Discussion

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LARIVIÈRE : Je voudrais souligner l'action du CIBA 32644-Ba non seulement sur les vers adultes, mais également sur les formes très jeunes. J'ai été frappé par cette action, aussi bien dans les essais sur les souris infestées par *S. japonicum* que dans ceux sur les singes infestés par *S. mansoni* ; peut-on espérer que nous sommes peut-être, avec ce produit, sur la première voie d'une chimioprophylaxie préventive ? Je dis bien sur la voie et il me paraît intéressant de poursuivre les études orientées vers la possibilité d'une chimioprophylaxie. Je ne sais si c'est l'opinion du Docteur SADUN, mais je crois en tout cas que les communications des Docteurs YOKOGAWA et SADUN ont soulevé l'éventualité de ce problème.

SADUN: Thank you very much. I certainly agree with you whole-heartedly, I did not feel it was up to me to emphasise this at the moment, for fear that I was perhaps trying to draw too many parallels between experimental animal studies and field conditions. I do believe, however, that the totally unexpected findings on the prophylactic action of this drug need further investigation and if they are confirmed, we may have some most interesting possibilities, especially affecting individuals under special conditions, such as troops stationed in endemic areas for a short time, or tourists or engineers visiting such areas.

LARIVIÈRE : Il y a peut-être une dose minimale qui à ce moment-là justement pourrait être extrêmement intéressante au point de vue de la chimioprophylaxie.

SADUN: And again the fact that we tested the prophylactic action of the substance by giving it on 4 consecutive days and found that it worked almost perfectly. It might even be effective when given over a much shorter period.

LAMBERT: Can you give any explanation for the activity on very young schistosomules and adult worms and for the lack of activity on intermediate stages? Dr. LARIVIÈRE has asked for a biological explanation if possible.

SADUN: Of course, as you know, I cannot give any definitive answer, but I could speculate on this point. First of all, this is not a unique phenomenon. It has been found with other drugs, such as TWSb and S-688. These drugs are all active at the moment of penetration and also after the onset of egg-laying. It seems to me that this may be due to a combination of the parasites during the first 2 weeks, at which time the schistosomules are migrating through the lungs to the liver. At this time and in these locations they may be much better protected from the activity of drug. Another point might very well be the physiological changes that the parasites undergo at this time. It has already been shown that marked physiological and immunological changes take place between the cercaria and the schistosomule stages. A third factor may be related to the development of the reproductive apparatus, since it has been

shown that the drug has a marked affinity towards the ootype and egg development. I would also like to speculate on the possibility that mature adults may be more susceptible because of their location in the mesenteric vessels, where there is a higher concentration of ammonia and other products derived from the metabolism of the bacterial flora in the intestinal lumen. That is a hypothesis that has already been put forward on many occasions, but—to my knowledge—it has never been fully demonstrated.

DODIN : Quelle espèce de bilharziose font les singes que vous employez ? Bilharziose chronique ou une bilharziose aiguë qui les tue si vous injectez des doses fortes de cercaires ?

SADUN: Bilharziosis in these monkeys tends to become chronic. Rhesus monkeys usually undergo a spontaneous cure approximately 1 year after the time of exposure. There is a gradual reduction in the number of eggs in the stools. Eventually, eggs are no longer found in the stools, but worms are still present in the intra-hepatic circulation. Finally, after a few more months, the worms in the liver are eliminated. At that stage the monkey becomes quite resistant to super-infection and will resist infection of 50,000 cercariae, whereas normally in the primary infection it will not withstand more than 800 to 1,000 cercariae.

DODIN : J'ai essayé à Madagascar des infestations de 200 cercaires sur « lémur fulvus » ; elles tuent le lémurien, qui fait une bilharziose aiguë avec syndrome dysentérique aigu ; le lémurien meurt en 45 jours. Or, si je donne du CIBA 32644-Ba en même temps que la cercaire, je n'arrête pas l'évolution ; si je traite 6 jours ou 10 jours après l'infestation, je n'ai pas d'évolution bilharzienne. N'y a-t-il donc pas une susceptibilité de la part de l'hôte au cours du traitement ? Est-ce que cela tient au lémur qui donne une évolution différente ?

STRIEBEL: I should just like to reply to your question and that of Dr. LARIVIÈRE. I think that it is important to take the tissue reactions of the host into account. They differ considerably from one organ to the other and from one host species to the other. Some weeks ago, we found adult *S. japonicum* worms as well as mature eggs in the lungs of hamsters. We were astonished by the complete absence of inflammatory or connective-tissue reactions around the worms and the mature eggs. I think these differences should be responsible for the varying activity of the drug in different hosts and for different stages of the developing worm.

PETERS : Dr DODIN, comme vous avez commencé le traitement le jour de l'infestation et le Docteur SADUN le jour avant l'infestation, ne pourrait-il y avoir là aussi une raison des résultats discordants ?

DODIN : C'est possible, le temps d'absorption étant différent. Mais l'expérimentation montre chez le lémur qu'on a une évolution normale de la bilharziose en traitant à partir du jour de l'inoculation, alors que la maladie n'évolue pas si l'on traite à partir des 6e ou 10e jours après l'inoculation.

LAMBERT : Les observations que nous avons faites chez la souris infestée par *S. mansoni* concordent davantage avec les trouvailles du Docteur DODIN qu'avec les observations faites en utilisant *S. japonicum* chez la souris et *S. mansoni* chez le singe.

STRIEBEL: I think we must mention another fact here. As Dr. R. JAQUES of CIBA has shown, CIBA 32644-Ba has the effect of suppressing the development of immunity, and if treatment is administered simultaneously with infection, this suppressive action is found. There is no reaction at all on the part

of the host towards the infective stages. Dr. SADUN treated before infection took place; and afterwards there may have been a rebound effect of immunological reactions, which could have destroyed the invasive stages of schistosome. This could be an explanation for it.

SADUN: I am a little sceptical about this. First of all, although in *S. mansoni* we began treatment 1 day before exposure, in *S. japonicum* treatment was started on the day of exposure. Secondly, we are dealing here with treatments which lasted 4 days and immuno-suppression is unlikely to depend exclusively on the first day of therapy. Although different degrees of cellular response in different organs unquestionably account for the varying susceptibility of worms to the action of the drugs, or to immune responses in the host, one should not overlook the fact that these are primary exposures. It has been shown experimentally that in primary exposures the cellular responses around the cercariae at penetration and schistosomules during migration, are minimal. It is only in secondary exposures to infection that massive cellular responses occur at the level of the skin, in the lungs, and eventually in the liver. Furthermore, the relative role played by humoral and cellular factors in the mechanisms of defence against schistosomiasis still requires further elucidation. Are the cells observed around and in the worms killing them, or are they scavengers removing the debris after the worms have been killed by drugs, an abnormal host-parasite relationship, an unfavourable environment, irradiation, or humoral host factors? In other words, are we accusing the street-cleaners of being the litter-bugs?