Discussion

Discussion

SADUN: Is there anyone who has been working with *S. haematobium* and *S. mansoni* and would like to give his opinion of the effectiveness of this drug, that is to say, its real value as an effective agent in the treatment of schistosomal infections, and indicate how the results obtained compare with those achieved with other drugs? I for one feel that almost any discussion we have on one drug must involve comparisons with other drugs.

LARIVIÈRE : A mon avis, comparé aux autres produits que nous avons essayés, il ne fait aucun doute que le CIBA 32644-Ba est le plus actif et le mieux toléré des traitements que nous connaissons jusqu'à présent.

DODIN : Il n'y a qu'un problème évidemment : c'est toujours la question de multiplier les cas, et quand nous aurons des observations portant sur des milliers de cas, nous aurons peut-être effectivement des variantes quant au pourcentage de l'efficacité. Mais en dehors de cela, pour le moment, il nous apparaît que ce médicament constitue, même pour moi, le meilleur que je n'aie jamais vu dans le traitement de la bilharziose, aussi bien dans *S. haematobium* que dans *S. mansoni.* Mais, bien entendu, c'est la pratique qui va nous amener à modifier peut-être notre opinion.

DA SILVA: Taking into consideration the fact that doses of 25 mg/kg/day were effective in *S. haematobium* infections, and that *S. haematobium* is more sensitive to the older drugs than the other species, we decided to start with higher doses. Although the number of our cases, 48 in all, was not large, I have never seen results like these in the treatment of *S. mansoni* infections with other drugs.

FAIGLE: Professor DA SILVA, you said that *S. haematobium* is more sensitive to treatment than *S. mansoni.* This may be true of the antimonial drugs, but it is probably not true of the CIBA drug, because the *mansoni* type lives in the mesenteric veins in which portal blood circulates, whereas the *haematobium* type lives mainly in those vessels in which peripheral blood circulates. As I pointed out in my paper, the concentration of the biologically-active drug is much higher in portal than in peripheral blood and therefore the therapeutic effect on *S. mansoni* may be as good as, or even better than, the effect on *S. haematobium.*

DA SILVA: I hope that this will be confirmed by further observations, but I should like to remind you that the same thing would happen with Miracil compounds. *S. haematobium* is more sensitive to Miracil than *S. mansoni.* I do not remember all the facts about the metabolism of Miracil compounds and about the concentrations of the drug in the portal system; nevertheless I know that studies on these lines were carried out by Dr. GÖNNERT.

STRIEBEL: I think we should mention that the metabolites of Miracil are also active whereas we believe that the metabolites of CIBA 32644-Ba are inactive, which makes quite a difference.

BLAIR: I find it a little restrictive to discuss parasitic infections, because it is not parasitic infections we are going to treat with this drug, but people; and people do not have a simple parasitic infection. The difficulty is that people in Brazil are only interested in *S. mansoni* and the people in some areas of Africa are only interested in *S. haematobium*. Nevertheless, many doctors in other areas of Africa are interested in both parasites in the same person. The problem of double infections is increasing. I hope you understand what I mean: these patients also have amoebiasis.

If I may offer an opinion, I should say that, as regards *S. haematobium,* I think the results with CIBA 32644-Ba are far superior to those obtained with any other drug, bearing in mind the impracticability of using antimony on a large scale. We all know the danger of antimony, although we hear very little about the deaths that occur. No country is prepared to broadcast how many people have been killed as a result of antimony treatment. In one small town in my own country, two people died in one week. But, of course, nobody publishes these things widely. Therefore the safety factor is a very important point.

If I may be allowed to return to the question of "effectiveness", I think the difficulty is to know just what is needed: in Africa it may be a course of treatment that is perhaps 100% effective against *S. haematobium* (because I feel that we are very nearly reaching this figure) and 70% effective against *S. mansoni* in the same patients. What are we to do? Should we try to give everybody a dose which will cope with both, or should we try to treat only one infection? It raises all sorts of problems.

SADUN: Is there any further comment that anyone would like to make on the basis of his experience as to the effectiveness of this drug in relation to *haematobium* or *mansoni,* or to combined infections?

DA SILVA: We may say that Professor PRATA's results were not so successful as mine. I wonder whether this is because the problem of reinfestation arose in Professor PRATA's cases? As you know, Bahia is the home of schistosomiasis in Brazil and I don't know whether the patients were exposed to new infections during the 8 weeks before treatment. What I do know is that the results of schistosomiasis treatment in Rio were always better than the results in Bahia; perhaps there are other reasons, but this is certainly one.

PRATA: It is quite possible that in endemic areas reinfections may play a part. For the present, I should simply like to give briefly my opinion of this new CIBA compound. It is effective against *S. mansoni* infection. Probably it is at least as good as antimony, but it is too early to draw any comparison between the two groups of substances as regards effectiveness. We must follow up the patients for longer periods to make sure of this.

SADUN: I think this is quite clear and I appreciate very much your relating CIBA 32644-Ba to other drugs because, again, I feel that if we had a yardstick it would be so much easier for us to visualise what we mean. "Good" and "poor" are very relative terms and it becomes very difficult to define them unless we relate them to something already known.

I should like to emphasise what Professor DA SILVA just said, especially in the light of the results we have obtained in experiments in monkeys and mice which indicate that the drug is totally ineffective against migratory schistosomules. It seems quite possible that in endemic areas, where exposure is constantly taking place, all of the worms in the mesenteric vessels may be eliminated but the schistosomules survive. These will then reach maturity some weeks later and produce eggs. It might therefore be worth while con-

sidering the possibility of a 2-stage treatment, first taking care of the adults in the mesenteric vessels and then, a few weeks later, of the schistosomules, which might by that time have become adults.

The other point that I think Dr. JORDAN stressed very strongly yesterday, is the factor of intensity of infection. In endemic areas one is probably dealing with a much heavier infection and this may to a certain extent influence the effectiveness of the drug.

FRANCO: Yesterday I spoke about a selected group of patients with *haematobium* and *mansoni* infections, treated under conditions that excluded the possibility of pre-infection or reinfection. This group consisted of 14 patients with *haematobium* and 8 with *mansoni,* or to be more exact, 8 with *haematobium* only, 6 with *haematobium* and *mansoni,* and 2 with *mansoni* only. After 4 months all the patients appeared to be cured. In the same areas, I also had 2 groups of 25 patients with *S. haematobium* infections only, who were treated with other drugs. I obtained a cure rate of 60% after 4 months' treatment with a thioxanthone derivative, and with the other antimony drug 80% of the cases were cured. If you would like me to quote comparative figures for the different treatments carried out under the same conditions in patients living in the same geographical conditions, the cure rates after 4 months were 80% in 25 patients treated with the antimonial drug, 60% in those treated with the thioxanthone derivative, and almost 100% in those treated with CIBA 32644-Ba.

JORDAN: With regard to *S. mansoni,* the results I obtained were comparable to the results obtained in antimonial treatment with TWSb compound, using identical methods. The results are very similar, but I think they could be improved if we could lengthen the course of treatment.

As to the question of reinfection and the problems involved in treating patients in endemic areas, it is difficult to differentiate between a relapse and reinfection, but I think Dr. BLAIR has made a point in saying that he is surprised by the small number of apparent reinfections. Previously there was no doubt whether a patient had been reinfected or not. I think we now have a drug that produces a definite optimal cure and we know that reinfections do not occur immediately. I think this question of reinfections occurring soon after treatment is grossly overrated. The results that I have obtained so far (and we are following up the patients for 2 or 3 years after treatment), suggest that when a definite cure is achieved, reinfection does not appear very rapidly.

We have heard a lot about immunity in bilharziasis. Now, if immunity exists in bilharzia, is it going to be destroyed immediately after treatment? I rather doubt it. And I think Dr. BLAIR's observation that apparent reinfections do not occur proves that this drug is very much better than the others.

SADUN: This raises another point which may perhaps warrant some comment; namely, if this drug acts selectively on the females, and only on the females, we may have a system whereby a few worms may remain in the host, enough to maintain the immunity of the individual, or at least to delay the loss of immunity. This might be preferable to a treatment which will completely eliminate both males and females and produce an increase in susceptibility in weeks or months to come. Of course this is highly speculative, but it is something that we may consider later on when making recommendations, since the answer can readily be found in experimental animals, bearing in mind, of course, that to extrapolate immunity from experimental animals to humans is somewhat dangerous. However, nothing else can be done until we obtain human volunteers.

COUTINHO: With regard to *S. mansoni,* I should like to emphasise two points: firstly, in my experience, the follow-up periods are not long enough to allow

us to assess the parasitological cure in *S. mansoni* infections. I have obtained very good clinical results, but in my experience, and also evidently in that of others, a period of 4-5 months is not sufficient to show whether relapses occur in some cases.

The second point concerns a very interesting feature of this drug as compared with antimonial therapy, namely that it could be employed in the treatment of most advanced cases. As I mentioned yesterday, we used it in hepatosplenic cases and even in a cardiopulmonary case, in which antimonial therapy is contra-indicated. This is a point which I should like to stress.

JORDAN: Professor DA SILVA, you obtained 38 cures in 38 cases. Could you say something about the technique of stool examinations used in these cases, please?

DA SILVA: Yes. Well, I have to admit that I could not apply the Bell technique after the meeting in Geneva, because my associates found it quite time-consuming. We are now trying a new technique developed by Dr. F. S. Barbosa, which gives both qualitative and quantitative results, but we have reached no conclusions as to its value so far.

In my cases we used the Hoffmann sedimentation technique (for at least two hours) and in some cases we used the Stoll counting technique. As a matter of fact, we rely much more on rectal biopsy and take at least three samples of the mucosa, which are carefully examined by my co-workers.

JORDAN: Am I right in believing that you said some of the cases you treated showed a positive biopsy but a negative stool before treatment?

DA SILVA: Yes. This happened in seven cases in which repeated stool examinations were negative. We usually perform three stool examinations. But in some of the cases in which stool examination gave negative results, rectal biopsy showed a large number of viable eggs. In one of these cases we found about 45 eggs, though the stool examination was negative in three samples. In Brazil, as you know, Dr. CHEEVER is trying to make comparisons between the number of eggs in the stools and also in the rectal scrapings, and the number of worms revealed by the perfusion technique at autopsy. He has not found any relationship, but I think this a new field which should be explored.

DODIN : Une question sur le problème des œufs morts dans les bilharzioses urinaires surtout et au sujet de l'élimination d'œufs morts qu'on trouve le 3e ou 4e mois même après le traitement : est-ce qu'il s'agit d'une femelle qui pond anormalement, ou est-ce qu'il s'agit d'un reste d'une élimination ancienne d'œufs de schistosomes, d'un reste de granulome tissulaire ?

DA SILVA: I have some observations on European schistosomiasis cases who were under control for three years. Before treatment they showed mature and other living eggs, with miracidia as well as black eggs. I had the opportunity to follow two of these patients and to perform several rectal biopsies. I never found viable eggs in these cases again, but only shrunken eggs which persisted for two years. The patients were quite well and I think they could be considered parasitologically cured.

LAMBERT : A ce sujet, nous avons de nouveaux essais en cours actuellement ; il est déjà possible de dire que chez des souris traitées au CIBA 32644-Ba, guéries à la recherche des parasites à l'autopsie, nous avons encore trouvé 10 semaines après la fin du traitement des nids d'œufs non viables dans la muqueuse intestinale de l'intestin grêle et du colon, des œufs dans la lumière intestinale. Dans le foie de ces animaux, on trouve également des œufs altérés et des fragments de parasites ♂ en pleine autolyse. Cet essai se poursuit pour

déterminer la durée de persistance des œufs dans la paroi intestinale, chez des animaux traités 8 semaines après l'infestation, et dont les parasites n'ont donc pratiquement pondu que pendant 2 semaines.

Si nous extrapolons en clinique humaine les faits observés, la probabilité apparaît très grande pour une élimination ovulaire de longue durée, même si le malade est parasitologiquement guéri ; sa parasitose en effet, au moment du traitement, dure généralement depuis des mois ou des années et l'accumulation tissulaire des œufs pondus est infiniment plus grande.

GRÉTILLAT : C'est ce que j'avais remarqué aussi sur les petits ruminants où les œufs vivants disparaissent pour la plupart dans les 15 jours à 3 semaines après le traitement, mais il y a des « black eggs » qui persistent et on les retrouve disposés en amas plus ou moins importants.

DODIN : Au sujet de l'activité, je voudrais encore signaler 2 cas particuliers. Un cas présentait un bilharziome de la vessie, sans dilatation des uretères. Il a été traité 7 jours avec 25 mg/kg et 1 mois plus tard, le bilharziome avait complètement disparu. La vessie était parfaitement normale et ne présentait plus aucune lésion évolutive. Depuis il n'y a plus eu d'élimination d'œufs.

Une autre malade, c'était une jeune fille de 16 ans, opérée à Tamatave par le Docteur Fouré. Elle avait une occlusion intestinale aiguë. Le Docteur Fouré est intervenu et a trouvé une énorme tumeur interprétée comme une tumeur maligne. Il nous adressa une biopsie pour étude anatomo-pathologique. La tumeur était inextirpable, ayant envahi le colon et métastasé le foie. Pensant à une tumeur maligne, le chirurgien signalait cependant la présence d'œufs de *Schistosoma mansoni* dans les selles. Cette jeune fille a été mise en traitement au CIBA 32644-Ba. Elle reçut 25 mg/kg de poids pendant 7 jours. Un mois plus tard, la tumeur avait fondu. Au point de vue anatomique, on a trouvé des cellules géantes entourées de cellules épithélioïdes, de macrophages et d'éosinophiles. Un mois après le traitement, le chirurgien est ré-intervenu. La tumeur avait disparu. Le transit était rétabli. Il y avait encore quelques granulations péritonéales. Ces granulations étaient de type bilharzien, avec des œufs phagocytés par des cellules géantes. Il n'y avait plus aucune inflammation péritonéale. On a noté une importante éosinophilie dans ces granulations qui n'avaient plus qu'un volume absolument mineur. C'est surtout le mode de disparition du bilharziome qui reste difficile à expliquer.

SADUN: Now what about *S. japonicum*? That was the great surprise of this meeting and I wonder whether our colleagues from Japan or the Philippines would like to say anything on this subject?

YOGORE: In the first place, I should like to say that, judging by my experience with the patients I treated, we can exclude any possibility of reinfection, since all these patients were in Manila, which is not an endemic area. Secondly, the patients were treated after staying in Manila for at least 2 months, therefore there is no possibility that migration forms were still present which would later mature in the body.

I do not think the results I have at the moment warrant any statement on effectiveness and I should like to follow up these cases for at least six months. I have seen relapses with antimonials occurring about six months after treatment. I feel that I should wait at least this long before deciding whether or not I have achieved a parasitological cure in the cases I have treated.

BANZON: At our research laboratories, we also deal with cases from endemic areas transferred to a non-endemic area, that is to say Manila. So the problem of reinfection definitely does not affect the patients I described yesterday. Since we do not yet have any very effective treatment for *Schisto-*

soma japonicum infections, we are resorting to a sort of a quantitative determination of the effectiveness of drugs by performing egg counts in these patients. As I mentioned yesterday, egg counts in the 46 control patients we had under observation showed that there was a more or less marked reduction in the number of eggs following treatment with CIBA 32644-Ba. Of course, the number of patients we treated was very small and we shall probably be much better able to assess the efficacy when we have studied more cases. Apart from the toxicity, we are more or less happy about the results, as far as the reduction in the number of eggs is concerned.

SADUN: What you are saying implies a big limitation. In view of the small number of patients and the short duration of the follow-up, if one can disregard toxicity compared with other drugs, the results on effectiveness seem to be promising as regards efficacy.

YOGORE: There are encouraging signs. That is as much as I should like to say at present.

YOKOGAWA: I agree with Dr. YOGORE's opinion. In Japan we have used the sodium antimonial tablets and sometimes we have observed relapses six months after treatment. It is true to say that we need more time to study the cases.

JORDAN: Regarding the first paper by Dr. BANZON, I was very interested to hear that he had used the filtration staining technique. The average egg output is given as 48.3 eggs per ml. Could Dr. BANZON tell me what this represents in terms of eggs per 24 hours?

BANZON: It was a 24-hour stool collection.

JORDAN: Was this made up to a volume of 2000 ml or of 1000 ml?

BANZON: It was a 1000 ml suspension.