

## THE PLACE OF CLOMIPRAMINE IN PSYCHOPHARMACOLOGY GEORGE BEAUMONT

### **Start from the start**

My career has been very varied. In the very early days I did some psychiatry. I think it was either my 4th or 5th job when I was a resident in Howard Kitching's Unit. At the time he was well known in Manchester. But I really began by wanting to become an obstetrician and gynaecologist. I went quite a long way along that path but then became disenchanted because some of my colleagues, who were then senior registrars, were not getting consultant appointments until their early 40s. It seemed as though there was going to be a long wait so I decided to change course. With the benefit of hindsight it was a mistake because the situation began to improve shortly afterwards - but I wasn't to know that.

So, I gave up obstetrics and gynaecology and decided to become a GP. I wanted to broaden my experience so I took the psychiatric job and also worked for a while in paediatrics. I entered general practice in Stockport in 1960 and soon developed quite an interest in psychiatry.

However, as time went by the workload steadily increased, there were some problems with partners and I became very disillusioned. One Saturday, while I was on duty, I was reading the BMJ over lunch and in it I saw that Geigy Pharmaceuticals were advertising for a medical adviser. Really just as a "flyer" I applied and to my surprise I was offered an interview. It was a complicated time in my life, too, because my wife had just had our daughter and I was trying to organise things at home as well as sort out my future. However, to cut a long story short I was offered a job.

I think that what interested Geigy was not only what I had done medically but also that when I was a medical student I had been President of the Union. I had done a lot of committee work, as well as being heavily involved in politics. I think they were intrigued by this combination of medical training and experience in administration and public life.

There were, in fact, 2 jobs available, one in rheumatology and one in psychiatry. I could pick which ever I liked. My reasoning was - since that I had never done any rheumatology but once did a job in psychiatry, I ought to take the psychiatric post.

In those days, the industry was rather "primitive". There had been little development in regulatory affairs and were no formal registration procedures for drugs. It was all very simple. When I arrived at Geigy I was somewhat astonished. I was given an office and then asked my boss, Dick Gosling what am I supposed to do. His answer was very simple - "we would like you to look after some of the old psychotropics and you can evaluate a new one we have called clomipramine and see what you make of it". So with that limited brief I had to sort myself out and learn about what we now call pharmaceutical medicine.

Clinical trials were relatively simple in those days. A patient entered an antidepressant trial simply if a physician "thought he was suitable for treatment with an antidepressant drug". This was the only criterion used to select trial subjects.

So we started a series of studies with clomipramine. I don't remember exactly when it was that I began to suspect that there was something different about clomipramine compared with the

other than available antidepressants. There were little signs in the literature that there was something special about this compound. To be truthful I think that the first person to recognise that clomipramine might have some other interesting properties was a Frenchman called Guyotat. He made a passing reference to its use in a review of a series of patients treated in an uncontrolled study. However it was a discovery that Professor Lopez-Ibor was running in a Unit in Madrid in which clomipramine infusions were administered to patients with a variety of psychiatric disorders that really stimulated my interest. In those days there was a certain popularity for administering antidepressants by infusion.

### **I thought it was the only one that was actually produced as an infusion ?**

It may have been the first, I am not sure, but subsequently, there were others. Whether there was really a sensible rationale for infusion rather than oral use, I don't think we knew. In the first instance we felt it was something just worth trying. However, I did eventually come to the opinion that there was a rationale for intravenous use. This was based on observations of treated patients. Clomipramine is highly sedative when given intravenously but not when given orally. If you went to any of the hospitals which had established an intravenous infusion unit, you could see all the patients fast asleep. I suspect this is something to do with first pass metabolism. When infused, not all the drug is metabolised, as it is following oral administration, and some reaches the cerebral circulation in its unchanged form.

As far as Lopez-Ibor's use of clomipramine was concerned, I was particularly impressed by the success claimed in obsessive compulsive disorder. It struck me that maybe this was something which made clomipramine different from other antidepressants. This was probably a marketing view rather than a medical one. I was looking for a niche for the compound and I thought "well nobody else has used antidepressants in OCD". At that time I had no idea how common OCD was but it seemed a possibility.

I had already made contact with a number of psychiatrists in the UK and they were using clomipramine. I suggested that they might try using it in obsessive compulsive disorders. Their reaction was favourable since it was acknowledged that it was a difficult condition to treat and resistant to any drugs available at the time. Anything, they thought, that worked would be a tremendous therapeutic advantage. I arranged for 4 or 5 of them to visit Madrid. I had been in touch with Profesor Lopez-Ibor and asked if we could visit his hospital. He made us very welcome, entertained us and told us about his work with clomipramine. We were all excited by what we heard.

When we came home were established a number of uncontrolled studies looking at the use of clomipramine, given either by infusion or orally, to patients with OCD. Straight away we encountered difficulties. We had no means of accurately measuring the effect of the drug. There was no generally accepted rating scale for OCD. A literature search led us to the Leyton Obsessional Inventory and we used that for some projects. We also "invented" a scale of our own. It was rough and ready by today's standards, but importantly measured features such as avoidance, resistance and interference. The end results were encouraging. Patients seemed to be improving - of course there was no placebo control.

Around this time we went to Canada for a joint meeting on The Management of Obsessional and Phobic Disorders. Some Canadian psychiatrists had already become interested in what we were doing. This was subsequently reflected in the fact that clomipramine was licensed quite early in Canada, whereas great difficulties were experienced in the United States.

I think the next important milestone was reached when Isaac Marks became interested. He ran an important study but he was very reluctant to deprive any patient of what he considered were the benefits of behaviour therapy. This made it very difficult to establish proper controls. However, some positive results were obtained. Subsequently Isaac Marks suggested that only patients who were also depressed obtained benefit from clomipramine. I don't accept this view because the protocol was designed to specifically exclude significantly depressed patients. These so called depressives who benefitted were only showing scores of less than 14 on the HDRS and I don't believe this indicates "significant depression". Nevertheless Marks concluded that the drug was no better than placebo in relieving symptoms of OCD, that it was no different to any other antidepressant and that behaviour therapy was the treatment of choice.

Stuart Montgomery questioned these conclusions and suggested that we ought to perform a placebo controlled study in which the issue was not complicated by the offer of behaviour therapy. Montgomery, therefore, performed the first definitive placebo controlled study which established that clomipramine was effective in the management of obsessive-compulsive disorder.

It was about this time that I left Geigy pharmaceuticals as it was then. My reasons for leaving were essentially personal. When I joined the Geigy company, the medical department was based in Manchester and subsequently in Macclesfield. When the merger between Geigy and Ciba took place the department was relocated in Horsham. At that time I had children who had reached crucial stages of their education and both my wife and I had widowed dependant mothers who were growing old and needed our attention. We had a family meeting at which it was decided that although I had been offered an important post in the new department, there was no way that we could leave the Cheshire area. I therefore left Ciba Geigy and with some reluctance returned to part time general practice, setting myself up at the same time as a freelance medical adviser. With one of my new GP practices I also established a contract research organisation.

There are a couple of features of the Geigy experience which ought to be mentioned. At the same time that we were investigating the use of clomipramine in OCD we were also looking at its use in phobic disorders especially agoraphobia and social phobias. At that time the concept of panic disorders had not become well established but looking back I think that panic was a feature of phobic disorders that interested us.

I mentioned that after I left Ciba Geigy I was involved in the establishment of a contract research organisation. The company was mainly concerned with trials in primary care. We recruited and trained GP investigators. Although we worked in a variety of clinical areas we tended to specialise in the evaluation of psychotropic agents. This meant that I had already been involved in the development of general practitioner research whilst at Geigy. I had set up a General Practitioner Research Group and used it extensively for antidepressant studies. I recognised early on that there was a great difficulty in finding suitable or adequate numbers of

patients in psychiatric clinics. One really had to go out into the community and use well trained GPs to look for patients with depression, phobias, agoraphobia and so on.

**Just to chase the Ciba-Geigy end of OCD a wee bit further, how much does the industry create the market? Since Anafranil of course we've had the major surveys in the States which have shown that upwards of 4 million people in the States have OCD and by inference somewhere like 1 million people in the UK must also have OCD. These surveys have been sponsored by Ciba-Geigy, so to some extent we've got a situation where Ciba are now creating the market. Any comments ?**

Yes. I think that to some extent the industry can create a market. If you look back at the history of clomipramine, the idea of using it in OCD started in the Medical Department but I have to admit that I did have the possibility of a marketing advantage in mind. When you are faced with a wide range of drugs, like antidepressants, you are trying to find something which makes your drug of a special interest to investigators and subsequently prescribers. As soon as I realised that there might be something which set clomipramine apart from the other antidepressants, I vigorously pursued it.

Of course as soon as I started to get some favourable results, my marketing colleagues became extremely interested and anxious to pursue the indication. But I have to say that initially the interest only seemed to be in the UK. We got little encouragement from our European colleagues. They came into the project later in the day. I don't think that at first they realised the potential.

The big opportunity, which would not arise now, came when it was time to licence the drug. There is another strand to this story which is what happened to the licensing of drugs. When the evaluation of clomipramine started we are talking about the days even before the establishment of the Dunlop Committee. Eventually the CSM was set up and the Medicines Act came into force. But in those days companies did not have registration or regulatory affairs departments. As far as clomipramine was concerned I literally had to write every word of the submission. I did nothing for 3 months but sit in my office and write it starting with basic chemistry and working my way through to the clinical results. In addition to the documentation in support of the depression indication I also included the results of our OCD studies. We were very fortunate because the indication was approved right from the early days. It would, I think, have been much more difficult now. But, of course the result was that clomipramine was the only antidepressant approved for the treatment of OCD.

At the beginning I don't think we realised that all this had anything to do with the 5HT story. But when we realised that there was an effect in OCD and maybe in social phobias and agoraphobia, we asked ourselves what is different about this drug. When we looked at the profile we realised that although by no means selective, clomipramine was the most powerful inhibitor of the reuptake of 5HT then available. The situation was complicated by the fact that clomipramine is metabolised to desmethyl-clomipramine, an inhibitor of noradrenaline reuptake. We began therefore to wonder whether the use of intravenous clomipramine, and particularly the success claimed by Lopez-Ibor, fitted the 5HT story.

**Just one last point did Arvid Carlsson interface with you at any point or did he get his ideas about 5HT independently?**

No. He did not interface with us. He may well have interfaced in Europe, I don't know, but there was no direct link with us at that time. Later on when we began to think in terms of 5HT, people looked at the more selective 5HT reuptake inhibitors and asked whether the anti-OCD effect was a property common to all of them. They do appear to have this but clomipramine remains the "gold standard" to which everyone must aspire. I believe that in some countries, such as France, you must show that a drug is as effective as or more so than clomipramine before you can have it licenced for the treatment of OCD.

**How does it feel to have been associated with one of the most significant psychopharmacology stories?**

It has been quite a thrill. I would not claim that we started it. It was started by people like Lopez-Ibor but I think we pursued it more energetically than others. What then began to happen was an old familiar story. Everyone at that time thought that OCD was an unusual, bizarre and rare condition but as soon as you have a treatment for a condition you discover that it is more common than everybody supposed it to be. What is so exciting now is that there is a lot of epidemiological work emerging which indicates that OCD is a relatively common condition - a condition also which may be comorbid with depression.

After I left Ciba Geigy the company seemed to be lose interest in psychopharmacology. There was a hiatus when very little seemed to happen. Now they have brofaromine but even that seems to have been allowed to fall behind the competition. I think this loss of interest to some extent extended to carbamazepine especially to its wider potential uses.

I was slightly involved with carbamazepine at one stage when I was leading the psychopharmacology team. Of course the success of carbamazepine was due to the work of Alan Galbraith but his main interest was in epilepsy. I started to pick up the suggestion that it did have some applications in the prophylaxis of bipolar disorder but this was not given a high priority by the company at that time. Now of course it has been developed for that indication especially internationally. To some extent however I feel that Ciba-Geigy opted out of psychopharmacology.

**Why do companies do that. Why do they opt out of what is potentially a huge market?**

I find it difficult to understand but I suppose they had important products in other areas of medicine - like rheumatology and cardiology - which they wanted to exploit and which therefore deserved more interest and attention.

I tend to feel that companies often perceive these areas as 'real medicine'. I believe that the problem we have with psychiatry even pervades the industry, in that people do not consider psychiatry a worthwhile area to work in compared with for example, the treatment of hypertension and ulcers. These conditions constitute proper medicine whereas psychiatric disorders do not. So companies get more excited about anti- rheumatics, anti-hypertensives and so on than about antidepressants. I think this is why Ciba-Geigy lost its way in psychiatry.

**You have had an initiating role in another area of psychopharmacology, namely the psychopharmacology of sex. With recent reports that up to one third of younger men**

**have premature ejaculation problems, something that 5HT reuptake inhibitors may help significantly, this seems an area that is set to grow. Could I get you to tell me how all that came about?**

There were 2 chance findings that started it. The first was at Winwick Hospital in Warrington where there was a clomipramine infusion unit. I used to visit the hospital regularly to follow the progress of a trial. I went into the unit one day and talked to some of the patients. One of them, a bright guy and in fact a research chemist, was being treated for depression. I asked him what he thought about clomipramine and in particular whether he had experienced any side effects. "It does funny things to your sex life" he replied. I asked him to explain. " I come here for five days and go home for the weekends" he said, "when I was beginning to feel better and more interested in sex I found that when I had intercourse with my wife I could not ejaculate. I suspected it might have something to do with the treatment. I did not want to stop taking clomipramine altogether (he took capsules at weekends) for fear of slipping back but what I found was that if I fiddled with the dose I could control the way I ejaculated. I could slow it down or stop it altogether".

I was intrigued with this finding so I contacted Ray Goodman, a sexologist working in Manchester. He too was interested in the observation. Since Ray was running a clinic for the treatment of sexual disorders I suggested he might do a trial of clomipramine in premature ejaculation. He agreed to perform an open study. When I looked at the records of patients in other studies I realised that fairly big doses of clomipramine caused men to have failure of ejaculation altogether and I suspected that even higher doses caused failure of erection. So I wondered what the effect on premature ejaculation was of low doses and whether one could 'titrate' the dose to produce the desired effect. So we used small doses in Ray Goodman's trial and found as little as 5 mg or 10 mg would have the desired effect.

The results aroused considerable interest. The trial also showed that it was not necessary to take clomipramine all the time . It could be taken in a single dose about 4 hours before intercourse. Of course this kind of treatment does introduce an element of planning into sexual relationships - spontaneity is rather destroyed.

About the same time was the second chance finding. In those days we used to receive what were called case report supplements. What happened was that if one of the representatives called to see a doctor and he or she reported something untoward, this was written on the form. All of them came into the office. One of the jobs of the then multi-purpose medical adviser was to answer all these queries. When I came in in the morning there would be a pile of reports on my desk and I would write to all the doctors concerned. One day I picked up a report from a GP working near Peterborough. He had said to our representative "you know that women who take clomipramine can't have an orgasm". I thought this was a very interesting observation for it fitted in with our findings about ejaculation. I went to see the GP who gave me a very good description of a female patient who had been put on clomipramine and who complained bitterly that she was unable to achieve orgasm. When she stopped the drug she was orgasmic again. So we started to enquire more into this area and examine some of our trial reports and found that not only did males report interference with ejaculation and even interference with erection at high doses, but females were sometimes anorgasmic.

It is interesting again, with the benefit of hindsight, to see what is happening now with the new 5HT reuptake inhibitors. There are similar reports of these drugs interfering with ejaculation and sometimes with orgasm.

We have never really got to grips with sorting out the psychopharmacology of this - was the effect peripheral or central? It is something I would like to have done but there was a certain amount of opposition from the company at that time. In fact I got into trouble with the Managing Director after presenting the findings for the first time at a conference in the Channel Islands. I didn't know the press were present - in fact I don't think they were - someone must have leaked the story - but when I walked into the office on the Monday morning following the conference, the MD came into my office, infuriated, and slapped down a copy of one of the tabloids on my desk. "What the hell's all this about George?" There in the paper was the claim that a new wonder drug improves your sex life.

The company was somewhat Calvinistic in its philosophy and I was told "lay off this subject - we don't want this kind of publicity". So I never really pursued it energetically, although I have always retained my interest in the sexual effects of drugs. I ought to mention that after the initial reports we were involved with a number of people, including Barry Everitt, who were looking at what you might call the psychopharmacology/ anatomy of these effects. But as I say we did not pursue it as energetically as we should have.

The idea that the pharmaceutical industry might develop drugs for sexual disorders was something quite unheard of in those days. It is interesting to see that now there are people coming from pharmaceutical companies, as they did at the BAP meeting in Cambridge, saying "here's a great area of opportunity". It has always been one of those neglected areas despite the fact that sexual problems are very common.

**With all the publicity on drug treatment of OCD in the US these days does it ever seem like they are re-inventing the wheel?**

Yes. In the 70s I made several trips to the United States with the Geigy team who were appearing before the FDA in an attempt to register clomipramine. Many obstacles were put in our way, mainly in relation to toxicology, and it became very obvious that clomipramine would not get a licence in the USA for depression despite its acceptance and popularity elsewhere in the world. Eventually we gave up.

Clearly there was a demand in the States for clomipramine at that time especially for the treatment of OCD. I think some was brought in from Canada where it was approved. Sometimes parents and relatives would come to the UK to try and obtain clomipramine. I would be sitting in my office and the telephone would ring from a London Hotel. The caller for example, would say "I have brought my wife over from the States, she has terrible obsessions, can you supply me with some Anafranil?"

Gradually interest in the States grew (there were always a few enthusiasts) and although there was reluctance to accept our original claims, eventually they had to. Recently clomipramine has been licensed in the US for OCD. Now, of course, there is a flood of publications and booklets from Ciba Geigy. Much of what is being said was described in the UK 20 years ago. I must admit I am mildly amused for it does seem like the Americans are reinventing the wheel.

**Could all this have been done these days. Could the OCD story have happened if it were all starting off now?**

I have great doubts whether it would happen now. You have to refer back to the regulatory situation as it was in those days. Then it was possible, as I used to say, to play hunches. I used to like the phrase "flying a kite". I would go to my boss and say "how about flying a kite on this one. It looks as there may just possibly be something in it". You have to remember that serendipity played a major role in the discovery of many medical treatments not least in psychiatry. The discoveries of both the tricyclics and the monoamine oxidase inhibitors in depression were purely serendipitous.

In the early days there was not the strict regulation that there is now. Now, without a CTX at least, my boss would not be able to allow me to play my hunches. So you have to prepare a substantial dossier before you can "just try something" and the company would probably think it was not worth the expense.

I wonder whether companies would play hunches now. They have to go for the 'big chance' and I suppose that in psychiatry the big chance would be depression. The attitude would be that depression is a multi-million pound market and we want our share of it - we can't be 'playing around at the fringes with strange conditions like OCD and phobias". So I wonder whether if history were to repeat itself the same thing would have happened now.

**You've also had a role in setting up the Diploma in Pharmaceutical Medicine**

When I joined the industry in 1966, it was becoming respectable to be a pharmaceutical company medical adviser. But if you look back at the history of doctors in the industry in years gone by they did not have a good reputation. It was a standing joke that the industry was the place for doctors who had been struck off and abortionists. It was the only place where they could work. I'm sure it was not as bad as that but that was the joke.

Those of us who worked in the industry felt increasingly that pharmaceutical medicine should be a speciality in its own right. There were developments, both in the UK and in Europe with regards to accreditation and specialised registration. I, and others, became concerned about how the doctor in the pharmaceutical industry might fit into any new framework. Was he or she in danger of becoming a second class citizen?

At one time you could move about easily in medicine. You could move out of practice into industry then back into practice either general or hospital. As the years have gone by this mobility has become increasingly restricted. You have to do it the right way following the approved training courses. So it became obvious that it was necessary to establish some kind of status for doctors who worked in the pharmaceutical industry.

At that time most of us were members of the Association for Medical Advisers in the Pharmaceutical Industry - AMAPI for short. I have had various offices in the association including that of Chairman. Some of us in AMAPI started to think what we could do to improve our professional situation. We consulted various learned bodies including the 3 Royal Colleges of Physicians. They said they could do nothing until we could establish that there could be a



proper course of training that could lead to a professional qualification. We had to show that pharmaceutical medicine was a subject that could be taught and that pharmaceutical physicians could be trained.

I was serving on the AMAPI Committee at the time and I was given the task of setting up the first training course in pharmaceutical medicine. It was run on a modular basis over a year. Having done this the Colleges then accepted the principle that pharmaceutical medicine could be taught and the Colleges of Physicians of London, Edinburgh and Glasgow agreed jointly to grant a diploma in Pharmaceutical Medicine. The examination came under the aegis of the Edinburgh College and was held there.

The problems that AMAPI then faced was that, by its nature, it was not a training organisation. The course needed to be embraced by some academic institution. We thought that ultimately the diploma would lead to specialist registration. That hasn't actually happened. However, pharmaceutical medicine has now moved farther with the establishment of a faculty. Shortly we will have an examination for membership of this faculty of pharmaceutical medicine of the RCP which will be on the same level as the MRCP, FRCS, MRCPsych or similar professional qualifications.

But returning to the 70's, I and my colleagues tried to interest academic institutions in taking over our course. We found considerable reluctance and we were in a catch 22 situation - if no one could be trained there would be no one for the Royal Colleges to examine. To cut a long story short I eventually persuaded the Welsh School of Pharmacy in Cardiff to take over the course. Since then the Diploma in Pharmaceutical Medicine has become well established.

Cardiff has since also established a course for a Diploma in Clinical Science for clinical research executives or associates who are scientifically but not medically qualified. A course for a qualification in Regulatory Affairs has also been established. I was to some extent involved in the Diploma in Clinical Science and was the first external examiner.

There is, of course, a problem for non-medically qualified scientists working in the medical departments of the pharmaceutical industry. What is their career structure? They cannot become a medical director because by definition a medical director has to be medically qualified - but that's another story which has created problems even with the BAP.

### **Do you want to carry on with that?**

Its an old story really. The pharmaceutical industry was not developed by doctors. In the first place it was developed by chemists and pharmacists. It was not until we started to be concerned about the safety of medicines that doctors were needed in the industry. So in the days when I entered it, doctors were a relatively new phenomenon. One immediate problem was financial as much as anything. The industry found it had to have physicians because the world was changing but the chemists and pharmacists, very bright people, were very reluctant to accept this. Moreover, salt was rubbed into the wound because the industry had to pay the sort of salary that a physician could earn as a hospital consultant or general practitioner, in order to attract the right people and such a salary would be in excess of what the pharmacists and chemists could demand. So you had a situation where you had people who were better informed and had been more involved in the drug development process having to accept

'upstarts' from the medical profession who know less but earned much more. It was a difficult situation at that time.

It was not, of course, quite the same as the CRA situation which in a sense has come about for the opposite reasons. The industry has found that because physicians are so expensive it, can pursue research by employing people with other scientific qualifications, who are not as expensive as physicians. The problem for the CRA, however, is the lack of a career structure. It is not really possible to get to the top of a medical department if you are not medically qualified. To progress you need to move into marketing or product management otherwise you are in limbo.

CRA's have tried very hard to improve the situation. They have established their own professional organisation and they have their diploma but I still feel that they have an identity crisis.

### **Can we pick up your role in the BAP story?**

Those of us who worked in the industry had been meeting with physicians from hospital practice and academia regularly. In my case it was with psychiatrists. But apart from the old RMPA meetings there was no forum where we could all get together. When we did meet it was purely on a clinical trial level. There was a need for a more general exchange of ideas.

### **Who in particular would you meet?**

One would immediately think about people like Alec Coppen and Max Hamilton. We wanted a forum where, as I have said, we could meet not in the context of 'you're being paid for a clinical trial' but in a much freer atmosphere where we could exchange ideas.

I think several people had thought about setting up some sort of association about the same time. That was not really surprising because we all 'chatted' to each other at conferences, at the bar or over dinner. So the same thought would be going through several peoples' minds.

I thought that Trevor Silverstone and I were the first to think about it. We were attending a meeting of the ECDEU in New Orleans. We had dinner together at Antons and breakfast at Brennans. I don't remember whether it was at dinner or breakfast but at some stage we said why don't we set up an organisation in which industry and clinicians can get together. So we returned from New Orleans full of enthusiasm only to find that we had been pre-empted by David Wheatley, Sydney Brandon and Anthony Hordern - all people who I knew well and with whom I had worked in various ways. So I suppose they were the people who really started it. They were the people who wrote the famous letter which started the ball rolling.

Eventually a group of about 20 of us got together in the RSM to set up the organisation. Of course David Wheatley was involved as was Anthony Hordern, who was then working at Kings, as well as Sydney Brandon, Alec Coppen, Max Hamilton and so on. From the industry there was an important person, who doesn't get mentioned nowadays - that's Gerry Daniel. Gerry worked for Squibb and was very interested in schizophrenia. In the first instance it was industry physicians and clinicians who met and I suppose this was at the root of some of the suspicion that other people had for what we were doing.

We had no bad intentions - it was just the way it happened. Initially there were several sources of criticism. For example some people thought we should have set up a body associated with CINP and Philip Bradley. At first he was very much opposed to what we were doing although eventually he joined us.

I was elected to the first council and took the post of meetings secretary. I had the task of organising the first BAP meeting. I am ashamed to say that the result was disastrous. I managed to attract about 25 people to the first symposium at the RSM. When I look at the success of the BAP meeting in Cambridge now I realise how paltry those early efforts were. David Wheatley took over from me and did much better. Eventually the meetings became quite well attended.

I suppose that the first really big meeting was the fateful one in the Channel Islands which created so many subsequent problems. It was something of a watershed really. Perhaps because the impetus in planning the meeting had come from people on the industry side, like Gerry Daniel and myself, our idea was to put on a really superb event, which I supposed we modelled on the kind of meeting the industry would organise. In fact I was very much responsible for the selection of the venue. I had already organised many meetings in Guernsey. So I introduced the BAP to a professional meetings organiser who I knew. He suggested a new hotel in St Pierre Port called St Pierre Park which had excellent conference facilities. We thought it was a wonderful idea - we would have everyone together in the lovely island of Guernsey. Little did we realise what would happen. In a sense that was really when 'the bubble burst' as far as the non-industry, non-clinician side of the organisation was concerned.

The views seemed to be that this was just a 'bun fight' for wealthy clinicians and pharmaceutical company personnel and that the rest of the members could not afford this kind of thing. I think that many of them felt that unless there were changes in the organisation they could not continue to support it. And a number boycotted the meeting. There has never been a meeting like it since. Inevitably we had to move to the frugality of student rooms and university venues.

Of course I was not meetings secretary at the time but because I was involved in the choice of venue, I have to accept some of the blame.

Going back in time I played another role in the association. It needed a constitution. I had been involved in constitutional affairs as a student politician and as President of the Union at Manchester, had been involved in revising its constitution. I brought it along as a model to a meeting and Max Hamilton who was then Chairman, said "seeing as you know so much about constitutions you had better write one for the BAP". So in collaboration with Max I produced the first constitution. Although it has been modified since I think it is still basically the one that we wrote.

**It appears to be the outline on which the ECNP constitution was also built. What were the contents of the early meetings, what were the issues, programmes**

One of the earliest which I set in motion was on the sexual effects of drugs. The proceedings were published as a monograph which I think is still around. This choice reflected my early interest in the subject. As I said I did not make much progress with the company so I suggested that it might be an area the BAP would consider. The meeting was held at Queen Charlotte's Maternity Hospital.

Other meetings were on subjects like the measurement of depression. I remember that one of the first meetings I organised was on the teratological effects of psychotropic agents. I was interested in the subject particularly of drug effects in pregnancy and lactation. The meeting was held at the RSM and I recruited some good speakers but there were only about 25 people in the audience. I was very disappointed. Strange how this has since become an important issue but few psychiatrists or psychopharmacologists seemed to be very interested in it then.

**What about the BAP council meetings during the early days? What were they like, what were the interactions like, what were the issues?**

In the early days they were very friendly. Most of those on council were either academic clinical psychiatrists or people from industry. But gradually others, like Paul Spencer from UWIST, became involved. Most of the problems that we had were arose outside the council. We thought we were doing a decent job and there was a good group all of whom got on very well together. The flack was all coming from outside - from bodies like the Institute of Psychiatry.

**Tell me about the Institute of Psychiatry**

Well, I don't think I really understood why they seemed to take exception to what we were doing. I suppose that in a way I felt they were adopting something of a holier-than-thou attitude. Firstly I suspect that they were extremely wary of any kind of relationship between psychiatry and the pharmaceutical industry. Secondly I think they felt that we were setting certain standards that we were not entitled to.

One of the biggest problems of all was the name. Nobody could think of a satisfactory name for the association. Initially the name British Academy of Psychopharmacology was suggested. With the benefit of hindsight this was foolish since by calling it an academy, we seemed to be establishing 'academic' standards. Perhaps that was what caused the Institute of Psychiatry to object. I suppose people thought of the title academy because there were bodies in the world that took the title 'college' - the ACNP and the CINP for example. You might ask what right has the CINP to call itself a college - its really just a group of people who get together and formed an organisation.

So I think the name had a lot to do with the problem. Malcolm Lader for example objected to what we were doing and so did Philip Bradley. There were also objections from non medically qualified psychopharmacologists who said the BAP was no more than a marriage between the marketing orientated arm of industry and clinical psychiatrists who would earn fees by performing clinical trials.

It took a long time to overcome these prejudices. Eventually we did although Tim Crow never accepted us.

**The other view that was actually put forward by Tim Crow was that if clinical people were going to do proper science they should be in the appropriate scientific organisations such as the British Pharmacological Society, what do you think of that?**

It is all very well to say that but if you go back to where we started the rationale had a lot to do with clinical trials. Psychopharmacology needs well executed clinical trials. We cannot make any progress in terms of applying the principles of psychopharmacology unless we subject products and ideas to proper clinical trials. By the nature of things most clinical trials were set up by the industry. The industry's standards were sometimes open to criticism so we wanted to involve clinicians in a dialogue in order to help improve our standards. On the other hand clinicians would not do many clinical trials without our help. As I have already said we wanted to create a forum in which interactions could take place. It is all very well saying you should join the right society. What society should people who worked in industry have joined if they wanted to achieve these aims? The comment about joining the right society is nonsense really. There was a need for a forum in which the relationship between the people who produced the compounds and those who assessed them clinically could be developed.

**You've had an interest in eating disorders also?**

My original interest in anorexia really stemmed from observations that clomipramine could cause weight gain irrespective of any change in appetite. We received a number of anecdotal reports that anorexics benefitted from clomipramine. The thought we had was that you might be able to institute drug therapy initially and then provide psychotherapy. The issue became somewhat contentious because although some clinicians were using clomipramine others were against the idea of using any kind of drug in a disorder which they considered to be essentially "psychological". I did have some contact with Arthur Crisp but we never really pursued the subject. It fascinates me now to see that manufacturers of SSRIs, whilst not claiming success in anorexia, are doing so in bulimia. But of course bulimia didn't exist at that time. Russell introduced the idea some time later. Nevertheless I did feel that the eating disorders was an area of psychiatry I would like to have explored more. I think recent experience supports the possibility that there may be important relations with 5HT.

**As well as the eating disorders, you've had an interest in sleep?**

I suppose that my interest in sleep began in a very routine way. Whenever you are investigating a psychotropic drug there is a standard package of investigations which needs to be done. This will include studies on the effect of the drug on sleep.

As far as clomipramine was concerned there were a few important spin offs of this approach. We found that with TCAs, especially clomipramine, there was suppression of REM sleep after the first dose. This observation leads one to ask why is it that the drug has a dramatic effect in the brain following the first dose and yet it does not significantly alleviate depression for several weeks. Clearly the drug has entered the brain, and is acting immediately - so what is the explanation?

One thing we did believe then was that REM suppression and antidepressant activity were in some way related. Some people still hold this view. Of course there is a shift in the patterns of

sleep in depression. However at that time it had not been suggested that REM latency might be a marker for depression. Although we had a lot of ideas I don't think we pursued them as vigorously as we might have done.

One thing, however, that we did pursue fairly actively with David Parkes, was the possibility that a compound like clomipramine, being such a potent suppressor of REM sleep might be useful in the management of narcolepsy. The outcome of the trials performed is now reflected in the conventional wisdom that although clomipramine has little effect on narcolepsy itself it is a valuable drug for the management of cataplexy. I think that clomipramine is still the first line treatment for this condition.

Another area of interest which we have not so far mentioned was the management of pain. Again this originated from anecdotal reports that the addition of antidepressants to an analgesic regime was of value especially in some chronic pain conditions. I set up a research project, mainly centred in UWIST and a whole series of papers resulted from this. The group in Cardiff were already interested in opiate receptors.

I think that what emerged was the concept that pain and depression are probably rather similar processes. Depression is, if you like, a kind of mental pain. I think that there is some evidence for a common mechanism. I don't think that it is just a question of low pain thresholds in depression which revert to normal when the depression is treated with an antidepressant. There is some other property of antidepressants that is associated with the relief of pain. We published a number of papers on this subject and I organised several conferences on pain and its management.

It is very interesting to see that clomipramine is still considered to be an important compound even though it has not been energetically promoted since the late 70s. I think the psychiatric community has recognised that it is a drug that has important qualities. For example, it has become the 'gold standard' in OCD and in the area of resistant depression it is still one of the most favoured drugs for inclusion in 'cocktails'. I think it has been recognised that there is something rather special about clomipramine. Even though rather neglected by Ciba Geigy in the UK for 13 years it is, interestingly, still a market leader in some countries.

**Let me switch completely to the issue you raised earlier about GP trials and also the role of Gps in the development of psychopharmacology and the BAP.**

We identified the need for general practitioner trials long time ago and it was for this reason that, when I was working with Geigy Pharmaceuticals, I established a general practitioner clinical research group. I needed relatively large cohorts of patients for some of our clinical trials. It was clear that these were not to be found in psychiatric practice. Even if they existed at all recruitment would take a long time and there were considerable marketing pressures to get things done quickly.

We knew from the results of epidemiological sciences in general practice that, for example, there was a large number of depressed patients many of whom were not being treated. Perhaps we were somewhat ahead of our time when in the late 60's and early 70's we decided to recruit GPs, train them how to recognise and rate depression and then use them as

investigators. I think we were among the first groups to use video film of patients for training purposes and organise inter-rater reliability exercises.

You can draw a more recent parallel when you consider developments with the new anxiolytic agents. If you want to perform trials in generalised anxiety disorder (GAD) and go to psychiatrists in search of suitable patients they cannot find them. The only place that you will find subjects who fulfil the criteria for GAD are in general practice so you have to accept the same policy that we adopted for depression.

The GAD situation raises a more general issue. At different times the availability of certain types of patients is at a premium. When the betablockers and subsequently the calcium channel blockers were being developed a "virgin" hypertensive patient was "worth his or her weight in gold" because every company wanted to put them into clinical trials. This has recently been the case with GAD and in consequence very large fees have been paid to clinical trialists. I must say that I find it just a little disturbing when patients like this in general practice are worth so much.

Certainly I feel that research in general practice has contributed considerably to clinical psychopharmacology. Some of us who were involved in this development were also prime movers in establishing the BAP. I firmly believe that drugs need to be tested in the environment in which they are ultimately to be used. Somehow I feel that the BAP has rather lost its ways in respect of this aspect of psychopharmacology.

### **Should phase II work be happening in general practice.**

There are 2 ways of looking at the question. You could argue that patients in general practice are not particularly "clinically" depressed. They are really people with stress related problems and depressive symptoms who are likely to recover spontaneously and therefore do make good clinical trial subjects. Alternatively you could argue that the patients who psychiatrists see are not representative of the universe of depressed patients. They may be non responders who have had considerable previous exposure to psychotropic agents or their depressions may be complicated by social and personality problems.

I think that if we really believe in the DSM III R approach to major depressive disorder and dysthymia and if we train our investigators properly, large cohorts of patients can be identified in general practice who fulfil the diagnostic criteria. I certainly believe that it will be easier to find them there than in psychiatric practice. By the same token you are not going to be looking for bipolar disorder in general practice - you will only find that in psychiatric practice.

This means that it is entirely justifiable to consider performing phase II studies (late phase II at least) in primary care settings. In a sense this brings me back to my comments about psychopharmacology. Psychopharmacology is not just an ivory tower exercise - important though that may be. If we want to know how drugs behave we will need to know how they are used and with what effect. This then takes us beyond the conventional clinical trial. We have all had the experience of trying to extrapolate the results of clinical trials to everyday practice only to find that some of the optimism expressed was unfounded.

**In terms of who actually makes the contributions to psychopharmacology who do you think it is, do you think it is the marketing people or is it the people who "see" the molecules, the chemists**

The truthful answer has to be that they all do. Looking at the question historically I think that it would be fair to say that in the early days scientists made little contribution to the development of psychotropic agents. Clinical observation was more important. Two of the most important advances - the discovery of the MAOIs and the tricyclics - were entirely due to serendipity.

Following the clinical observation that these substances relieved depression, the scientists looked at their actions discovering for example that tricyclics inhibited the reuptake of noradrenaline or 5HT. To assume however that these observations explain what is happening in depression is a rather large. The 2 may be totally unrelated. I suppose that when you see how nowadays scientists can "construct" compounds that "fit" receptors there is a lot more "science" about than there used to be. Nevertheless, we have to be very humble and remember that some very recently introduced psychotropics owed their discovery to a large element of serendipity.

It is not just clinical observation or science, however, that determine whether drugs succeed or not - political, economic and commercial factors all play a part. We should not lose sight either of what might be called cultural considerations. Diseases are not universal - they exist in some cultures and countries but are unheard of in others. I well remember when I worked in the industry being asked to organise a clinical trial programme on psychovegetative dystonia. I was told that it was a very common condition (in fact in one European country it was the commonest reason for sickness certification). I never really found out what it was never mind showing the effectiveness of drug treatment. One of the great imponderables about marketing drugs is why drugs succeed in one country yet totally fail in others despite trials being done in the same indications, using the same protocols and employing 'the same rating scales'. There are many examples of one country's 'best seller' being a non entity in others, such as viloxazine in South America and maprotiline in France.

**Is part of the problem that we have had no really new drugs since the mid 1960's.**

You could say since the late 50's. Yes I think it is. We have made great strides in reducing side effects and toxicity but as far as clinical efficacy is concerned we have really made very little progress.

**What about the question of risks and benefits. Are we going to end up with no clinical work at all?**

This issue worries me very much. The relationship between risk and benefit has changed dramatically and I suspect that the pendulum has swung too far in the wrong direction. I accept that one of the principles of medicine is "first do no harm". But we are in danger of reaching a situation where in trying to avoid doing any harm we do not do any good either. Risks that were once acceptable are now unacceptable. Everyone - patients, doctors and particularly lawyers - have to accept that there is an element of risk in every medical procedure. When I am asked this question I always recount one of my early experiences as a house officer when I saw a young, healthy 21 year old die from swallowing an aspirin. It



sounds ridiculous - he had a headache, swallowed an aspirin, had a gastric bleed and no-one could stop it.

It seems now that we are reaching a situation where no risk however slight can be accepted .  
Medicine is becoming increasingly defensive. Drug evaluation is particularly vulnerable.  
Because of such problems as indemnity, insurance and the use of placebos we could find that it is virtually impossible to perform clinical trials. I think we shall never again be in a position to 'play hunches' like we used to do.