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Discussion

SADUN: I should like now to turn to the question of toxicity. There is no need to point out that toxicity is relative. Obviously, if we were dealing with a remedy for headaches, the occurrence of toxic effects would make the cure worse than the disease; however, a few side-effects may be less disturbing in a drug that can cure such a serious disease as schistosomiasis. When discussing this aspect it might therefore be advisable to relate our observations to those made with other drugs used in the treatment of this particular disease. I think we should also try to differentiate between effects which may not necessarily be attributable to the drug and those which appear to be specific results of the treatment.

BLOCH: With regard to side-effects, would it not be useful to agree on some sort of a definition of what can properly be called a side-effect? For instance, I think that the dark appearance of the urine can scarcely be regarded as a side-effect; this is what one would expect. On the other hand, I am sure we should not place convulsions and severe mental effects in the same category as the headaches or lack of appetite reported. I also think it would be very helpful if the speakers would try to classify their side-effects according to severity and also with regard to the manner in which the information is reported. We could then make a valid comparison of the data supplied by the various investigators. A good deal depends on whether the patients are asked in a more or less suggestive way whether they did not have a little heartburn, or whether they really volunteer the information. I am afraid that at the present time it is very difficult to assess the relative value of these data.

DA SILVA: I agree with Professor BLOCH. I think we could establish some rules that would enable us to standardise side-effects according to their severity. As far as my own cases are concerned, most of the side-effects were very mild and yielded to symptomatic treatment. There was only one case in which we had to interrupt treatment as a result of side-effects. But, even so, I think that by using symptomatic drugs it might be possible to avoid interruptions in the treatment.

POWELL: I was impressed by the large number of side-effects encountered by Professor COUTINHO in his 20 patients, although in many cases they were, I think, minor ones. I wonder if he could tell us how many of these patients showed no side-effects?

COUTINHO: I am not very sure about that, but I think almost all of the patients displayed side-effects. The majority were minor ones and I have already described the others. I recall only 2 cases without any side-effects.

POWELL: I asked about the side-effects because I had emetine in mind. If I remember correctly, the incidence of side-effects provoked by emetine is reported by different authors to vary from something like 3% to 80% of their cases. Personally, I am a 3% man, as far as emetine is concerned. I fully

agree with what Professor BLOCH has said about trying to arrive at some standard classification.

STRIEBEL: I would like to ask Professor COUTINHO about the incidence of oesophageal varices in Recife. Could there not be a relationship between the case of haematemesis which was mentioned and oesophageal varices?

COUTINHO: In our experience, the incidence of oesophageal varices is very high. In our clinic I made a review of these patients for a thesis on portal hypertension in schistosomiasis. In 80 patients, we found oesophageal varices in 80% and gastro-oesophageal haemorrhage in about 45%; a very high incidence. We believe that gastric haemorrhage in this patient was not due to the drug itself, but to a predisposition. I divide the secondary effects into 2 groups—mild and severe symptoms. Only two patients had severe symptoms.

DA SILVA: I think there are some variations in the groups of patients under discussion. Professor PRATA conducted his experiments in a naval establishment, where everyone has stool examinations. In my cases, most of the patients have some complaints, but as a rule they are not very ill. In the case of Professor COUTINHO I think he wished to know what effect the drug had in very severe cases. I have not yet started treatment on such a basis, but I think it is very useful to have this drug for the severe cases. We are now going to start trials in groups of people who are not sick, such as school children, and we shall then have more opportunity to observe different groups.

BLAIR: The point which I would like to mention here is that in highly scientific discussions of this nature we tend to concentrate on individuals, but we must remember that the world is composed of millions of people. The people who are going to give the treatment are not concerned with individuals, they are concerned with communities. And the ones who have the disease are the children; it is the children who have the high egg-output and, owing to their habits, they are mainly responsible for the transmission of the disease.

I do not think the question of side-effects in children or adolescents as opposed to adults has been discussed yet. It seems to me that when this drug is given to children in the doses recommended, the side-effects are nil. Most of the side-effects have been observed in Europeans, who seem to be more neurotic than other races. I think Dr. RUAS has said that the side-effects were proportionate to the social status of the individual, and I think he made a very good point there. Now, if in fact the drug is going to be given to children and people living in conditions conducive to the spread of the disease and thus constituting a danger to public health, there is no need to worry about side-effects. Fortunately, investigations have shown that there need be no fear of teratogenetic effects. In any case, provided we are treating people up to the age of 12, one need not be very much concerned about this aspect.

I think we should try to form some idea about what the next steps should be. I should like to see the duration of treatment reduced as much as possible and treatment carried out on lines of the French practice in Africa, that is to say, the patients being kept out of hospital and treated in their own environment whenever it is possible. The ideal is to reduce the duration of treatment as much as is possible without sacrificing its efficiency.

RUAS: In 1000 patients, I compared the side-effects in three age-groups: 0-4 years, 5-14 years, and over 14. The side-effects increased with the age of the patients; in small children, as a matter of fact, side-effects were almost nil. It seems to us that there is no significant difference in the frequency or intensity of the side-effects whether the drug is given in a single daily dose or in two daily doses. We noted no difference in side-effects with the various therapeutic schedules.

SADUN: I think three of the factors mentioned—the age relationship, the IQ-sophistication relationship, and the difference, or absence of difference, between one or two doses as regards side-effects—are very important and deserve consideration.

DA SILVA: The only comment I should like to make is that the investigators in Lourenço Marques have contributed a great deal to our knowledge of the treatment of schistosomiasis with CIBA 32644-Ba. For this reason I should like to express my congratulations to them.

FRANCO: I should like to ask those who have conducted trials with this drug in amoebiasis to tell us how the side-effects in amoebiasis without schistosomal infections compare with the side-effects in schistosomiasis. If there is a relationship between side-effects and the intensity of the infection in schistosomiasis, I should like to know what side-effects are encountered in amoebiasis where no schistosomes are present.

POWELL: We have observed a small number of, I think, very significant side-effects; and, of course, amoebiasis is due to amoeba and not to the schistosome, so I do not think the schistosome can be held responsible. In the ECG tracings there have also been a great many T-wave changes, and I should say that they are more common and just as pronounced as they are with dehydro-emetine. In the trials we have started we shall continue to regard the drug as being perhaps as toxic as emetine, but we may be quite wrong. This is purely a precaution.

SADUN: Dr. POWELL is in a position to test this drug against amoebiasis and against schistosomiasis, and in patients with both; he is working in perhaps the only area where an adequate answer can be found to the question, which of the side-effects are due to the disease and which are due to the drug. If I may make one further comment, our patients are adults; they are not neurotic.

If we are discussing toxicity we must only take account of the side-effects that we can reasonably assume to be a result of therapy and not of the patients' imaginations, or of leading questions put by the investigators.

Are there any other comments on side-effects or toxicity?

DA SILVA: In view of the mental side-effects which have been described, we should perhaps use the drug more carefully than we would a Miracil compound. Reactions, of course, occur much less frequently with the CIBA product. I think we should take the personal history and the family background of the patient into account. In some cases supportive therapy could be used in order to avoid these complications before the patients are given the drug.

SADUN: This is a very important point and I think it will come up again in the recommendations. In the same connection, I wonder whether anyone has had any experience with the use of this drug in patients with Chagas' disease. In view of the ECG changes and possible cardiac toxicity it would be valuable to know whether these were more noticeable in patients with Chagas' disease than in those without; if so, perhaps someone would care to comment.

PRATA: We treated patients with acute Chagas' disease with this drug and it had no effects on the circulating trypanosomes; there was no severe reaction in these cases.

DAVIS: I was interested to hear of the high incidence of severe side-effects mentioned in the last three papers. *S. japonicum* flukes have the reputation of wandering throughout the body much more than *S. mansoni* and *S. haemato-*

bium. I was wondering whether the high incidence of mental symptoms could be due to aberrant location of adults or eggs in the central nervous system.

BANZON: I should like to say something on this subject. Generally, clinical cerebral schistosomiasis as seen in the Philippines is manifested by epileptic seizures preceded by an aura which may be motor or sensory; the patients may have tremor of the fingers or numbness of the right hand before a generalised convulsion appears. However, in the two cases I had, convulsions took place more or less instantaneously and disappeared after a short time. Both these patients, by the way, developed convulsions twice during the course of treatment. One patient had a convulsion on the third day of treatment and the other on the fourth day. In the latter case the liver was slightly palpable. The other patient may be considered as normal in all respects, except that schistosomiasis ova were present in his stools. Both these patients are children. I have not yet seen cerebral schistosomiasis with clinical manifestations in children in the Philippines.

YOGORE: I should like to answer the question in part, because one of the 11 patients that we have treated probably had cerebral schistosomiasis; this patient received 25 mg/kg per day. Of the three patients who were receiving 25 mg only this one completed the treatment. He had these cerebral manifestations before treatment, but he did not develop the psychosis that was found in the other patient. So I do not think that the psychosis we observed in two patients is related to cerebral schistosomiasis.

YOKOGAWA: Our results were quite different from Dr. BANZON's and Dr. YOGORE's. Patients treated with CIBA 32644-Ba complained of many subjective symptoms, but said that the symptoms due to this drug were much milder than the symptoms they had experienced during treatment with antimony compounds.

BANZON: I should like to add something more. We recently had one female patient who developed psychosis after the 7th dose, i.e. at the beginning of the 4th day of treatment. There was no history of psychosis in her immediate family. These manifestations were more or less acute and disappeared four days after the drug was withdrawn. The same patient also developed haematemesis as a result of vomiting before the psychosis set in. She was the only one in our series who had splenomegaly and was considered to be in the advanced stage of the disease. We believe that the haematemesis was provoked by the vomiting rather than as a result of a direct drug action. Furthermore, we had patients who, as I mentioned, were quite indifferent to their environment. They made no response when spoken to. One patient did not even know his name. This temporary amnesia might also be some form of central nervous disturbance.

FERREIRA: I am afraid that this kind of discussion is leading us into a very complicated field. We cannot speak of cerebral schistosomiasis on clinical grounds only. As far as my own experience is concerned, I only make the diagnosis on the basis of post-mortem examinations.

YOGORE: I should like to draw attention to our recent work in the Philippines. We have been able to demonstrate certain antibodies in the cerebrospinal fluid of patients with cerebral schistosomiasis confirmed at operation; so perhaps a clinical diagnosis of cerebral schistosomiasis may be supported by appropriate laboratory examinations.

BANZON: I should just like to make some comments about the toxicity. Dr. YOKOGAWA and myself dealt with out-patients who were more or less in the

very early stages of schistosomiasis; Dr. YOGORE on the other hand was dealing with in-patients, and mostly patients in the later stage of the disease. As far as toxicity is concerned, Dr. YOGORE's and my findings were more or less the same; Dr. YOKOGAWA, however, had milder toxicity reactions in his series. I was just wondering whether there are other factors to be considered in connection with these toxic reactions. Probably severity of the infection plays a part, since we have perhaps found higher egg-counts than the Japanese investigators.

YOKOGAWA: Compared to Dr. YOGORE's or other results, the side-effects in our patients were much milder than with antimony.

SADUN: This, of course, does not necessarily correspond with the experiences of the Philippine group.

Is there any comment anyone would like to make regarding the need for further work on *Schistosoma japonicum*? If I understand correctly, all three of the investigators who have just reported are planning to extend their studies in the future. I think there is no doubt that further studies are needed on all parasites, but the need might be even more urgent as regards *S. japonicum* and *E. histolytica* on which we have as yet less information than we do on *S. haematobium* or *S. mansoni*.

HUGONOT : A la suite de ce qui vient d'être dit, on remarque d'abord une chose, c'est que le CIBA 32644-Ba est beaucoup mieux toléré en traitement ambulatoire qu'en traitement hospitalier. Je pense que cette différence est due au fait que l'appréciation de tous les symptômes subjectifs de l'intolérance dont on a parlé — qu'il s'agisse de céphalées, de douleurs abdominales, de lombalgie ou d'anorexie — est très difficile à l'hôpital. A l'hôpital, ces manifestations subjectives sont certainement contagieuses, je dirais même, épidémiques, dans une salle où tous les malades reçoivent le même traitement. L'un se plaint de céphalées, l'autre aussi. Je crois également que l'on conditionne peut-être plus facilement les malades à l'hôpital. On risque de les suggestionner. Quand on leur demande : Est-ce que tout va bien ? Ils vous répondent en général que ça va bien, mais si tous les jours on les questionne : Avez-vous mal à la tête, avez-vous mal au ventre, etc., finalement il y en a toujours qui ont mal quelque part. Je pense que si l'on adressait le même questionnaire à notre assemblée, on trouverait peut-être une proportion de troubles analogues, sans cependant qu'il y ait intolérance, tout au moins pas de cette même manière, au CIBA 3644-Ba.

Cette appréciation des troubles subjectifs en matière de thérapeutique est une chose évidemment extrêmement délicate, et je me demande si éventuellement sur une catégorie de malades ne présentant pas une affection grave (je pense ici par exemple à ces amibiases intestinales que nous avons au Maroc), il ne serait pas intéressant — car nous ne sommes alors pas tenus à un jour près pour les traiter — de faire avec un placébo une expérience en double-feinte, une expérience aveugle. Mais pas en commençant par le traitement du médicament actif suivi du placébo, parce que dans ces cas-là on s'aperçoit que le placébo donne le même pourcentage d'intolérance et le même pourcentage de succès thérapeutique que le médicament, mais en commençant d'abord par le placébo, par exemple pendant 5 jours, et en faisant ensuite le médicament pendant 5 jours également. Nous aurions ainsi une différence beaucoup plus sensible entre le placébo et le médicament que dans des séries parallèles, parce que là aussi le coefficient personnel de celui qui pose les questions est indiscutable. Je craignais en particulier chez les amibiens qui sont polarisés sur leur tube digestif que ce genre de questions ne les conditionne. En tout cas, ce fait est extrêmement frappant et je regrette personnellement d'avoir commencé le traitement hospitalier et de ne pas l'avoir fait am-

bulatoire. Cela nous aurait permis d'avoir une expérience beaucoup plus vaste. Il n'est jamais trop tard pour bien faire.

POWELL: We certainly plan to extend our studies. We need a lot more information and in order to obtain it we shall have to test the drug in a great many more cases. As I said, we may make comparative trials with other amoebicides. I cannot think of anything else we could do with the drug in amoebiasis, except perhaps change the dosage schedule.

SADUN: Could we perhaps discuss what could be done as regards further studies in amoebiasis and *S. japonicum,* for instance the use of properly controlled trials?

POWELL: It is very difficult to have untreated controls or patients receiving only placebos in acute amoebic dysentery or amoebic liver abscess, because they would die; so we are unable to use controls in that sense but we almost always run two drug trials together. In other words, we never have all the patients receiving the same drug. This provides some form of control. In addition, we do follow up emetine treatments for a year or two as a standard procedure to make sure that the disease in Durban has not changed and we consistently get much the same sort of results with emetine.

SADUN: What I had in mind when I mentioned controls was not, of course, the untreated control, which I realise would not be possible for ethical reasons; but I was wondering whether, in addition to what you just mentioned about other drug controls, it would be possible to use schistosomiasis patients as controls of the amoebiasis treatment, and vice versa?

POWELL: Yes indeed, we certainly intend to do so. If we test the drug in schistosomiasis patients we shall certainly make ECG tracings to compare the effects of this particular drug on the ECG in schistosomiasis and in amoebiasis.

SADUN: There might be also some patients with trichomoniasis that have neither amoebic nor schistosomal infections and would thus be ideal subjects for further control groups. I think this might be even more necessary as regards *S. japonicum* in the Philippines. If you could obtain patients from non-endemic trichomoniasis or amoebiasis areas for treatment with the drug, then perhaps you might be able to determine definitely the role, if any, that schistosomiasis per se plays in some of the symptoms.

COUTINHO: I am doubtful as far as amoebiasis is concerned. Why can we not try the drug in cases of common chronic amoebiasis and not only in acute dysenteric cases? According to the papers presented in this symposium, only amoebiasis patients with dysentery and liver abscess were treated. I should like to know why we should not try the drug in common chronic amoebiasis, because diarrhoea and constipation are the usual complications in my country.

POWELL: The answer is that we find it very difficult to ascribe specific symptoms to these people in Durban, so it is extremely difficult to standardise the subjects. As far as the asymptomatic, or, if you like, mildly symptomatic cases are concerned, I think it is very difficult to assess criteria of cure in these cases; a very long and careful follow-up and very many stool examinations are necessary.

COUTINHO: I do not think these are valid reasons, because we have many patients with sufficient signs and symptoms, such as diarrhoea, loss of weight and many others, and we have to treat these patients. I should still like to know why the drug should not be tried in these patients.

SADUN: I do not think anyone would say that it should not be tried; of course, you may be able to do so since you are in a position to differentiate.

I can sympathise very well with Dr. POWELL's problem because we have the same problem in immunology. Every time we try to evaluate an antigen for amoebiasis, we end up by having to ask the group at Durban to send us sera or anything of that nature, because the aemoebiasis patients that we have in the United States are for the most part chronic amoebic cases, with symptoms that we cannot fully define. All we can say is that they have some symptoms and may have some amoebae, but first of all we do not know what relationship exists between the amoebae and the symptoms, and secondly, sometimes we do not even know whether the amoebae are truly pathogenic or not.

DA SILVA: May I add that sometimes they get worse with treatment.

SADUN: I do not believe that this should in any way discourage those who, like yourself, are in the fortunate position of being able to select such a group and trying to treat it.

BLAIR: It seems to be generally accepted that the use of antimony drugs in patients suffering from tuberculosis is a contra-indication. Tuberculosis is much more widespread in the world than Chagas' disease in Brazil or trypanosomiasis in Africa. I think it would be interesting in some future work to exhibit this drug in patients who have active tuberculosis and are perhaps being treated with PAS and INH, and see whether the same difficulty arises. You do not use antimony therapy in a patient receiving treatment for tuberculosis; this is one of these things that everybody seems to know, but that are not to be found in print. I think it would be very interesting to know in the future whether you can give therapy freely to patients who are under active treatment.

BLOCH: I should like to expand Dr. BLAIR's statement a little. It is only by chance that we became aware that some patients had been treated simultaneously with INH-PAS and this drug, and one would have to know much more about the interaction of various drugs given at the same time before one could confidently administer these drugs simultaneously. It is known that drug interaction does occur and that the side-effects of one drug may be greatly increased by simultaneous medication with another. I think, therefore, that since the accepted course of treatment is so short one should actually recommend that this drug should not be combined with any other until we know for sure that such combinations are harmless.

ARFAA: In our trial we had a patient with clinical symptoms of tuberculosis. He was given this drug for 5 days, that is, he received a full course of treatment, but we found that he had dyspnoea and anorexia. This is one case where the effects of treatment and the side-effects were observed in a patient with tuberculosis.

SADUN: What is the minimum effective dose? Is it necessary to give 30 or 25 mg, or even 20 mg? Do we have any information on this subject?

DA SILVA: I think we should continue to give 25 mg over a period of 5 to 10 days. I hope that within a few months we shall have more information on the drug.

FERREIRA: I should like to say that the minimum dose used so far was 15 mg and the maximum dose 55 mg/kg daily.

PRATA: Toxicity was greatly increased when more than 30 mg were used. One of my patients who received 40 mg developed fever.

DA SILVA: Children should perhaps be given higher doses. I think this is a general rule applying to all chemotherapeutic agents. Perhaps there are less

toxic manifestations, but the effect is smaller because of the more rapid metabolism. I do not know whether there is any information about this.

POWELL: I think it has been suggested that it might be possible to use a lower dosage in amoebiasis. In my opinion this is unlikely to be effective. One gets the impression that we should like to improve our results by pushing up the dosage, but toxicity is our limiting factor. With regard to dosage, the position is somewhat different in amoebiasis from that in schistosomiasis. I have already had an opportunity to talk to Dr. FAIGLE about the possibility of using a higher dose in cases of amoebic abscess. He suggested that this would not be successful. We should also like to have more knowledge about tissue concentrations of the drug, because in a great many cases the amoebae have spread beyond the liver. This is, however, outside the scope of the present discussion.

SADUN: I feel just as strongly about this as you do. This is perhaps one case where an exception can be made to Dr. BLAIR's remarks that we had to discuss parasites rather than people, because of the different behaviour and possibly the different location of the host. The impression one gets from your paper is that in amoebiasis we are perhaps already operating close to the lower limit. On the other hand the impression one gets as regards treatment of *S. haematobium* infections is quite the opposite; perhaps I am mistaken, but I think one might possibly obtain comparatively good results there with lower doses than those which were used at the time. Is this correct?

Would someone who has been working with *S. haematobium* care to speculate on the possibility of obtaining satisfactory results with lower doses than we have employed so far?

DAVIS: I do not think that this is a matter for speculation. I think that it is a thing which should be done and I hope to do it on my return.

RUAS: The cure rate we obtained in this kind of treatment was about 95%. When higher doses were tried the side-effects were not severe.

SADUN: I think this again justifies our making a distinction between the lowest effective dose and the duration of treatment, bearing in mind the possibility of using a single daily dose. You may have noticed that in the very limited series of experiments in monkeys we found no significant difference whether one or two daily doses were given. This does not really have any bearing on the results in man, not only because of the difference in the hosts, but also because much higher doses may be given to monkeys than to humans. I was wondering whether anyone would like to comment on whether it would be sufficient to give one dose a day, or whether two daily doses are necessary?

FRANCO: In our experiments we have treated two groups for purposes of comparison. The results obtained with one single dose were the same as when two daily doses were given. Each group comprised 50 patients.

SADUN: I think this is most important in the light of what Dr. BLAIR mentioned in his original paper. The 12-hour schedule is not suitable for human beings; they prefer either an 8-hour or a 24-hour schedule. I think it would make the trials much more practical if one of the latter were adopted.

BLAIR: I think the ideal would be to give only one dose a day and reduce the duration of treatment, if possible, rather than to cut the dosage. I really think that Dr. DAVIS would be much better to try a 1, 2, 3 or 4-day schedule at the present doses, rather than attempt to lower the daily dosage schedule. This may not be so, but at the present moment I am frankly not concerned by the stories we have heard about toxicity.

RUAS: I agree with Professor DA SILVA, but I must say that I am now giving higher doses to children than to adults. Up to 15 kg body-weight I am giving 30 and 35 mg/kg. The side-effects in adults are much more pronounced than in children.

POWELL: I should like to know whether other people here would find a different strength of tablet useful. I got the impression from several papers that dosage would have been simpler, if one had had a 250 or 300 mg tablet. It would certainly help us with our patients.

SADUN: I noticed a great deal of nodding going on while you were speaking. I wonder if I may refer this question to Professor BLOCH.

BLOCH: This is the first time that this problem has come to my attention. It would be quite easy to supply tablets of lower strength and probably even larger tablets which could easily be halved or quartered and would therefore satisfy individual dosage requirements. This is one of the few problems that we can solve easily.

POWELL: I should just like to make a point about the breaking of tablets. This is not always completely satisfactory in African hospitals. In many cases the nursing staffs are used to handing out one or two tablets, and they forget to break the tablets, which can create difficulties.

BLAIR: Dr. RUAS raised the point about the dosage in children and adults and said that he was giving a higher dose in children. Now, is he doing that because his results at the normal dose in children were unsatisfactory? I know that this has been said of other drugs. We have heard all about the child liver being a much more efficient detoxicator and that it therefore has to be assaulted harder if any therapeutic effect is to be achieved; but we have found that this drug is equally effective in children, quite small children—I think the youngest child we have ever treated was 4 years old—and I don't see why we should have to change. At the risk of appearing to be a heretic, I shall go even further and say that I do not believe in calculating doses in milligrams per kg of body-weight. What we are trying to do is to distribute milligrams of the drug throughout the body. Presumably as far as this drug is concerned, we are trying to get micrograms of it into an important place. I feel that the idea of giving so many milligrams per kilogram of body-weight may be all right in order to avoid treating a very small child with too big a a dose of the drug, but I think we should draw the line at a certain weight and forget the mg/kg principle after that. I do not know whether that is an acceptable view. We have tried this approach deliberately in some very heavy people; we have given the drug to a person weighing 104 kg, which is just about as heavy as a human being ought to be at all, and he really had very little trouble after receiving a very large dose of the drug. I think he had to take about 27 tablets. Now, is this a question that should be studied more thoroughly? If Dr. RUAS has evidence that the mg/kg body-weight method does not work in children, then we have to know now, otherwise there may be a lot of difficulty in future trials.

RUAS: I am trying to use higher doses in children in order to see if I can shorten the duration of treatment. The most practical treatment scheduled had a duration of four days, but I am now trying to reduce that to three or even two days giving one single dose a day. I do not know yet what the results will be; I have not followed up the patients for a sufficient length of time. However, as soon as I can, I shall tell Dr. BLAIR and the others. With regard to the mg/kg method, I agree with Dr. BLAIR; but when conducting trials I think it is better to standardise so that the results from different centres can be com-

pared. For this reason I am continuing to weigh the patients and give daily doses in mg/kg of body-weight.

BLOCH: Generally speaking, what Dr. BLAIR says applies of course to every drug. Once a drug is out of the experimental stage one usually ceases to weigh the patient before he is given his medication and as a result medication on a mg/kg basis varies by a factor of at least two. An adult weighing 52 kg may generally be given just as much as Dr. BLAIR's big patient who weighed 104 kg. Although I have no proof, I agree that children should probably be given a slightly higher dose per kg, and the danger of overdosing in children can be minimised if you group the children into two or three age categories—up to age 6, 6-12, and so forth. The same problem, of course, arises in connection with all drugs.

BLAIR: I think Dr. RUAS has misunderstood my point. I understood from what he said that he was giving a bigger dose to children because he felt it was necessary. I did not realise that he was giving a bigger dose to children because he wished to shorten the treatment. That, of course, answers my question.

SADUN: I think we are fairly clear about the type of experimentation which is needed, and we might return now to the question of toxicity. I wonder whether anyone feels that further studies are desirable and would like to suggest specific studies that might be undertaken to determine the possible toxic effects of this drug on the circulatory system, the heart, the reproductive system or any other system you care to mention.

DAVIS: I am in favour of continuing to do electrocardiograms, although I am not sure that very much more information will be amassed than is already available. I think that the main thing that will emerge in the future is a picture of the frequency of ECG changes of one sort or another and I think this will be a major factor in directing clinical attention to the cardiovascular system.

SADUN: In that connection perhaps a decision on some standards for classifying these symptoms would be helpful in comparing the results obtained by various investigators. Does anyone think that there is any need for basic laboratory studies, for instance on the ECG? I was very much impressed at the W.H.O. conference by Dr. Cotten's study on the pharmacology and toxicity of antimonials in the circulatory system. Is there any need for similar studies in connection with this drug?

BLOCH: I think our studies are being continued along exactly these lines and I should also like to remind you that very little is known about the incidental effects of most drugs on the ECG. I should not be surprised if a number of commonly used drugs were found to provoke all kinds of ECG changes.

DA SILVA: I should just like to say a few words about the results of the ECG determinations. We found an increase in rate in one case, disturbances of ventricular recuperation in eight and inverted T-waves in one case only. I do not think that these changes are significant. They are more marked in patients receiving antimony compounds, but even so, there is no definite correlation between them and the occurrence of fatalities.

COUTINHO: I observed that the incidence of side-effects is higher when the infestation is very severe. The ECG changes are very infrequent, in my experience, and in any case milder than in antimony treatment. This is a point which should be emphasised.

DA SILVA: I do not believe that the parasites or the metabolites of the parasites have anything to do with changes in the ECG tracings. I think it was Professor Dias of Belo Horizonte who demonstrated 15 years ago that people with diseases other than schistosomiasis, or even healthy people, may develop the same ECG changes. I believe this fact is quite well established. However, I cannot say whether the same applies to the problem of CIBA 32644-Ba.

BLOCH: If I may just ask a question, Dr. LAMBERT, you said it is well known that emetine and antimony have a cardiotropic effect. Do they actually accumulate selectively in the heart muscle?

LAMBERT : Brown et Schulert ont montré que la concentration de l'antimoine est plusieurs fois plus élevée dans le foie, les érythrocytes, la rate, les reins et le cœur que dans le plasma. Quant à l'émétine, Gimble et collaborateurs ont montré que sa concentration s'échelonnait de la façon suivante, du tissu le plus riche au plus pauvre : foie, reins, rate, poumons, cerveau, cœur, muscles squelettiques, sang.

DAVIS: It has been shown both in animals and humans that antimony can be deposited in the myocardium.

SADUN: As regards the reproductive system, is everyone satisfied that the work done so far provides enough information?

LARIVIÈRE : Il y a un problème sur la toxicité qui n'a pas été mis en évidence en dehors du travail expérimental de GRÉTILLAT, mais qui ne donne pas la symptomatologie subjective, c'est la possibilité de donner cette thérapeutique à des femmes enceintes ; est-ce que c'est possible ? Car nous rencontrons quand même souvent le problème de traiter des bilharzioses chez des femmes enceintes et est-ce que ce produit peut être donné sans voir augmenter considérablement les manifestations d'intolérance ?

DODIN : Nous avons traité deux femmes enceintes qui, en fait, avaient une albuminurie et il fallait déterminer si cette albuminurie était bilharzienne ou si cette albuminurie était d'origine grossesse. La première était enceinte de 5 mois, elle a accouché normalement d'un enfant parfaitement normal ; elle a mieux supporté le traitement que la plupart des autres. La deuxième femme était enceinte de 4 mois, elle avait également une albuminurie due à son hématurie bilharzienne et on n'a eu aucun problème.

RUAS : Je ne voudrais rien affirmer de définitif, mais j'ai quand même déjà traité près de 15 femmes enceintes. Notre attention n'a été attirée que par le fait que les effets secondaires seraient plus fréquents, mais pas plus graves chez les femmes enceintes que chez les autres. Il est difficile de savoir si les symptômes observés, vomissements en particulier, étaient dus au traitement ou s'ils existaient déjà avant.

PETERS : J'aimerais demander au Docteur GRÉTILLAT s'il a déjà des résultats avec des brebis traitées pendant les premières semaines après la conception ; je crois que tous les animaux que vous avez traités l'ont été pendant le troisième ou le quatrième mois. Est-ce exact ?

GRÉTILLAT : C'est exact ; mais dans une expérience en cours 8 brebis ont été traitées 3 semaines après la conception. Ces brebis ne mettront bas que vers le mois de juillet. Tout ce que je peux dire pour l'instant est qu'elles n'ont pas avorté et que je n'ai observé aucun accident. C'est dans cet essai que nous chercherons d'éventuels effets tératogènes.

BLOCH : Je voudrais ajouter que l'expérimentation standard pour découvrir des effets tératogènes possibles est en cours et est partiellement déjà com-

plète ; elle n'a jusqu'à présent absolument rien montré. Evidemment, avec cette toute nouvelle substance il se pose la question de traduire ces trouvailles expérimentales sur la femme, et là nous ne sommes pas plus avancés qu'avec n'importe quelle autre substance.

LAMBERT : Sur le plan expérimental, aux doses thérapeutiques chez la souris portante et chez la souris allaitante, nous arrivons aux mêmes conclusions que le Docteur GRÉTILLAT : aucune toxicité n'a été observée sur la mère et le fœtus pendant la gestation et après la gestation, pendant l'allaitement. A part ce que viennent de dire les Docteurs DODIN et RUAS chez la femme enceinte, il n'y a, je crois, aucune autre observation connue à ce sujet.

DAVIS : To avoid any embarrassing situations in the future, I should like to know whether this substance is excreted in breast milk?

LAMBERT : Cette question n'a pas été étudiée ; l'étude de l'excrétion par le lait, chez la souris, est impossible et nous ne disposons pas de matériel marqué C^{14} en quantité suffisante pour le faire chez la chèvre.

DAVIS: I just wondered whether it were excreted in breast milk and then coloured the infants' urine. If it is, you would get a lot of anxious mothers.

DODIN : Dans le problème de la toxicité, j'ai été très frappé hier par les coupes des testicules des singes traités par le Docteur SINARI, et je me demande si en réitérant des traitements on n'arriverait pas à obtenir des anticorps antitesticulaires. Le Docteur SADUN peut peut-être répondre à cette question. En réitérant des traitements à la suite des coupes que nous avons vues hier, il y a certainement une résorption des protéines testiculaires, et à la suite d'un deuxième traitement est-ce que l'on ne doit pas avoir des anticorps antitesticulaires qui risquent non pas par la toxicité du produit, mais par auto-immunisation amener des catastrophes ?

BLOCH : Ayant fait des essais pendant longtemps, pas particulièrement avec cette substance, je crois pouvoir répondre négativement. En expérimentation il est impossible d'obtenir des anticorps autologues, sauf en utilisant des doses très fortes d'adjuvant complet ; sans adjuvant complet, vous n'avez jamais d'anticorps testiculaires.

DA SILVA: I should like to know whether anyone can comment on the possibility of using the drug as a prophylactic and suppressive substance, or on the possibility of studying the drug from the public health point of view.

SADUN: I wonder if anyone has any suggestions either for experimental work in the laboratory or for work in the field which might help us to answer some of the questions connected with the possible prophylactic use of this drug?

FERREIRA: I am afraid that at present we do not know enough to speak about this aspect.

DA SILVA: I agree with Professor CRUZ FERREIRA, but something has to be done along these lines. Perhaps we shall soon have more information on the effects of the drug in long-term treatment. This is an important question. Visitors to endemic areas can pick up infections in a very short time.

DAVIS: Our present knowledge on the prophylactic use of the drug in human beings is a little scant. I wonder whether the emphasis in human disease should not be changed from prophylaxis to suppression. The drug may be of some use in this way.

SADUN: This is what I had in mind when I spoke of "public health control"; actually "suppression" would be a much more appropriate term. As

Professor DA SILVA pointed out, people often travel nowadays from non-endemic to endemic areas, and in a very short time they become exposed and infected. These persons are, if anything, more vulnerable than others, because they have no acquired immunity to speak of, if that plays any major role. Some means of preventing or even delaying such infections has to be found. The measures that have been used up to now—molluscicides and sanitary engineering—have been complicated; a prophylactic drug would be much more effective, and its development might take long enough to justify our consideration of the question now. This leads to the question of public health control. Although black eggs are still found, viable eggs do not appear in most of the treated individuals; as a matter of fact they seem to disappear even after very low doses or a few applications of the drug. This may suggest a means of suppressing the disease, of interrupting the transmission cycle. What kind of studies could be recommended and who is in a position to undertake them?

BLAIR: We have made a start with a trial of the drug in suppressive management. I am still rather vague about how it should be done but I think that in an area of high transmission the whole population could be given a dose for 2 days in each month, regardless of whether they have confirmed infections or not. An appropriate series of stool and urine examinations might then be made, let us say every three months to see what happens. In Africa, where irrigation projects are being developed, the public health people are absolutely terrified of what might happen, particularly with regard to *S. mansoni;* and the molluscicides are not promising. Now for the first time we seem to have a drug that is more promising, so I think that instead of concentrating on dose schedules, etc., we should decide that a few people who have the opportunity should try some very simple form of suppressive management. I know the original workers would shudder at this, but even if the number of eggs can be reduced from 10,000 an hour to 60 an hour by such a measure, then the suppressive management is very good indeed and the transmission cycle will be effectively interrupted.

SADUN: Especially since the presence of miracidia or viable eggs in water does not necessarily mean that the miracidium will succeed in invading the snail; the miracidium may have been somewhat disturbed by the therapy to the extent that it will no longer succeed in infecting the snail or, if it does, will no longer be able to produce cercariae.

DAVIS: I whole-heartedly agree with Dr. BLAIR on the question of suppression and I do not think we should get ourselves involved in arguing about details concerning dosages. The principles of methodology will vary in different epidemiological situations, but we all know what we want to do. I would put in a special plea for the early commencement of trials in special epidemiological situations, for example in island sites or in some of the peculiar places found in Africa, where the disease may occur at the bottom of the hill and not at the top. Studies in such captive populations may give more rapid and clear-cut results than in hyperendemic areas where constant ingress and egress of the population favours transmission and sometimes blurs the picture. I fully agree with Dr. BLAIR that this is the thing which we must look into.

SADUN: Laboratories such as mine, although not equipped for clinical work but none the less with a modest competence in experimental work, might be able to help the clinicians and field-workers with their tasks. If there is anything you feel might be desirable, I hope you will let me know.

We have already discussed briefly the relationship between intensity and

duration of infection and the effectiveness of therapy. Perhaps by comparing results obtained in patients who have come from non-endemic into endemic areas, or vice versa, where it is possible (especially in the former case) to assess fairly accurately the age of the parasites, with results obtained in individuals with infections of much longer standing, some striking differences may come to light. I think this may be worth testing.

I am afraid we shall now have to close this very stimulating and informative discussion. I have been reminded many times that discussions should be like women's skirts: long enough to be decent, but short enough to be interesting. I should like to call upon Professor CRUZ FERREIRA for his final remarks after which Professor BLOCH will say a few words.