Discussion

Chairman: DR J. O'H. TOBIN

CHAIRMAN: Today's session is really divided into two parts. The first is to discuss what we have heard this morning and the second is to try and assess the feeling of participants on the possibility of setting up some collaborative study on herpes encephalitis, with perhaps the establishment of a therapeutic trial. There certainly appears to be quite a lot of enthusiasm for a multi-centre trial.

Let us now discuss this morning's papers.

DR A. H. TOMLINSON: Dr Rappel, you commented on the fact that many of your patients showed a rapid improvement 12-36 hr after idoxuridine. I wonder if this could be attributed to something other than the antiviral action of the drug. After perhaps a fortnight's illness, there was this comparatively sudden improvement. I find this difficult to attribute solely to the stopping of virus replication. Could it be caused by the cytotoxic effect of the drug? Could it be something else?

DR M. RAPPEL: I find this a difficult question to answer. I can say that we have all seen this. It seems not to be related to the Intensive Care Unit, which might also be part of the treatment of the patient. One of the most striking cases I have seen was of a patient who underwent a surgical decompression, who was in a coma, Grade III-IV, which means nearly dying. The temperature was very high, blood pressure fluctuated frequently from high to low, and it was obvious that he was within a few hours of death. He was in this state for 6 days after surgical decompression. So, at this stage, we started chemotherapy, but all the rest of the treatment was just the same. I saw a drop in the temperature about 20 hr after the beginning of the idoxuridine therapy. The coma also disappeared and 2 days later, he was able to speak a little, and so on; so that was a striking case. He eventually died from bronchopneumonia, but this occurred 2 or 3 months later, and at necropsy, it was shown that the inflammatory process was extinguished and no longer active. There were only scar lesions. The drug obviously worked very quickly indeed. What happened really, I don't know; of course, the brain swelling is probably a reaction to necrosis, but how the drug had such a dramatic effect, I don't know.

DR D. SUMNER: The figures of Dr Rappel about the value of steroids are striking and do not have to be stressed. I wonder though, Dr Rappel, if you could tell us what steroids they were? Dexamethasone, or prednisone, or what?

DR M. RAPPEL: Most of the patients in my series were treated with dexamethasone, either intravenously or orally, 16-20 mg. Two cases were given hydrocortisone, but most of the cases were given dexamethasone.

DR D. SUMNER: The one that died?

DR M. RAPPEL: Dexamethasone.

DR L. A. LIVERSEGE: Could you say something about the quality of the survival?

DR M. RAPPEL: I can only speak for the cases that I have seen personally. The majority of my series is drawn from the literature and from personal communications. The survivor is a girl of 11, she is at school, she is perfectly all right. It is 2 years since she was decompressed and had idoxuridine. She now has no memory loss and seems to be perfectly all right. I have heard this from the parents and the school-teacher, but more I cannot tell you.

DR B. E. JUEL-JENSEN: I did quote this yesterday. Of eighteen people treated with idoxuridine in Oxford, there were about 65% survivors. Half of these, if I may make this rough characterization, were cabbages, totally useless to themselves and to others, and half led some sort of useful life. I have to ask Dr Oxbury whether anybody has escaped entirely?

DR G. D. W. MCKENDRICK: I think we ought to look very carefully at the most interesting figures provided by Dr Rappel. There was 73.5% mortality in untreated cases culled from the world's literature. In most of these cases I think he said the diagnosis was made at necropsy. Now, he only needs another 200 or 300 cases to be undiagnosed for the mortality in that group to be the same as in the treated group, because I think it is a fair assumption that the diagnostic index in those institutes which have been treating this condition is very much higher than in most hospitals.

CHAIRMAN: I think this is very true, Dr McKendrick, but I think it raises a question which we might well discuss when we talk about the collaborative study. People tend to publish their successes and not their failures. I imagine, however, that a considerable number of cases have been seen personally by the people gathered here today. It might be possible to review the cases which have been seen, say, over the past 2 or 3 years, or since treatment has been introduced. This might be a method of getting some more reliable information.

DR M. RAPPEL: I think that 1966 is the real milestone, because it marked the first idoxuridine therapy. It is impossible to compare today's figures with those obtained, say, 15 years ago. In those years, not only was there no chemotherapy, but Intensive Care Units were not known, so the only useful information will be obtained from cases which appeared after 1966. I would like to suggest that we obtain collaboration from the group of people working in Bordeaux. There are a number of keen pathologists and clinicians and they have considerable experience in herpes encephalitis. Most of their cases have not been treated and they have lost sixteen or seventeen patients. Their rare survivors had all been operated upon. I am not suggesting that Bordeaux could be used as a control group, of course, but nevertheless, I

think that their results could be usefully compared with the treated results of other centres.

MR G. P. DUFFY: Could I ask Dr Rappel if he has any information about the criteria of diagnosis in the nine cases which he mentioned which were treated with steroids, and their state of health at the time the treatment was stopped? From the figures he provides, one could very well argue that the way to treat herpes encephalitis is just to give them steroids and not do anything else at all. I am, however, very doubtful as to whether one should actually use steroids at all.

DR M. RAPPEL: Yes, I have had the same doubts myself, but I think that most of the cases received treatment when they were actually in coma. I don't think that they were in any way different from the other cases.

MR G. P. DUFFY: You don't think that these cases were allergic encephalitis?

DR M. RAPPEL: Oh no. The problem as I see it is that in most of the cases, if not all the cases, steroids were given not very early after the acute onset of the disease and one may believe that at this stage, the virus was no longer the most important factor. The brains were very swollen and this may have been the major cause of the patient's problems. Personally, I would not like to give steroids only 4 days after the onset of the disease because I think there is too much virus about and it would be dangerous. Of course, steroids, together with either IDU or Ara-C, might be a useful combination. In other words, it is my feeling that we must first try some antiviral drug before giving steroids. In two cases in my series, dexamethasone was given to the patient only 3 weeks after the acute onset. The patients had spent some time in local hospitals before diagnosis was reached. I imagine that at that time the quantity of virus in the brains was not great.

DR B. E. JUEL-JENSEN: I would just like to ask the same sort of question, because I too am uneasy about steroids. It may be that it is right to use them with a good antiviral drug, nevertheless, there is considerable evidence that herpes in rabbits and zoster in man can run wild if steroids are given. I am therefore unhappy. Were these nine cases Dr Rappel treated with steroids proved to be cases of herpes encephalitis?

DR M. RAPPEL: Yes, these cases were proved to be herpes encephalitis.

DR D. SUMNER: I certainly have one case unequivocally proven by virus culture, that was treated with dexamethasone alone, and who did very well.

PROFESSOR T. C. HALL: I would like to speak in support of Dr McKendrick, the implication being that a control group may be necessary in any trial and I would like to refer back to something which Dr Ross said yesterday. In her series in which the diagnosis was obtained on histological grounds, she had twenty cases, in which there were thirteen deaths; this is 65%, not very far from Dr Rappel's untreated series. She also had eighteen cases which were more or less unconfirmed diagnoses based on clinical and antibody data. In these there were two out of eighteen deaths which is the same as one out of nine and this is what we see, both with steroids and with Ara-C. So that, if there were, in addition to those 229, a more difficult-to-diagnose group, and if this more difficult-to-diagnose group had a spontaneous death rate of only 12%, then I think this is a reasonable possibility and

should be taken into account in the design of any prospective study.

DR C. ROSS: Yes, let us get this straight. These twenty cases with a firm diagnosis were all severely ill and had been admitted to the Neurological Institute. The eighteen with a probable diagnosis of herpes encephalitis, on the basis of clinical and serological findings, had generally less severe illnesses. They were in peripheral hospitals and received no chemotherapy. Although only two of these eighteen have died, some have had neurological sequelae and others are in mental hospitals.

PROFESSOR T. C. HALL: This is the real point. In addition to the 229 untreated cases with a survival of 30%, it might well appear that another untreated group had a survival rate of 8%.

DR C. ROSS: Yes, but that brings out the point that if success of treatment depends on how early in the illness it is commenced, it may be necessary to commence treatment before laboratory diagnosis is made and certainly before serological diagnosis is established. Is it possible to start treatment when you first begin thinking about a brain biopsy?

PROFESSOR T. C. HALL: Yes, that is another very good point. I think there is something absolutely miraculously inhibitory about the use of anti-tumour drugs, that is to say, inhibitory on the action of the physician rather than its action on the growth of the tumour. People are afraid of these drugs and when one considers the lack of toxicity obtained in an antiviral dose, and, on the other hand, when one considers the massive onslaught to which other types of patients are sometimes subjected with very doubtful forms of therapeutic measures (for example, porta-caval shunts, etc.), I think that we are being very shy with antiviral chemotherapy. If we balance, on one hand, the impact of the disease and, on the other, the difficulties inherent in an early diagnosis in comparison to the relative ease of diagnosis in convalescence, it seems to me that one should go ahead and treat all suspected cases, diagnosis or no diagnosis. Even though there may be no specific virological test it should be possible to sort out the cases retrospectively.

DR C. ROSS: It seems to me that demonstration of a rising antibody titre to herpes simplex but not to varicella-zoster is very much a specific virological test.

PROFESSOR T. C. HALL: Precisely. You can get confirmatory evidence. I would submit that it would be better to treat a large group of herpes patients, but later, to handle separately the group which have had virological studies. This would be better than holding up therapy. I think we ought to define some criteria for certain of the suspects missing a brain biopsy, but that, on the other hand, we ought to treat all cases. The control group should not be left wholly untreated.

DR T. FLEWETT: I was talking about this last night with some of the neurosurgeons and there are two points. First of all, I think that all the ventricular fluids that we have looked at in cases of acute herpes encephalitis have grown the virus very readily. I understand that Dr MacCallum's experience has been somewhat similar. I am told that it is pretty easy to perform a burr-hole through the skull, insert a needle and take out the fluid. This might perhaps be considered a little less troublesome than doing a brain biopsy. Perhaps if one spun down the

cerebro-spinal fluid and looked at it with the electron microscope, this might provide another useful test. I wonder whether this approach would be better than a formal brain biopsy because I suspect that once there are the indications to do a formal brain biopsy, one has waited too long.

MR G. P. DUFFY: Of course, a brain biopsy isn't really a particularly hazardous procedure. I don't really believe it is hazardous to the patient. I don't think it is any more harmful to take a piece of brain than to take some ventricular cerebro-spinal fluid. The real reason for doing a brain biopsy is that one has an alternative diagnosis; that is the possibility of a cerebral abscess. You would have to do something about this fairly quickly and there is no alternative but to have a look at the brain. I would suggest that a brain biopsy is not an emergency procedure.

CHAIRMAN: Is that generally agreed among neurosurgeons?

I would like to refer back to the question asked by Dr Tomlinson concerning the very dramatic effect of chemotherapy. Dr Tomlinson suggested that it could not be virus inhibition. Now, in the study of two cases of cytomegalovirus infection, we found that in those cases in which the virus excretion was reduced, it took 3 or 4 days before there was any drop in the virus concentration in the urine or throat swab. We also found the same sort of thing in a case of neonatal herpes, where treatment did not inhibit virus excretion in the throat for 3 or 4 days. This suggests that delaying treatment for 24 hr might not affect the virological diagnosis in the way Dr Ross has suggested. It may therefore be possible to start treatment immediately, even before the patient has been transferred to a neurosurgical centre. I don't know what the experience of other people has been in following virus excretion over the period of days during treatment, but this has been our local experience.

DR B. E. JUEL-JENSEN: Is it realistic, Mr Chairman, to fuss very much about 3 or 4 hr, because if we get a move on, this is the time it takes? The neurosurgeon can do his needling and get the piece of brain within the hour. My colleague on my left will give me the answer within another hour and by the time he gives me the answer, the patient has gone back to the ward.

PROFESSOR K. MCCARTHY: Mr Chairman, may I take this opportunity of raising another problem? We are all gathered here today to study the problem of herpetic infection of the central nervous system. There is one disease that happens very rarely, but which might happen, and that is simian herpes virus infection. May I ask all

delegates to keep a careful watch for such possibilities. There is a whole range of simian herpes viruses which may lead to trouble, and now the British Government has relaxed the quarantine regulations for simians, it again has become possible for these animals to find their way into the pet trade.

CHAIRMAN: I think we must now close this discussion and decide if any collaborative attempt should be made to assess the effect of antiviral compounds in herpes infections, especially in those syndromes where their efficacy is still uncertain.

The meeting then proceeded to discuss this proposition and it was decided to set up a working party of interested clinicians, pathologists and virologists to consider in detail what kind of approaches were possible in solving the question of treatment, especially in herpes encephalitis. Of those present, the following were proposed and agreed to join the working party:

DR L. A. LIVERSEDGE (Chairman)
 DR M. LONGSON (Secretary)
 PROFESSOR HUME ADAMS
 DR D. B. BROWNELL
 DR P. BUXTON
 MR G. P. DUFFY
 DR T. H. FLEWETT
 DR B. E. JUEL-JENSEN
 DR F. O. MACCALLUM
 DR G. D. W. MCKENDRICK
 MR J. D. MILLER
 DR J. M. OXBURY
 DR M. PIKE
 DR M. RAPPEL
 DR R. N. P. SUTTON
 DR I. WILKINSON
 DR T. HALL (Corresponding Member)

CHAIRMAN: I now call on Professor Evanson to close the meeting.

PROFESSOR J. M. EVANSON: Well, as a non-neurologist and a non-virologist, I really just initiated the countdown and have seen the lift-off for what I hope will be a profitable collaborative venture. I am really very pleased at the way the meeting has gone and we shall now leave the experts to take over.

It just remains for me to say that we have enjoyed it very much, we hope you have, too, and we wish to thank all participants for their excellent contributions.

DR F. O. MACCALLUM: I would just like, with my colleagues, to join in our thanks to Manchester for a very excellent 2 days.