar on the tea estates in Assam[45].

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For those of us who have used tartar emetic it is obvious that its severe side effects made an alternative desirable. Bramachari in 1920 developed the first pentavalent antimonial: urea stibamine[55]. A more stable pentavalent antimonial by Schmidt in Germany in 1936 under the name Solustibosan (sodium antimonyl (V) gluconate[63]) had the advantage over the earlier Neostibosan in that it was stable in water and could be stored in solution until ready for use. Also it could be given intramuscularly, intravenously and subcutaneously since it was not irritant to tissues even in a hypertonic solution. It was first produced by Bayer and shown to be effective in kala-azar in India and China[36 46]. The Wellcome product Pentostam is sodium antimony gluconate. An alternative pentavalent antimonial, Glucantime (N-methyl-glucamine antimoniate) was developed at the end of the Second World War. Early studies of its efficacy in both cutaneous and visceral leishmaniasis appeared in French literature[21 57]. Its value in patients with mucosal lesions was reported from Brazil in 1952[15]. Today Glucantime is produced by Rhodia in Brazil and is widely used. Pentostam is not available here.

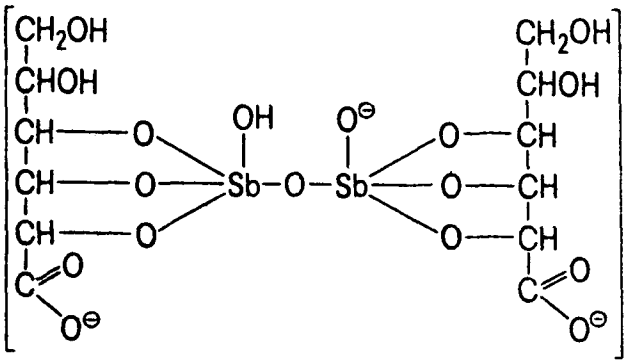
The mode of action of these drugs in leishmaniasis is unknown.

Glucantime and Pentostam

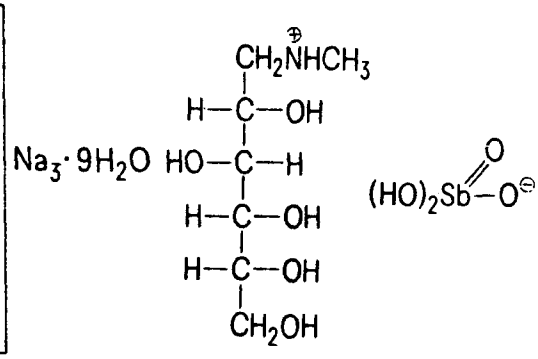
These are the only two pentavalent antimonials available commercially. Both are initially manufactured as white powders (approximately 34% antimony content) and are readily soluble in water. Both solution are best kept in the dark since they may undergo chemical change if exposed to the light.

Since they don't have defined chemical formulae they are difficult to standardise. Steck[67] gives the formulae for the two compounds illustrated in Figure 1. It has been suggested that toxicity is not necessarily related to antimony content[31]. Activity and toxicity may vary from batch to batch[3]. The author has personal experience of this with both drugs. It is worth citing a comment on the pentavalent antimonials[32].

FIGURE 1



Pentostam



Glucantime

"These drugs, under whatever name, are simply solutions of antimony pentoxide in a highly hydroxylated organic medium and making them is cookery, not chemistry. One can make such a drug to contain any amount of antimony, and to have any degree of toxicity; one has to choose a method of making it which provides a reasonable product, with reasonable activity and reasonably low toxicity. When one puts it into a patient about 80 or 90% of the antimony it contains is excreted by the kidneys in the first few hours, so one is relying on what is left in the animal, soaked into the tissue cells, which later reduce it to trivalent antimony (Goodwin & Page 1943). This is the killer, hopefully, of the parasite but unfortunately sometimes of the patient." A variation in anti-leishmanial activity in different ampoules of Glucantimme has been noted in an *in vitro* system[43]. A revaluation of this problem is long overdue since pentavalent antimonials remain the drugs of choice[1]. There appears to be little different in action between Pentostam and Glucantime[8] although a good comparative trial has yet to be done.

Glucantime is marketed in 5 ml ampoules containing 1.5 grams of the drug meglumine antimoniate and 425 mg pentavalent antimony (the equivalent of 85 Sb^{v} mg per ml). Pentostam is presented in 100 ml flasks each ml containing 100 mg Sb^{v}. The ampoule has an advantage over the flask for treatment in the field since ampoules are less liable to contamination by local people applying repeated injections for patients. These applicators usually can only give intramuscular injections. The volume using Pentostam is 15% less, reducing local pain a little when large doses are applied intramuscularly.

It is difficult to get accurate information on sales of these drugs from the respective companies but it can't be that good, since both companies have tried to terminate manufacture, possibly because of the difficulties of standardising these products. Only an outcry from the medical profession, who have no real alternative for treatment, prevented this measure. Certainly in our field area the price of one ampoule of Glucantime to the patient has been as high as two American dollars after various intermediaries have taken their cut. In June 1984 a bottle of Pentostam cost £63 over the counter in England (RA Neal: personal communication). This explains why patients forced to self treatment buy so little Glucantime; often less than ten ampoules. They simply cannot afford more. Our recommendation for a patient with mucosal disease weighing 60 kilograms in the initial treatment course is 120 ampoules of Glucantime as a total dose. Governments are aware of this problem of cost. India and China faced with epidemics of kala-azar made their own pentavalent antimonial. Brazil recently completed the last steps of Glucantime fabrication at a government level but the resulting product was not satisfactory. In Brazil and Venezuela the ministry of health provides Glucantime free to applying physicians. We benefit greatly from this arrangement in our field clinic in Três Braços, Bahia, but even for us, a field project with government support, often Glucantime is not available. The cost buying hundred of thousands of ampoules must raise difficulties when considering other health priorities. An attempt has been made to map in Brazil the importance of leishmaniasis based on notifications and requests for Glucantime but this certainly underestimates the size of the problem[25].

In 1984 SUCAM bought 392,329 ampoules of Glucantime. The Ministry of Health has calculated it will buy 600,000 ampoules in 1985 (JBF Vieira: personal communication). Rhodias' 1985 price to SUCAM per ampoules is 6,732 cruzeiros (about 1.2 American dollars). How much profit Rhodia makes per ampoule is not known. Wellcome have no interest in marketing Pentostam in Brazil. The author knows of two attempts by the Brazilian government to produce the drug neither of which has been successful. India is producing a satisfactory sodium stibogluconate (RA Neal: personal communication) and this might be a cheaper source of drug, if demand continues to increase.

Absorption, distribution and excretion

Some aspects have been reviewed by Beveridge[3]. Many antimony drugs like tartar emetic are too irritant to be given by mouth but Panayotatou[53] cured a case of infantile kala-azar by instillation per rectum of a trivalent salt. In our current situation perhaps her observations should be followed up and the value of the oral route for pentavalent antimonials reviewed in suitable animal experiments.

Parenteral pentavalent antimony achieves peak blood levels within an hour. Intramuscular injection results in a slightly lower, later peak than intravenous application but this makens little difference[12]. The drug is rapidly excreted in the urine[28 51]. After 6 hours blood leves have fallen to less than 1% of peak values and more than 80% has been excreted in the urine[59]. Thus patients are voiding the greater part of the drug they receive. This raises the interesting possibility of interfering with this rapid excretion and therefore using smaller doses to achieve the same effect. Because of the potential toxicity of antimonials this implies another series of animal studies. The hamster is not a good model for such studies since the kidney is composed almost entirely of long loop nephrons. The dog would be a more suitable model to mimic the human situation.

About 12% of the antimony dose is retained with a half-life of 32.8 ± 3.8 hours[12]. With repeated injections a rise in the base line level of retained antimony can be observed over the initial five days of treatment. Some of this antimony is thought to be reduced to the trivalent state[30] and trivalent antimony compounds may be less effective than pentavalent in killing Leishmania[35]. Much the retained antimony is concentrated in the liver and spleen[27 58]. These is no information on how much of this antimony is present in the skin or mucous membranes although it is probably a very small amount. Yet in skin or mucosal lesions it is this fraction that must be important. There is some rationale then for attempting local antimony treatment in skin ulcers[1 65]. Some success in animals has been noted with Pentostam cream[42] which is now being tried in man. Obviously such local treatment is insufficient for organisms causing systemic disease or those which produce metastatic lesions.

It is the antimony retained in the tissues which is thought to be responsible for toxic effects. Trivalent compounds bind more to tissues (*eg.* red cells) and their toxicity is marked in comparison to pentavalent compounds that are rapidly excreted in the urine. For this reason pentavalent antimonials are recommended today in higher uninterrupted doses than in the past.

Complications of antimony therapy

While the toxicity of pentavalent antimonials is much less than trivalent compounds it is not negligible. Most side effects appear at the end of courses of therapy suggesting they are the result of cumulative effects of tissue antimony. However there are exceptions. We have seen a single intravenous dose of 5 ml Pentostam given to a man with cutaneous leishmaniasis result in profound cardiovascular collapse with marked fall in blood pressure, sweating, and clouding of conciousness. A similar dose the next day gave the same result. There was no history of previous antimony therapy especially Pentostam. For this reason we now advise a 1 ml intravenous test dose before commencing a course of therapy. We have reported in the literature anuria following a total dose of only 33 grams of Glucantime drug (9.3 grams Sb^{V})[61]. Recently we have seen a woman with mucosal disease who developed such severe shoulder arthralgia after 8 days Pentostam therapy she could not raise her arms. This improved within a day of cessation of therapy. Further attempts to commence antimony therapy resulted in her developing this symptom after a single dose of antimony and treatment with this drug had to be abandoned[7].

An occasional complication occuring during the first week of treatment is oedema and erythema of granulomas, associated sometimes with haemorrhage, and we have illustrated and reported this finding in mucosal disease[60]. This is a particularly serious complication if the laryngeal aperture is a already reduced. For this reason we recommended that a

Table 1 – *Detailed side effects using 5 different treatment schedules in mucocutaneous leishmaniasis.*

Side effects	*A*	*B*	*C*	*D*	*E*
	30 cases	*20 cases*	*18 cases*	*21 cases*	*7 cases*
Arthralgia	17	18	2	10	
Myalgia	8	9		4	
Anorexia	7	6	8	5	4
Nausea	3		8	2	1
Vomiting	2	1	1	1	
Fullness	1				
Epigastric pain	1				
Waterbrash		1			
Abdominal pain		1			
Itching	1				1
Fever	2				
Weakness	2				1
Headache	3		2	2	4
Dizziness			1		
Palpitations	1			1	
Insomnia			2		
Nervousness		1			
Pyrogenic shock					4
Facial oedema		1			
Herpes zoster	1		2		

A) Glucantime 28mg/kg/day Sb^V for 10 to 12 days in series with intervals of 15 days.
B) Glucantime or Pentostam 20mg/kg/day of Sb^V during a mean of 30 days.
C) Glucantime and Nifurtimox (Lampit) in doses of 29mg/kg/day Sb^V for 15 days and 10mg/kg/day for 30 days respectively.
D) Pentostam 10mg/kg/day of Sb^V for 30 days.
E) Amphotericin B in a mean of 2.3 grams total dose.

tracheostomy set be by the bed of the patient during the first week of therapy with facilities to do an emergency tracheostomy. A similar syndrome occurs with amphotericin B therapy so it is not a drug effect. One possibility is that the death of the tissue Leishmania promotes this reaction in a manner similar to the Jarisch – Herxheimer reaction. Although corticosteroids have been recommended to control such reactions we have had no occasion to use these to date and they could have adverse effects[5 35]. Simply stopping the drug for a few days is sufficient as this phenomenon never recurs.

Sampaio[62] has recently analysed the occurrence of symptomatic side effects with four different antimonial schedules (Table 1) among patients admitted to our university hospital in Brasília. Common symptomatic side effects are arthralgia, myalgia, anorexia, nausea, vomiting and headache[1]. These side effects are commonest with high continous doses of antimony (Table 2). Herpes infection of the skin is a recognised complication of heavy metal therapy and occurred in our earlier series[62].

A granulocytosis has been noted[4] and we have seen low white blood cell counts develop while on pentavalent antimonial therapy.

In patients receiving antimonials the biochemical side effects mentioned in Table 2 were rises in the transaminases and alkaline phosphatase suggesting hepatocellular dysfunction[52]. Only in two patients taking antimonials was a rise in blood urea the biochemical abnormality. Glomerular lesions due to toxicity are very rare in our experience but a tubular defect is common with high dose antimony[70]. We have

studied tubular function after antimony therapy and it recovers rapidly in nearly all patients[71]. The tubular defect appears to be based on two mechanisms, interference with the action of antidiuretic hormone and a direct toxic effect on the tubular cells[26]. If lower doses of antimony are used this renal complication is uncommon[34].

Electrocardiographic abnormalities are also listed in Table 2 and appear to be more frequent with schedule A. In our early hospital studies we tried to give this dose schedule continuously but reported electrocardiographic changes in all three patients after 20 days continuous therapy[60]. 28 mg Sb^v/kg/day is approaching the toxic single dose of 30 mg Sb^v/kg/day[1]. The frequency of cardiac arrhythmias is related to the total daily dose of antimony[14]. The common ECG changes are T wave inversion and a prolonged QT interval but rarely severe even fatal arrhythmias have occurred[14 66]. It must be emphasised that all these side effects occur at high dosage in the patient with normal organ function; at lower doses electrocardiographic effects are not seen[44].

Many of these side effects occur together with maximal therapy. An illustration is our patient who resisted 30 days continuous Pentostam therapy (10 mg Sb^v/kg/day) and 2.5 grams amphotericin B but was eventually cured by 85 days therapy at a daily dose of 20 mg Sb^v/kilogram per day. On the 85th day he had arthritis with effusion of the left wrist and shoulder, a palpable liver and raised transaminase and alkaline phosphatase levels, diffuse alterations of repolarisation on the electrocardiogram and a renal tubule concentrating defect[41].

Table 2 – *Side effects of 5 different treatment schedules in mucosal leishmaniasis.*

	A	B	C	D	E
% Symptomatic	57	80	66	66	100
% Biochemical	23	26	37	26	40
% Abnormal ECGs	40	30	20	20	0

Treatment schedule A – 28 mg Sb^v/kg/day for 10-12 days repeated 3 times with an interval of 15 days.
Treatment schedule B – 20mg Sb^v/kg/day for a mean of 30 days.
Treatment schedule C – 28mg Sb^v/kg/day for 15 days plus oral Nifurtimox 10mg/kg/day for 30 days.
Treatment schedule D – 10mg Sb^v/kg/day for 30 days.
Treatment schedule E – Amphotericin B mean total dose 2.3 grams.

Toxic encephalitis associated with heavy metal therapy we have not seen nor can I trace a reference in the literature associated with pentavalent antimonials. One elderly lady in the field area who was given a daily dose in error exceeding 30 mg Sb^v/kg/day of Glucantime developed peripheral neuritis and exfoliative dermatitis. Fortunately both improved after cessation of therapy. Perhaps it is worth mentioning that we have never permanently prejudiced or lost a patient as a result of pentavalent antimony therapy in spite of using relatively high doses in over 1,000 patients.

Really the situation with regard to the use of antimonials, specially in the field, has not changed from the observation of Pessoa and Barretto[54] quoted below with relation to tartar emetic.

"Clinical experience in both visceral and cutaneous American leishmaniasis shows that the most satisfactory results are obtained using large doses in the shortest periods of time even if certain symptoms of intolerance are produced. We wish to call the attention of clinicians in general to this point for our experience shows that, many clinicians in the interior of the state, where the disease is prevalent, use, for fear of producing accidents due to intolerance to tartar emetic, excessively small doses of the product resulting in low treatment efficiency and a prolonged treatment time"[54].

Drug delivery in man of pentavalent antimonials

All drug doses are now expressed in milligrams of pentavalent antimony per kilogram per day so that schemes are standardised irrespective of the preparation[1].

As might be expected this is a most controversial area. Not only clinicians vary widely in their opinions as to the dose of pentavalent antimonials that should be used but even the two principal drug companies have different recommendations. For Pentostam the Wellcome Laboratories Ltd, Beckenham, England, recommend that adults (60 kg) be given intravenous or intramuscular injections of 10 mg Sb^v/kg/day for 7-10 days and that 2-3 cycles be separated with ten day rest intervals if additional treatment is necessary. For Glucantime Rhodia SA,

São Paulo, Brazil,recommend adults be given intramuscular injections of 17-28 mg Sb^v/kg/day for 10-20 days followed by a 15 day rest interval and a second cycle if needed. Both recommendations are now obsolete since the work done in Kenya showed that such rest periods are pharmacologically unsound since both drugs are rapidly excreted in the urine. This work which I have reviewed elsewhere[39], since it shortens treatment time, is the only practical advance for the patient in the treatment of leishmaniasis to appear in the last decade.

Yet one can sympathise with the drug companies since these recommendations are an enormous problem as evidence grows of differing susceptibilities to antimonials of various leishmanial species and the clinical syndromes caused by these parasites. Unfortunately comparative studies of different taxonomically defined leshmanial infections in man where similar doses have been used do not exist in the literature although a study is being prepared from Panama[13]. Many workers can't mount such studies. For example, in our work in Central Brazil *Leishmania braziliensis braziliensis* (Lbb) infection is so common we have very few other species indentifications in patients with mucocutaneous disease. Recently I have tried to design a simple table as a guide for antimonial use for Conn's *Current Therapy,* a didactic treatment text, and this is shown in Table 3. It represents an oversimplification and the fact is that the clinician has to exercise considerable skill in the use of antimonials taking into account the nature of the lesion, the probable infecting organism (this information is not available at the time of the treatment decision), the age and weight of the patient as well as any evidence of organ disfunction.

The smallest adult dose of Glucantime recommended in Brazil is one ampoule of Glucantime two times a week[49]. While this seems homeopathic to some and cannot be recommended it is possibly the only dose available, for reasons of cost, for a child with advanced kala-azar, anaemic and malnourished who has to be treated at home in one of the *favelas* in the cities of Brazil where kala-azar is currently endemic. The fact that Brazilian kala-azar responds to such a dose shows it has a high sensitivity although the relapse rate must be high. The highest daily dose advocated in Brasil is six ampoules of Glucantime a day[18]. This is well over the toxic limit mentioned by the World Health Organization[1] for a single dose and it is curious that few toxic effects were observed. It cannot be recommended. A Brazilian Ministry of

Table 3 – *Guide to the treatment response of different leishmanial species causing clinical syndromes with pentavalent antimonials.*

Treatment response	*Easy to treat Group A*	*More difficult Group B*	*Most difficult Group C*
Clinical form			
Cutaneous	Limited cutaneous lesions	*L. b. panamensis*	Diffuse cutaneous leishmaniasis
	L. tropica	*L. b. guyanensis*	*L. aethiopica*
	L. major	*L. b. braziliensis*	*L. m. pifanoi*
	L. m. mexicana	Post Kala-azar	*L. m. amazonensis*
	L. m. amazonensis	Dermal leishmaniasis	Leishmaniasis recidivans
		(*L. donovani*)	Skin granuloma due to *L. aethiopica*
	L. peruana		
Visceral or mucosal forms		Visceral leishmaniasis (*L. donovani*)	Mucosal leishmaniasis *L. b. braziliensis* *L. b. panamensis* *L. b.?*

Key. L = Leishmania L. m. = *Leishmania mexicana* group L. b. = *Leishmania braziliensis* group.
Note. Oversimplified, this guide does not take into account the exceptions to the rule. Relapse can occur in individual patients in all categories.
Treatment Group A – 10mg Sb^v/kg/day for 10-15 days.
" Group B – 10mg Sb^v/kg/day for 30 days or 20 mg Sb^v/kg/day for 15 days.
" Group C – 20mg Sb^v/kg/day for 30 days or more 20mg Sb^v/kg/twice daily for 15 days or more.

Health recommendation is one ampoule of Glucantime daily for 7-10 days; the course being repeated if necessary. In our recent experience it appears that this will close many skin ulcers due to Lbb; but will it prevent mucosal disease? Since in the past year we have had little Glucantime, we have many patients with Lbb who had to be treated with such a schedule (7 mg Sb^v/kg/day). They are under longitudinal observation. We have used four times this dose in the endemic area of Três Braços for years (28 mg/kg/day) and in our recently published studies mucosal relapse was almost unknown on short term follow-up[37]. The practical difficulties of giving such high doses under field conditions are considerable (20 cm^3 daily intramuscular dose) but they cannot be discussed here. Prata has never seen a kala-azar patient relapse in Brazil using similar doses in over 100 patients (AR Prata: personal communication) but they do rarely occur[20 68].

On the whole in terms, of frequency of treatment problems in hospitals in Brazil, it is mucosal leishmaniasis which causes most concern. Table 4 shows our results with the four antimony schedules previously mentioned in relation to mucosal disease in our hospital in Brasília[63]. Our analysis of the results of treatment with cutaneous lesions failed to show a difference between the four schedules but there is a difference between these in mucosal patients. Such data is extremely difficult to collect due to follow-up problems and as yet it does not lend itself to statistical analysis. However it suggests that 20 mg/Sb^v/ kilogram body weight for a mean of 30 days is the best recommendation. Bryceson in London has recently started to use this dose twice a day to further reduce hospital stay (ADM Bryceson: personal communication). Evidently we still have to define optimal schedules for antimony use.

Both Pentostam and Glucantime are best given by slow intravenous infusion over at least three minutes. No diluent is usually necessary unless the patient develops a venous thrombosis at an inoculation site. Intramuscular injection is painful but often necessary under field conditions where no doctor can be present for daily injection. One lot of Glucantime used in Três Braços produced several muscle abscesses. Pharmacokinetic studies show little difference in peak serum levels after application by these two routes[12]. An interesting study carried out at the Walter Reed Army Medical Center compared three methods of drug delivery in American soldiers with leishmaniasis. While all subjects were given the same total dose of 600 mg Sb^v/day this was administered either as a continous 24 hours infusion, in three divided eight hourly doses or as a single intravenous dose[50]. The latter method was shown to be more effective in terms of cure and incidence of subjective complaints.

In patients with evidence of renal, cardiac or hepatic disease an alternative may have to be sought depending on the clinical assessment of the patient. Patients with renal insufficiency become lethargic, anorexic, drowsy and weak after antimonial therapy[59]. Alternatives are the recommended second line drugs[1] namely Pentamidine which has few renal side effects or amphotericin B which is free of hepatic toxicity and cardiac effects are only related to potassiun inbalance.

Finally even high dose pentavalent antimonial will not cure all patients. We have reported a girl who

Table 4 – *Cure rate of five treatment schedules in mucosal leishmaniasis.*

Nº failed/ total number	*A* *11/26*	*B* *1/12*	*C* *3/7*	*D* *7/18*	*E* *2/8*
% Cure	58%	92%	57%	61%	75%
Mean follow up period (months)	18	8	19	12	12

Treatment schedule A – 28mg Sb^v/kg/day for 10-12 days repeated 3 times with an interval of 15 days.
" " B – 20mg Sb^v/kg/day for a mean of 30 days.
" " C – 28mg Sb^v/kg/day for 15 days plus oral Nifurtimox 10mg/kg/day for 30 days.
" " D – 10mg Sb^v/kg/day for 30 days.
" " E – Amphotericin B mean total dose 2.3 grams.

developed mucosal granulomas during antimonial treatment for her skin lesion due to Lbb[40].

Unresponsiveness

In brief recent work regarding disease response to total antimony dose suggests that high continuous antimony therapy is the best approach in recalcitrant disease for a favourable response. Syndromes such as are mentioned in group C of Table 3 require this approach. This is not to say that high dose antimony will always meet with success particularly in patients with mucosal disease[24 40]. Anergic Hansenoid leishmaniasis will fail to respond since the patient can't mount an immune response. The importance of unresponsiveness is difficult to assess since high enough doses have not been widely employed to date.

The term unresponsive is useful since resistance is often taken to imply parasite resistance which is not necessarily the case. Patients with fatal antimony unresponsive kala-azar had parasites which showed a normal response to antimonials in animal models indicating a host defect[20 32]. On the other hand at least in Kenyan kala-azar there is evidence in cell cultures[2] and in animal models of parasite resistance to antimony[33]. Unfortunately similar experiments have not be possible with Lbb since it cannot be induced to grow in *in vivo* cell lines. However Moreira[43] has examined one of our most suspect Lbb isolates in terms of resistance and it shows diminished sensitivity in her promastigote culture system.

The World Health Organization[1] suggests we consider primary unresponsiveness as no clinical or parasitological improvement on initial therapy and secondary unresponsiveness where relapse occurs after one or more courses of apparently successful treatment. To illustrate how difficult it is to discuss this subjet with the recent changes in dosage schedules India which recorded a 13% relapse rate in kala-azar is said to have reduced it to zero by doubling the antimony dose[1]. Certainly a risk of minimal dose therapy is the emergence of parasite resistance to antimonial treatment.

Concluding remarks

The last two decades have seen great advances in our understanding of the taxonomy of Leishmania using biochemical[29] and immunological[56] methods. Today this is seen as an essential first step to unravelling the complexities of the epidemiology and clinical picture of human disease. At the University of Brasília we were the first to use the monoclonal technology developed at Harvard in such field studies[17]. We are dealing in Três Braços, Bahia, with what appears to be virtually a monotransmission to man of Lbb. We are still defining the clinical picture based on this taxonomy. Similar data on other important parasites in Brazil such as *Leishmania braziliensis guyanensis* will doubtless be available soon. New clinical entities are being defined; for example we are preparing a report on disseminated cutaneous leishmanisis caused by Lbb[16].

In contrast to this exciting field in epidemiology, prospects for advances in the chemotherapy of leismaniasis are gloomy. I never imagined when I qualified in medicine 25 years ago that I would review antimonial therapy in 1985. Heavy metal therapy was the mainstay of 19th century medicine. The experts in this field today are physicians treating leishmaniasis. There has been no advance in drug formulations for primary therapy that has benefited the patient for forty years. Parental pentavalent antimonials are still the drugs of choice for most of the forms of leishmaniasis.

I will not discuss why this is so, although I have definite views after confronting hundreds of patients with Lbb infections and often not having even antimony to offer them. Let us adopt a more positive approach. The fact is that there is only one pharmaceutical company and one research institute seriously involved in developing new drugs; namely the Wellcome Research Laboratories in America and England and the Walter Reed Army Institute of Medical Research in Washington. Two drugs, an 8 aminoquinoline (WR 6026)[10] from the latter and Allopurinol riboside from the former[47] have entered clinical trials. Preliminary information suggests that neither may be suitable for our problems with Lbb, but even if this is not so, I may well be an old man before I see such oral preparations used in our field clinic. This is because clinical evaluation is a lengthy process and involves testing initially in kala-azar and limited skin leishmaniasis before it can be used for an organism causing metastatic disease. Also we ourselves routinely do a trial in hospital in Brasília before a drug can be taken to the field. The evaluation of each of these trials will take several years.

Another possibility is the use of liposome linked antimony which has given promising result in animals[11]. There is some evidence that this is more effective in cutaneous lesions than the free drug[9]. The

one patient with Kenyan kala-azar unresponsive to free antimony treated with liposomes failed to respond[35]. Both the research groups mentioned are involved in this development. Although if it ever came to human trial this approach would still imply injection therapy it would abolish the need for these painful, prolonged, injection schedules. I have no doubt that the single most important advance in the control of leishmaniasis is the development of more efficient drug therapy[38] in terms of an oral inexpensive treatment of short duration. Such a drug would be equally useful both in kala-azar and in the mucocutaneous infections of rural areas. With ministry support we are currently testing ketoconazole but this hardly falls into this category.

The last word is perhaps better said by the father of one of our patients in the endemic area of Três Braços where they are as familiar with Glucantime as we are with aspirin[48]. He asked me why if we had been working there for ten years we were still using this drug and had not found a more convenient therapy. I explained that we were dependent in the field, at the end of the line as it were, on the research of other colleagues and nothing had appeared to date. "But will it", he insisted "so that I don't have to walk 5 kilometres with my daughter to get her injection?"

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