DISCUSSION: DAY 1, SESSION 1

Dr. Nicholson: Does Professor Spencer use any screening tests deliberately to determine if a compound is likely to have adverse effects?

Professor Spencer: In determining the profile of neuropathological activity, one has to accept that activity may be potentially useful or not useful, or even disastrous. When examining the profile for a particular agent, the pharmacologist has to assess whether particular central effects are likely to be useful or harmful. In other words, the profile should give information about its possible useful effects. Just as a secondary evaluation would develop the theme of what is useful and how useful it is, so one should also accumulate information on pharmacological actions which may highlight potential side-effects.

Consider imipramine and desipramine. Most people would accept that desipramine produces less sedative activity in man and this can be demonstrated very easily in the neuropathological profiles of the two drugs. Examination of the phenothiazines reveals that some of them are more sedative than others. Those, such as promazine, which are classified as sedative prolong barbiturate sleeping time more than those at the other extreme of the spectrum, like fluphenazine.

Dr. Martins: What are the speakers’ opinions on the value of anti-aggressive activity as a test for identifying potentially anxiolytic agents?

Dr. Kumar: It was certainly very valuable when the benzodiazepines were first studied. A visitor to the laboratories noticed that vicious monkeys were tamed by benzodiazepines. At that time it was thought that this indicated a potential use in the treatment of schizophrenia. Benzodiazepines were therefore first tested in the treatment of schizophrenia. It was later found that they were useful in anxiety states. I am not so sure that anti-aggressive activity has proved to be of any greater predictive value of anxiolytic actions of drugs than other existing laboratory techniques.

Professor Spencer: If I were giving a list of secondary techniques for evaluating anxiolytic drugs, I should include a number of anti-aggressive tests. I know of no anxiolytic drug which does not prevent aggressive behaviour in small laboratory animals or, for that matter, in monkeys too. This is an instance, as Dr Kumar has already said, where the connections between animal studies and man really are empirical.

Dr. Martins: Can I therefore assume that for both of you, these methods possess the limitations that all animal models have, but you do not discount them completely?

Professor Spencer: I hope my talk was not too discouraging. I was trying to indicate that there are problems. Providing these are accepted and understood you can work within the limitations of the tests. A large number of drugs have come out of this approach. If I was looking for anxiolytic drugs now I would certainly include septal lesions in rats as one of my methods of secondary evaluation.

Dr. Oswald: As I listened to Professor Spencer, I was very uneasy when I heard him say that if a drug possesses a described profile then it deserves investigation. It is just those that do have that profile that presumably offer nothing radically new. I wondered, for example, how lithium would have performed on the antidepressant profile. How is Professor Spencer going to avoid producing more of the same?

Professor Spencer: I did say that like tended to be alike. One of the points I tried to emphasize in talking about profiles was this. If there are two drugs, one in existence and clinically already widely used, and one a new agent with an identical pharmacological profile, then the chances are that they will possess similar clinical profiles too. I also suggested that one might consider performing a secondary evaluation if small changes in profile exist, because these may indicate significant clinical differences.

If I had the opportunity now of taking either desipramine, imipramine or other agents with their two profiles in a situation in which only amitriptyline existed, then I think I would forecast that desipramine would, because of its small differences in pharmacological profile, have a significant and a clinically useful difference. There is no doubt that small changes in profile may be useful in producing drugs which have clinical differences. It doesn’t give us the opportunity, though, of getting completely away from existing classes of drugs to introduce wholly new ones. I must confess that lithium would not show up in any antireserpine experiments.

Dr. McKay (Edinburgh): You mentioned looking at effects of drugs on specific anatomical areas in animal brain and perhaps being able to extrapolate to the human clinical situation. What other grounds have
you for believing that psychosis may in fact have its seat in the hypothalamus?

Professor Spencer: I tried not to suggest that psychosis had its seat in the hypothalamus, or even that chlorpromazine exerted its effects only on the hypothalamus. I simply stated that one could assume that some of chlorpromazine's important clinical effects were due to inhibiting hypothalamic function. There was no inherent suggestion that the psychosis was hypothalaminically based or that the drug itself was acting only in the hypothalamus.