THE ROLE OF BEHAVIOURAL PHARMACOLOGY IN PSYCHOPHARMACOLOGY
BRIAN LEONARD

Did you do pharmacology in University?

No. I did a medical biochemistry degree at the University of Birmingham from 1956 to 1959. It was a unique course in that those selected for it, of which there were only a maximum of 6 for any one year, were interviewed and the interview was primarily to find out those people who at a very early stage had an interest and a flair for research. Birmingham was essentially a research department, where there were something like 3 to 4 times as many postgraduate and staff members as undergraduates for the 3 year course. The other unique thing about it was that all of us had to get an ordinary degree in chemistry as part of our 3 year honours degree course and at the same time had to attend several of the basic science courses and some of the clinical courses that the medical students attended. The whole idea was to equip us as bench scientists but with quite a strong orientation towards clinical applications. It was the only course of its type in the country.

And what led you from that to pharmacology?

Well, it was a joint department of medical biochemistry and pharmacology. In the final year of the BSc course, we had a course in neurochemistry with Brian Ansell, who was the senior lecturer in Philip Bradley's department. Philip Bradley was again unique, as you know, he was the only professor of neuropharmacology in the country. So we had a two month course, including some practical work, where I came into contact with both Brian and Philip. There was just something about the CNS and the brain that I found exciting - it was nothing more than that; it was just a feeling that this was interesting.

An opportunity came then once I got my degree to do a pharmacology project. A grant came from the Tropical Products Research Institute, which was part of the colonial office in London. Alistair Fraser, the head of department was a World Health Organisation adviser on tropical diseases and he had very good contacts with things like the colonial office and so consquently this grant came into the department.

It was a grant for a post doctoral fellow together with one PhD student. The post doctoral fellow was a biochemist called Stan Sherrit, who's now working in the pharmacology department in Newcastle and he took me on as a research student. Basically he was not a pharmacologist and right from the very beginning, his approach was a biochemical approach. We had to look at a number of tropical products from Jamaica which were being used as medicinal plants. One of my first jobs was to screen about 100 plant extracts, which were sent over from Jamaica to us for testing.

Now that was extremely important because it meant that I had to learn - there was no-one there to teach me - how to screen plant extracts for pharmacological activity. It was a case of self- teaching. I had only had a small amount of specialist training in pharmacology. I had done quite a bit of neurochemistry because between times I had also gone down to the Institute of Psychiatry, to McIlwain's Unit, and done a short postgraduate course with Henry McIlwain and Richard Rodnight. And that taught me how to approach the neurochemical aspect but not the pharmacological aspect. So really for the first year, there I was in a laboratory which was not primarily oriented to the broad areas of pharmacology but having to produce results and therefore you learn with your fingers and that's precisely what I did.

One of the plant extracts came from the Jamaican shade tree called pithecolibium samanth benth. This contained a number of alkaloids which were being extracted very crudely and used

for treating unspecified mental illness but also for lowering blood pressure. We managed to work with a chemist in the University of Jamaica who isolated and partially purified some of these and he sent us the semi-purified alkaloids which I started working on. I then had to do a general pharmacological screen for activity on the gut, on blood pressure, on the cardiovascular system and so forth but then I could also now start looking at the brain because some of these alkaloids were convulsants and this really led me right into neuro- and psychopharmacology. So, I could then use all my experience in the area of neurochemistry to look at how the alkaloids were possibly affecting intermediary metabolism and so forth which was very important when understanding how the convulsants work. And at the same time from the pharmacological point of view I could start actually looking at antagonists and so on and get some idea as how these things work. You have to remember that we had no idea how convulsants were working.

In fact my first paper on the pharmacological properties of these alkaloids was published in Nature. In those days it was very easy to publish in Nature. Now you can't publish unless its in the area of molecular biology, which nobody understands and it's probably irrelevant anyway. In those days it was much genuinely broad journal for science, representing a range of different areas and scientific interests. That's where I published my first article and including the first self-experiment.

One of the tests I did was a local anaesthetic test. You could do this on the response of the guinea pig to pain following a subcutaneous infusion of the suspect local anaesthetic and we found that this compound did apparently reduce the response to pain. We then looked at a standard frog preparation and again the same thing happened. So we thought that it may be a local anaesthetic and what my supervisor and myself did was to send a sample over to the hospital to get it sterilised and then we each injected one another on the forearm to see what would happen and indeed we did find that it was a local anaesthetic. The problem was that we noticed that the numbness continued for a long time. In fact the numbness led to a necrosis. What we had done was to kill off the nerves cells and skin.

Because these alkaloids were going to form the centre-piece of my PhD, I also got training in toxicology because there was a section of the department specialising in toxicology. So it meant by the time I had finished in Birmingham I got a bench training - hands-on training in biochemistry, specialising in neurochemistry, general pharmacology, general toxicology and some neuropharmacology. No psychopharmacology as such. But the other important thing was also working during that time with Michael Chance.

He had a sub-department of animal ethology as part of this department of pharmacology and toxicology, biochemistry and mental biochemistry - Euan Grant, John MacIntosh and Michael Chance. Now in the area of ethology these people have really been very important and they are still going. Basically what they did was have colonies of wild mice and wild rats and they were actually for the first time really looking at the behaviour of these animals from a social point of view. So social ethology.

Where did they get this kind of idea....

It was very revolutionary at the time. Michael was trained originally as a pharmacologist but he was interested in ethology. Euan and John were trained as zoologists. So they came to the department of zoology to work with Michael to look at social interactions in wild rats compared to white rats which are highly inbred and probably don't show a lot of the complexity of beha-

viour that you see in the wild. They had runways and so forth with glass fronted one-way mirrors in front, so they could observe the animals in a natural as possible environment, looking at their interactions and different types of behaviour. They worked out, I think it was dozens, if not a hundred or more, different behavioural interactions which had meaning for the animal. This was long before computers. They had a system of coding to code different behaviours - when a strange male, for example, was put in a runway with the normal host male and that sort of thing. Now they took this one stage further because they then introduced drugs like barbiturates - you've got to remember this was all before the benzodiazepines and so forth, so there weren't that many. Or leptizol for example, a stimulant and then looked at the effects on drug treated animals with normal animals, in terms of social behaviour.

They showed me all these methods and what I tried to do was to simplify the methods to try and make it practical so that we could possibly bring a new dimension into drug testing in terms of the effects of drugs on social behaviour in mice. It wasn't terribly scientific on my part but it probably was, in retrospect, extremely important in bringing out the whole idea of studying the sort of behaviours which are relevant to the animal and then looking at drug effects on those complex social interactions - both acute and chronic drug effects.

What Chance and his colleagues were trying to do was to simulate what was happening in the real world of the patient. Because they also had, at the Uffculme Clinic in Birmingham, which was a psychiatric clinic, an opportunity to spend some time there looking with one-way mirrors at the behavioural patterns of patients. So there was a psychological dimension to this as well, which they then tried to see if it would simulate in any way in animals. This whole concept, retrospectively, I think was very very important because it did bring into this whole business of animal studies the idea that they are invaluable but only invaluable if it has meaning for the real world of the patient.

Who else was in Birmingham at the time. Obviously Philip Bradley ...
Philip Bradley, Brian Ansell ..Joel Elkes had left many years before ... Brian Keay was there. If you look back at the original work on chlorpromazine on the reticular activating system, for example, it was Bradley and Keay, who did it all. I knew these guys personally. We would have coffee together. Even as undergraduates, we were treated as though we were postgraduates. There was no such thing as staff, technicians and students. It was a small department. We all had coffee together and therefore you were expected to have opinions. And in our training for example, right from the second year onwards, there would be weekly seminars and we were expected to perform at least twice a year, in front of the whole class and staff, including the professor.

Among the others there was Robert Schneider, who really taught me what pharmacology I know. He was a colleague of Edith Bullbring, a German Jew who came over here in 1936. Interesting Quaker background, so not a religious Jew, but who was the only trained pharmacologist in the department. His interest was primarily in gut pharmacology but he taught me the discipline of setting these things up reproducibly and in fact we did several practical demonstrations together for the British Pharmacological Society.

Alistair Fraser I think was extremely important to me for 2 reasons. One his dedication to science. An extremely powerful figure. Very old fashioned in many ways. Quite authoritarian. What he said went; this was an empire and he was in charge of the empire. No one ever doubted what he said. He insisted on high standards of research. None of us were ever allowed to present, for example, at a British Pharmacological meeting or anywhere like that

unless we had been before the Professor. And it was always sound criticism. We were all taught right from the very first seminar as undergraduates, there are ways to present - you don't read and this sort of thing. So these standards of scientific and written communication were all part of the training.

How about clinical people like Alec Jenner.
When I started my PhD, that Unit was already breaking up. It had contained Alec Jenner, Alan Bolton, Peter Ramwell, again a biochemist. There were several technicians who were quite important on some of the early papers but again not known internationally. But Alec was really the centrepiece there - the circadian rhythm hypotheses all started there - he then went on to Sheffield. Now I didn't know Alec at all until much later on when in fact the Brain Research Association started with John Dobbing and people like this. The Brain Research Association was one of these anarchic organisations which was set up during the late 60's, which aimed to cross fertilise all the neurosciences from clinical right the way through.

An early BAP ?
Well it was much wider than the BAP. It brought in neuroanatomists, neurosurgeons, neurologists, some psychiatrists, a lot of behavioural people in the area of what would be brain and behavioural research now. Memory men, Steven Rose, for example was very much involved in the early days. Its kept going but its not as active now, not as well known but at that time it was quite important and Alec had a sort of peripheral interest in that, so that's really where I met Alec.

The guiding spirit behind the BRA I suppose would be John Dobbing who was the Professor of Child Development or something like that. He was a clinician but he also had a lot of interest in neuroscience. There was John Smart and Jen Sands at Manchester and they were very much involved in developmental psychology but looking at the behavioural aspects of development in animals and this sort of thing. Patrick Wall, in London, you know the famous pain man, was involved and Derek Richter.

Even as late as the early 60's you had a bunch of the physiologists really not being prepared to concede that chemical neurotransmission was for real despite the work of Marthe Vogt, John Gaddum, Derek Richter and others.
That's right but they had no impact on me at all. The impact came from the biochemists. For example, Crawford who was working in Gaddum's old laboratory in Edinburgh, was for a time working in the Queen Elizabeth Hospital in Birmingham which was allied in a way to our medical school. Robert Schneider knew Crawford and Robert's chief technician learnt how to set up the fundus-strip preparation to measure 5HT and I then learnt the fundus strip and how to measure 5HT. At that stage I didn't know what the hell 5HT was. It was something to do with the gut. Edith Bulbring's work on peristalsis had implicated it. That to me was the importance of 5HT. It was the gut. At that stage we all knew about D-receptors and M-receptors from Gaddum's work. But the neurotransmission angle only came in with talking to people like Brian Ansell and from going down to McIlwain and Rodnight's department.

Henry McIlwain's name is one that comes up every so often; was he important?
McIlwain was a wonderful eccentric. A very shy man but with an intense love of science, very dedicated as a teacher. If you look at neurochemistry in Britain at that stage there was only one unit and that was Henry's unit in London. In terms of the really fundamental work on brain slices for example - there's the McIlwain chopper which we still use for producing extremely small 1mm squares of brain tissue - then there was basic work studying respiration, studying

intermediate metabolism and studying the effects of drugs on intermediate metabolism. That was all Henry. If you look at the Biochemical Journal in the 30's 40's 50's, it was all Quastel or McIlwain. It was all in vitro work but nevertheless very important in laying the basis for looking at drug effects on metabolism - that not all drugs are working just on receptors, there is also is a consequence of that.

The only other group was the Richter group, which by the nature of the MRC was very much concerned with clinical aspects. To my mind that was an enormous weakness that there wasn't more cross fertilization between these groups. And I think personalities could have come in there because McIlwain was an extremely retiring sort of person. He wasn't the sort of guy you could have a joke with. He was quite reserved. Quite removed from his students but a very dedicated teacher.

He would run these courses that would last for a month to six weeks and I was lucky enough to be sent on one of them. It was 80% bench training. Now this is the difference between what is happening now in universities and what was happening then. Neuroscience is a practical science and a lot of it gets worked out on the bench and if you can't bloody well do it, go and do something else. So all of us were trained as bench workers. You thought with your hands.

What about the frustration a great many of these people, I'm thinking of Derek Richter in particular, had in terms of getting the clinical people to co-operate..
I think that's true but one thing to my knowledge never happened even at biochemical society meetings, because I used to attend biochemical society meetings, particularly the neurochemistry group, which was another very important way for us youngsters to move forward - you had the Brain Research Organisation and you had the Neurochemical Group of the Biochemical Society which was very active then - these were the sort of, if you like, professional groupings that we were allied to but you very very rarely saw the Richters and McIlwains coming together in terms of symposia and saying well now we're going from the brain slices through to man.

Richter did try and put together a few meetings through the 50's doing just that, trying to bring Elkes and the physiologists and the biochemists together in one place.
This is true but these were international type meetings. They didn't have an impact on us. We couldn't go. There was no money. Nothing whatsoever for us to go. So unless we were very lucky to have a head of department who says "well look there's a course now would you like to go on that course, or I'll send you on that course". By and large even going to Pharmacological Society meetings we paid out of our own pockets. You just lived cheaply and hoped for the best. So in terms of the impact on people at the bench level, you read it in the literature and so forth but these meetings didn't have much impact.

So, that was basically the Birmingham period. As I say, having to teach yourself, I have always felt was extremely important. You make terrible mistakes but you learn to think. You learn to challenge yourself at the bench and this was what we were all encouraged to do. You do the experiment and then argue a case against your peers within the group and they spared nobody. And that I think led to scientific independence and a critical faculty. If you weren't critical someone else was going to shoot you to bits and sometimes it was extremely tough. The Birmingham experience was probably the most important thing I had ever done. Being in that sort of atmosphere, which I have never been in it since. I've always been the loner since that time. Never had that sort of intellectual stimulus and cut and thrust which you can get with

dedicated scientists who are really turned on by what they are doing and excited about science. It was a unique experience which I think is largely dead now for all sorts of reasons and I think it's a great pity for young people.

Was there there same atmosphere throughout the UK at the time or was it particular to Birmingham? It did feature as one of the centres for emerging neuroscience...
I think there was a lot of optimism in Universities then. I can't judge - I was only at Birmingham and Nottingham in the UK for any length of period but I think there was a totally different attitude. There was a lot of optimism. Money was going into the universities. The Robbins report had come in the 60's and the whole idea was that you've got to open up Universities by putting money in and by looking at the whole educational system - why is it that the percentage of working class children going to university has not changed since the middle 30's and yet we have free education and all the rest of it. What the hell's going on and this was the first time that a Labour government attempted to try and reddress this. I think that was reflected in the whole ambiance of the University.

Admittedly we had a big advantage because all of us knew once we had got that degree, we were getting jobs and that made it worthwhile. Although I don't honestly think it would have made a difference because that the way we were. That was the ambiance of the University. You weren't doing the degree to get a job. You were doing the degree because you bloody well wanted to do it. And you were selected for those courses right at the very beginning because that's what you wanted to do and you didn't want to do anything else. For example, the year I was in, there were 5 of us, everyone is a Head of Department or a Head of a big Clinical Biochemistry lab. And that's the way it went until Fraser died - he had a heart attack and they amalgamated the department - and the whole thing changed.

From Birmingham you went to Nottingham.
Nottingham was a pretty clapped out University at least as far as science was concerned. There was a School of Pharmacy obviously set up by Jessie Boot and the major Chair in the School of Pharmacy was endowed by Boots. The School of Pharmacy was in temporary buildings. I applied for the lectureship and in fact I think I had just done my oral in Birmingham, when I was called for interview and offered a full lectureship in pharmacology in the School of Pharmacy. Jimmy Crossland was the Reader of Pharmacology. He had worked with Derek Richter way back in the old days in the Whitchurch Hospital in Cardiff. He was renowned for his work on acetylcholine in the brain and I suppose because of my interest in the CNS and I knew of Crossland's work, never having met him, I went there and I was very pleased to have a job so quickly. Basically I was responsible for some of the CNS teaching on the biochemical aspects of pharmacology which is what I did for 6 years.

I suppose to some extent out of my PhD work on the chronic effects of psychotropic drugs, and at that time Crossland had a vague interest in sedatives and barbiturates, we developed, I think for the first time, an animal model of barbiturate dependance by using sodium barbitol which is a long-acting barbiturate. We used it in drinking water whereas before people had been injecting the stuff, which gives you problems with central depressions and so forth. So really what I did was to start low doses in drinking water and then increasing the dose over a period of 2/3 months until you got dependent animals.

Then the trick was to actually look at what happens to the behaviour and again this was a novel area. I started doing work on multiple t-mazes. Now these experiments would take 2 or 3 months, every bloody day, including Saturdays and Sundays. You would have to go in and

work and by that time we were living in Nottingham and I had 2 kids and the kids would be on the back of the bicycle and one on the handle bars, going in to feed the rats on Sunday. But it was again broadening the behavioural studies and including also what I had learnt of the biochemistry. So for example, I did quite a lot of work and published it in biochemical pharmacology on intermediate metabolism, ATP, phosphocreatine and so forth, during dependence and withdrawal and seeing how the biochemical changes in high energy phosphates correlated with susceptibility to seizures and that sort of thing. Now at that stage we had just got the fluorimeter, a very old fashioned ..

That had come in just then?
No they had come in earlier but they were only becoming available for more general use during the 60's. The spectrophotometer was still being used for doing all our enzyme assays but the spectrophotofluorimeter was where you would produce a specific fluorophore which would fluorescence when specific wavelengths would activate it and that enabled us for the first time to accurately measure serotonin, dopamine and noradrenaline in brain. Before you could only measure those by a bio-assay. We were using the frog rectus abdominus muscle for example for measuring acetylcholine. And in fact it is still the most widely used method for measuring nanogram quantities of acetylcholine in the brain. There is still not a good replicable, HPLC or fluorimetric method for measuring acetylcholine in brain tissue.

So, the spectrophotofluorimeter was a real advance. They were still considered to be fairly sophisticated instruments in the middle to late 60's. We were lucky in Nottingham to have one and we used it to measure noradrenaline, dopamine, serotonin by using column chromotographic techniques but also using solvent extraction techniques. So you're talking about methods that were very laborious and retrospectively not terribly accurate but that it was the best we had at that time. Our work involved looking at chronic drug testing, looking for behavioural correlates of the chronic treatment and always looking for neurochemical correlates of the behavioural changes produced by drugs. I had 3 PhD students when I was at Nottingham, all of which have done well subsequently.

Another important thing during the Nottingham period was that I had my first sabbatical in the German Democratic Republic which was again a very interesting period. Politically I was still very active; this was an intense Cold War period and so on and as academics it impacted on us. I had been investigated by the Special Branch when I was an undergraduate at Birmingham - totally illegally. They actually raided my room. In fact some of the staff at the University actually protested about this on my behalf. So we were in a very vulnerable position. In Universities we were still safe. But outside the University it was a totally different matter. I was more or less told there were certain jobs that you will not get so don't apply.

But anyway during the latter part of the 60's, I was in contact with the Physiology Department in Birmingham, with Peter Ramwell and Ian Bush, who was the Professor. They had gone and taken their whole team to the States, to the Worcester Foundation and they were doing very very interesting work on the neurophysiology of steriods. During my period on staff in Nottingham I had looked at the chronic effects of ACTH on behaviour and showed for the first time that not only does one lower the seizure threshold but that you get a facilitation of learning and memory with steroid hormones. With the contacts with Bush and Ramwell and so forth I thought it would be very nice to follow up this whole business of the action of steroid hormones on brain.

They arranged everything for me - a 6 months research programme, money everything. A letter came through and so forth. So I went to the American Embassy and showed them all, yes fine Dr Leonard, now I want you to fill in this form and like a fool I was honest and on the form was "have you been or have you ever been or are you a member of these organisations" 1 - communist party, 2 - the British-Soviet Friendship Society, 3 - Campaign for Nuclear Disarmament etc etc, to which I put tick tick tick and 3 minutes later the man came back and said "well Dr Leonard we've got too many goddamm commies in the United States as it is, this is going to take a long time". So to cut a long story short I couldn't get to the States. And I was pissed off because as I say I was due this sabbatical period and I thought what the hell do you do. So through my other political contacts I was told well look there's a very interesting man in Leipzig who has spent 2 years working with Derek Richter

Who was that?.
Dietmar Biesold. He was probably the best trained neurochemist in the whole of the East block and he was trying to maintain international links. So I thought about it and thought why the hell not. So I went there and spent 6 months actually working with the Brain Research Institute in Karl Marx University in Leipsig. I was the only pharmacologist but I had training in biochemistry and this was grand. What we were working on was a very interesting area of neuro-ontogenesis, in other words looking at the neurochemical development of the brain in the rat - from one day old rats right the way through to adolescent rats, at the actual developments in hexokinase for example and shifts in glucose metabolites as those enzymes mature.

Now being a pharmacologist with an interest in behaviour I was of course interested in not only learning all the enzyme techniques but also then I introduced some basic behavioural methods into their group for assessing development and also looking at drug effects. This was a contact which I maintained and I still maintain with that group, which is still going despite all the appalling things that have happened since the wall came down.

Biesold himself was very much an anglophile but he was very patriotic. He was one of the few people who had left the party in 1953 following the Workers Revolt but because he was so good professionally and he had all the contacts and so forth they couldn't do much with him and so he was more or less allowed to carry on as Head of this Neurochemistry Department in the Brain Research Institute. Eventually he became Head of the Brain Research Institute and maintained international contacts right through the worst of the Cold War. He had Westerners from France, from Finland, from Holland, from Britain and from Ireland, actually going in and working in his lab and some of his youngsters coming out and working in their labs. He also maintained what I would call the best aspects of socialist thinking at that time in terms of open and critical discussion of what was going on around him indeed as well as highly critical discussion of what was happening in science in the West, which he knew.

When you came back you moved into ICI. My impression is that working within the industry in Germany and Switzerland from the late 19th century was very respectable. However, it was not so respectable to work in the industry in the US or the UK. Did you think when you were moving over to the industry in 68 that this was the end of the academic career in a sense of being able to move up the University ladder or in terms of being able to be appointed to offices within academic societies etc.
At the time I must say I didn't plan things like that at all. The thing that motivated me then and now is research and where can you do research. By '68 certainly the Department in Notting-ham was very sterile; nothing much was happening, there were no grants coming in. It was

quite an authoritarian structure as well. I personally felt that I ran the risk of becoming like so many British academics before and since - frustrated so you give up - after all there's nothing to make you work. You do your bit of teaching and that's it. You've got a good job, a pension at the end of it, long holidays if you want to take them, which many of them did within that Department.

And so you either then accepted that that was going to be the future and you just specialise in growing roses and flitting around at home or alternatively say enough is enough, I've had my experience with teaching and okay I want to do something else - full time research. This was the only way open at that time to do it. I had been to talk with Alec Jenner about the possiblility of going to an MRC Unit and there was nothing. Everything was very insecure - grants, post-docs, senior post-doc fellowships, okay you get them for 2 years, 3 years, maximum 5 years but by that time I was married with 2 kids, I wasn't willing to take that risk without security. Therefore when the job came up with ICI, I took it.

They didn't know what they were taking on but they gave me a lot of freedom. I can't remember ever in the 3 years that I spent there doing any screening work or any work of any possible use to them. Basically they wanted somebody to come in and set up, what we called neurochemical pharmacology. David Greenwood was the other youngster with me at the time. David had come from the University of Dundee. He was trained more as a pharmacologist. I had unlimited facilities for doing work, a couple of technicians to work for me and I could travel. This was a situation that I had never had before.

I think I published over the period I was in industry, both in Britain and in Holland, something in the order of nearly 80 papers. I intended that deliberately. If a compound had not been patented and I couldn't publish something, I wasn't going to touch it. So everything was done with a purpose and it was great fun. On the scientific side it was very productive but in terms of the politics it was appalling.

What came out scientifically.
Well there were two areas. I had long been interested in hallucinogens and this was work that I started in Nottingham. Along with one of the PhD students, we found one or two interesting things. One was an endogenous substance that modulates behaviour. This was a compound found in all mammaliam brain, including human brain, that had two effects on mice - in a low dose it produced a sort of coma and in a high dose it produced convulsions. I published a number of papers in Neuropharmacology on this material. The best we could do in terms of identification was to establish that it was as a glycopeptide. We still don't know what it was but a fairly low molecular weight glycopeptide.

At that time I had linked up with David Shaw, in Derek Richter's Unit, to get human brains from schizophrenics who had committed suicide and from control examples. And we found that there were differences in concentrations in this material. But the trouble was we never managed to identify it chemically. I never managed even in ICI to get the chemists to come along with us and tell us what the hell this stuff was. And I wasn't competent to do this. So that's where it stayed.

The other area that I was interested in while at Nottingham was drugs of abuse. Now that started with the early barbiturate stuff and then we started looking at LSD and hallucinogens. And that's where I started really getting into the whole business of neurotransmitters and

changes in brain dopamine etc. I continued that in ICI, where we had facilities to do all these sort of things - anything you wanted to do in terms of machinery, rats and things.

The work on hallucinogens there had an interesting connection with Porton Down, which I didn't know anything about. I was just told when I got there "oh you're interested in hallucinogens, that's interesting, well would you like to look at these different types of substituted tryptamines". It was wonderful. I had a whole pile of about 20 different substituted tryptamines and they said "we know nothing about these things at all, why don't you look at them". So I did and published a lot of biochemistry on them in Biochemical Pharmacology.

Then I had a telephone call from a guy from Porton Down, one day. And he said "oh I hear you've been doing some work", so I said "yes, it's quite interesting, I've sent the results in for publication". "How would you like to come down and talk to us about it?". This was really very interesting because I thought with my politics and everything "Jesus have they not twigged". So I said "yes I'll come, no problem at all". And I did. I got into Porton Down and was shown all around. Everything was very hush hush as it is in places like Israel. I naturally played stupid and asked questions about it. This was the Cold War period and the whole thing was being shared with the Israelis and so forth. Obviously there was a direct link between ICI and Porton Down for this type of research and I had come in on the periphery of it.

But anyway to cut a long story short, what I did then was to start some work on viloxazine, which was just coming in. Viloxazine was purely a spin-off from the beta-adrenoreceptor antagonist programme which Jimmy Black had started way back in the year dot with propranolol and so forth. In fact there was bugger all drugs in ICI at that time. They were still making their money on halothane, propranolol and one of the lipid lowering agents. They had virtually nothing else and their patents were going to expire so they picked up viloxazine fortunately. Dave Greenwood did a lot of the basic work on viloxazine and because of that I started getting interested in antidepressants and I thought this was an area that we should now be going into.

It was at that stage that I had a run in with the senior management at ICI over my politics. I was asked by a left wing newspaper to comment on the annual report for the Association of the British Pharmaceutical Industry, as a pharmacologist. So I did and it was published in London and within less than 24 hours I was in front of the Research Director. Very red faced, very angry, he threw down a photocopy and said "what's this". My name, Brian Leonard, was on it - not Dr Brian Leonard, and no address. Brian Leonard, Research Pharmacologist. They traced the whole thing through from Millbank, the Headquarters in London, to me. "What's all this?". So I said "it's what I consider to be an objective commentary on the Association of the Pharmaceutical Industry report, which I was asked to do" and I said "I don't think it's got anything to do with ICI, ICI's not mentioned. My title's not mentioned. Just a pharmacologist. I'm a private individual". "You work 24 hours a day in the industry, your only loyalty is to ICI, don't forget that. You are not going to get on very well in this company are you?" and that was it. I said "well, I think what you've just said is totally illegal and that I have a right to my own opinions".

Within 3 months I was in Holland. Mike Barratt who was Head of Pharmacology when I first went to ICI had left less than a year later and gone to set up a Pharmacology Department in Organon in Oss. Mike, shrewd politician that he is, realised when we met at a Pharmacological Society meeting in the summer, that I wasn't getting on too well with the management, and he said "have you ever thought about going abroad?". I said "not really" and he said "Holland's quite nice and they've got an interesting set up, very different from ICI, why don't you come

over some time and have a look?". So I went and looked and what they wanted basically was someone who would set up a Biochemical Pharmacology group to work with the behavioural people on a drug, which they couldn't understand, but it seemed to be an antidepressant, called mianserin.

I like the Dutch. Very tolerant people. Again very good facilities and certainly status wise they seemed as if they were going to treat you seriously. And there was a chance which I never had in ICI of really linking behaviour directly with the biochemistry and setting the whole thing up. The real challenge for me was to establish how the hell mianserin worked? The drug had been found purely by chance in a clinical setting on volunteers.

How?
It was developed originally, based on animal models, as an anti- migraine drug. And it was a very good anti-migraine drug. Sicuteri tested this in Italy; he was one of the many people involved in the serotonin hypothesis of migraine. He had shown that it was something of a serotonin receptor antagonist. Okay, it was clinically effective but it was shown to have a very sedative profile and a slightly hypotensive effect.

As it had an obvious sedative profile, the question was what's it doing in the brain. It was known to be an antihistamine and the suggestion was that this was just an antihistamine effect. Anyway it was then tested by Turan Itil in New York, who was very very much sought after then because he had a method of analysing the power spectrum of the EEG in volunteers and he could show that standard antidepressants produced a certain change in the power spectrum of the EEG. And he looked and said that the effect on the volunteer EEG is almost identical to imipramine, had the company ever thought of looking at mianserin as an antidepressant?" Organon said "no, because it doesn't do anything to do with the reserpine reversal test". That was our thinking at the time - totally mechanistic. Anyway, this led to an open study in depressed patients which showed it was antidepressant. It then went further and one of the first double blind studies was done in Cork in Bob Daly's department. So this caused a problem - we had an antidepressant that was not working like a MAOI or a tricyclic in any of the animal models or other tests. How could this be explained?

It has always hit me whatever about mianserin's credentials as an antidepressant, its effect in dismantling the orthodox theories and promoting new thinking has always been underestimated
Mianserin I think is totally under-estimated for its importance in the whole area of depression research. Because it was really the first genuine atypical antidepressant. There had been iprindole but that wasn't very potent. Mianserin was well established as an antidepressant. It's anticholinergic profile was negligible; our pharmacology department had shown very early on that it had virtually no cardio-toxicity. It was genuinely the new article.

So working with the behaviourists and basic pharmacologists and so forth, we thought "what the hell is going on with this compound". So I was worked on the neurotransmitter end of things and Henk Rigter and Henk van Riezen worked at different aspects of the behaviour and it was at that time that we realised that we had to look at chronic animal models of depression. We had got it all wrong. The reserpine model was just rubbish - all this acute stuff was not relevant because we had already shown that there were differences between the acute effects and chronic effects of mianserin on the turnover of amines in brain. Something was happening which could only happen chronically.

So this led you to the olfactory bulbectomy model?
Yes. It was just at that time that Keith Cairncross early in 73 had come on sabbatical from Australia to Manchester and Henk van Riezen had met him at a British Pharmacological Society meeting, invited him over to Organon and we all got together and had a chat. Working as a PhD in 1971, Keith Cairncross had shown that when you removed the olfactory bulbs of the rat, there was a hyperactivity which could be attenuated by chronic but not acute treatment with amitiptyline and also there appeared to be changes in noradrenaline.

Why would you ever do something like that .
Because if you look back, there's a literature that goes back to about 1911, to Watson working in the States. Presumably one of these experiments done purely by mistake. Anyway he had damaged the olfactory lobes of the rat and found that the animal became irritable and pugnacious. We now know that that rat was probably much more damaged than just the olfactory lobes. It had damaged the frontal cortex and therefore as a result cortical damage and so forth you got these changes.

This was followed up by a woman in New York called Pohorecki who looked at what happens when you remove one olfactory bulb on the concentration of noradrenaline, in the ipsilateral amygdala area. She found out that it lowered the noradrenaline content, suggesting that whatever was happening, the lobes the rat were not just involved in olfaction, it was much more important than that. There was a lot of behavioural and physiological literature, showing that the lobes in the rat were part of the limbic circuit, unlike in the human and higher mammals when they are not - they are solely involved in olfaction.
Keith Cairncross who was a psychologist knew that sort of literature. He was also interested in pharmacology and so he started to bring this together. It was a very very important finding. Now he came to see us and Henk van Riezen and Henk Rigter learnt how to take out the lobes. It seems difficult but it is very easy once you know how and I then started working with them on the biochemical consequences. So we formed a team looking at all aspects of the behaviour and biochemistry.

Basically we started to establish it as a model. But we only ever used it very much as a research model. What we did find at that stage was that mianserin was equally active as all of the tricyclics and MAOIs in normalising the hyperactivity and also some aspects of passive avoidance learning, which is defective, after bulbectomy. These were very laborious experiments. You were talking about two treatments, 2 -3 weeks every day. Industry hates that sort of experiment because it means weekend working. It means special handling. It means a totally different approach which industry doesn't like. These are research methods.

The whole area of models seems to have gone out of the window recently as we have plunged into molecular biology and all that. Do you want to comment on whether we really need models or not. Is it because, other than screening models such as the Porsolt test, they are not suited to the needs of industry ? There doesn't seem to be the same interest to build up complex models of behaviour where you are trying to correlate aspects of behaviour with biochemistry and trying to understand the interaction between the two.
I've got many many criticisms of industry but one of them as a scientist is the pure scientific reductionism that what we are seeing now - you know mental illness equals an abnormality of a specific receptor type in a specific brain region. Now this is bullshit. The brain is much more complex than that. But if you take that philosophy to its logical conclusion, all you need to do is to have a laboratory devoted to in vitro cloning of receptors and targetting particular receptor

types. Whether that has any relevance whatsoever you will only find out maybe four or five years down the line when you put the compound into man.

You see what they are doing now is they are short-cutting. They find a specific ligand for a specific receptor type in a test tube. They short cut doing the minimal amount of toxicology, the minimum of acute behavioural testing, the minimal amount of pharmacokinetic analysis and then they get the compound into man as soon as possible. Now sometimes that can work - I mean from a statistical point of view it can. Whether of course it has any relevance to what you've been doing on your binding and grinding of receptors is another matter. But in 9 cases out of 10 it probably won't work because that is not the way the brain works and it doesn't lead to any deeper understanding of the psychopathology of the illness for which you want better drugs.

These are all short-cut reductionist methods which were starting when I was in Organon and where the whole structure changed within Organon to meet good laboratory practice standards - so the bureaucratisation came in to the industry then .

Good laboratory practice means what?
What that means is, whereas before, when you submitted your data to the regulatory authorities, they would examine the basic data reports and that sort of thing but as long as the stuff had been written up reasonably well that was basically the end of it. With good laboratory practice which largely came out in the FDA in the United States, in order to get a drug even considered by the FDA, good laboratory practice had to be followed, even in Europe. Now that meant that all notebooks, every piece of data had to be available. It meant that at any time officials could come from the FDA, walk into the laboratories and say I want to see your data on A,B, C & D. So everything now had to be carefully recorded. And not only carefully recorded but in a certain way. So there was a total bureaucratisation of the laboratory. This was coming in when I was leaving to go to Galway in 1974. Towards the end of my time I was filling in bits of paper. I was checking that the right forms had been filled in when they were writing data from an experiment and all this then had to be categorised in a certain way to go into the archives.

So you became nothing more than a bureaucratic pen-pusher and the fun of doing an experiment without a protocol was lost. Very often, you know as a scientist you find observations coming about by accident and then you say "right let's quickly do an extra experiment now". You couldn't do that anymore because everything had to be done by protocol. And so it meant that the research became totally bureaucratised and still is.

So that's I guess why the industry now hives off that kind of research to University labs or other independent groups.
Well yes but there's less and less of that. Because if you can get away with this reductionist approach, you just have binders and grinders and you have a standard protocol and you could train a monkey to do it basically. In the end, once you've got the techniques worked out, why do you have to bother about research. And you see there is this argument against all of the animal models - okay what have they ever told us and not only that they have led us in the wrong directions in the past - as with the reserpine model.

But it goes deeper than that. There isn't even a coordination between the basic science departments and the medical department. So when you get a drug through into clinical trials, for example, you've got all this material coming back for blood testing but the basic scientists

have no interest and no look in on that at all. And so there's a distrust. Basically they would never say this, but there's a distrust between the medics and the scientists. Neither understand what the other's doing and couldn't care less. Basically, you can publish your binding and grinding experiments in Nature because its molecular biology. You can clone yet another receptor, great stuff for Nature and you've made it from a professional point of view but I think this is an utter disaster in terms of psychopharmacology. If you look at the number of large companies now who are doing what I call really fundamental neuroscience research, there are very few of them. These are the areas that can be cut you see because it's not going to help you ultimately register your drug.

I think all this needs total re-evaluation but there is no way in which this is going to happen in the near future, with the way in which industry is designed and the pressures upon industry by the regulatory authorities. It is not a happy place to be, any more than the Universities are now a happy place to be for research. So that's one of the reasons why I got out even though I had been very happy. It was a very good training for me in terms of research management - running a department. All the managerial skills that you would never have got in the University. It was a very positive 7 years in industry which I never regret but I would never want to be back there.

If ICI was odd the West of Ireland was an extraordinary next move.
Having spent seven years in industry, I knew I was an academic . The only way to make progress in industry is through management in terms of the business aspect. My politics, my whole philosophy is totally against that. It is the very antithesis to what I believe in. I went into industry to use it, but it was using me as well if you like.

When I was an undergraduate in 1955 I had hitched-hiked with a friend of mine all around Ireland. Hitching on the occasional lorry and bread cart and asscart and that sort of thing. There is something about Ireland that I've always, maybe from way back, previous generation of the family that's appealed to me. Maybe it's the sheer anarchy or the community thinking which I liked. Anyway there was an advertisement for a job in Galway and Crossland from my Nottingham days had in fact been doing some of the teaching to fill in over there, because the previous Professor of Pharmacology, who was basically a surgeon teaching therapeutics believe it or not, had died.

I saw the advertisement in Nature and asked Crossland about it and he said it's not only very run down - the Department doesn't exist; whoever is going to take it on is really going to have to put their back into it and get the thing moving. I applied. There were 8 of us interviewed. I arrived the night before at 1 am on the last train down. It was a November night, pissing down with rain, as only it can do in the West of Ireland. I had nowhere to stay. I walked out of the train station, up Eyre Square into the Imperial Hotel.

When I woke up the next morning, it was one of those wonderful days, the sun was shining, the sky was blue, it was just unbelievable. And I thought this was my sort of place - you just don't know what the hell's going to happen even down to the weather. So I went to the University and was interviewed by all sorts of people and I didn't know any of them. Four of the interviewees were from the United States, all Irish Americans, most of them senior to me. So I went for the interview and all the rest of it. And there was of course the Irish. I didn't know anything about Irish exams and when I turned up they said when are you going to take the Irish exam?

That night I went back to Helga and the kids who were still living in England and said "look I don't think any of this is going to come off but okay lets see what comes of it". Then I was phoned up by Sean Lavelle, Professor of Experimental Medicine, the other half of the joint department and he said "by the way you've got through all the faculties, you'll be offered it". So that was basically it.

I started on 1 September 1974. I had one empty hut. Literally an empty hut. It used to be the morgue for the regional hospital and I think they moved out the altar or something like that before I moved in. Nothing else. One thousand pounds, an empty hut and me on 1 September 1974. I thought this is going to be a real challenge. I must say Organon were very good to me. First of all they bought me a spectrophotofluorimeter. They gave money for other basic apparatus, about £10,000 - a lot of money in those days, to get me started and they have always been very good. But the University was just appalling. I didn't realise just how naive I was at the time.

I had to establish, totally from scratch, a proper scientific course in pharmacology for the medical students and ultimately for science students, with nothing. With not even a staff member. They gave me a technician, who is still with me, Brendan Beatty, since 1974. I managed to get some money from the Medical Research Council of Ireland, who were also very good to me in those days, to take on 2 PhD students and I got a bit extra money from Organon to take on a third. So I had 3 PhD students, one technician and me. It was only in 1978, over 4 years later that in fact they appointed a lecturer, Jim O'Donnell. Until that time I was virtually carrying the whole teaching load, research load, everything with virtually no money.

So, I knew it was going to be tough and indeed it has been. But most enjoyable. Largely because of the quality of people. They are wonderful people at undergraduate and postgraduate level and the staff. Now we've got, at the last count, with everybody thrown in with research technicians and so forth, of nearly 30 people at the postgraduate level.

Were you at the very first BAP meeting?
I was at the famous meeting in the RSM, chaired by Max Hamilton. There would have been about 70 odd people there. The whole thing arose because a group of psychiatrists, people like David Shaw, David Wheatley, Alec Coppen, Merton Sandler, wanted to set up an Academy of Psychopharmacology. They formed an ad hoc committee to do this and they wrote a letter, I seem to remember, I think it was to the yellow journal, more or less saying that this was formed. Now there were obviously the basic science side were rather upset about this.

Why were they upset?
Well they were upset because they were being excluded. The general feeling was that psychopharmacology is not just the prerogative of the clinicians. Psychopharmacology goes right across the broad from basic neurosciences through to clinical science. And here you had a group of clinicians trying to, if you like, take over psychopharmacology in Britain at the time.

People will argue the way things have gone that the basic scientists have gone down the neuroscience route without reference to clinical relevance and in actual fact that psychopharmacology as such really is a clinical enterprise and needs to be very closely linked to what can be demonstrated to happen in clinical populations?
No, I would disagree entirely with that. I think that it's both clinical and basic. The sort of people, that were involved, Bradley was obviously leading this, and their work was neuropharmacology - they were looking at the neurophysiology of reticular activating system. My own

work in the area of hallucinogens, for example, was looking at both behaviour and biochemistry of hallucinogens to try and really see at the molecular level what was happening and to try and explain this very sophisticated phenomenon that was occurring in human beings as a consequence of taking these drugs. So I wouldn't agree with that at all. I think that all of us thought at that time that psychopharmacology encompassed both the basic sciences and the clinical sciences and here we had a group of well known clinicians more or less usurping the whole of psychopharmacology and setting up this rather what we considered to be a pretentious Academy of Psychopharmacology to the exclusion of the basic scientists.

Can I push you on this one. The way the BAP has gone, I can agree with you that there needed to be some pharmacologists involved in because an awful lot of clinical people didn't know anything about pharmacology. But on the other hand if you look at the basic scientists who are now active in the BAP, they don't know anything about pharmacology either - they're neuroscientists and we're getting this tremendous tension within the BAP, between those who want clinical relevance and those who really want a neurosciences society.

Yes, but I think there always has been what you have called a tension, I don't know whether tension would be the right word, I think that's too strong a word, certainly in the past it would have been too strong a word. When the organisation was formed, basically we were saying that okay you have to try and explain at molecular level and a systems level what is going on when you give drugs and animal pharmacology and behaviour is relevant to that. In fact what came out of that meeting at the RSM was an agreement that this indeed should be the case and I think everybody recognised the mistake of trying to set up an Academy, largely to the exclusion of the basic scientists.

Anyway, it was a one day meeting - a very lively affair with Max Hamilton jumping up and down and telling people to "shut up, I'm in charge". It was very stormy but at the end of the day everyone agreed that we would move ahead together on this and the basic scientists came in with it and the new constitution was drawn up by Max Hamilton. I don't think I was at the meeting, which subsequently followed, with the adoption of the constitution and so forth. But I was a signed up member from that time. I must say, to begin with, it was a very quiet society. You were talking about summer meetings with 70 people, but of course it has certainly improved since that time and become very influential.

ACNP has recently fractured with Don Klein having set up the American Society for Clinical Psychopharmacology. His line is that ACNP are becoming too much neurosciences oriented and that's fine for the neuroscientists but it's not so good for psychopharmacology proper.

As a basic rat-ologist, I would have sympathy with Don's view. I think that's what all organisations like the BAP have to watch. The strength of the BAP in the past was a balance between clinical and pre-clinical psychopharmacology and its all too easy now to get into the trap with all this work in molecular genetics and molecular neurobiology to say you can explain the whole of mental illness in terms of some fundamental fault in an enzyme system or transport process or a receptor mechanism. Its a gross over-simplification and it stinks of scientific reductionism, which I think is extremely dangerous in any area but particularly in any area to do with neuroscience. I think it's very seductive as well. It worries me that we would go too much towards basic neurobiology in the BAP and I think it is something which has to be very carefully looked out for. The BAP must be a broad church in other words not a narrow sectarian group of acolytes around a concept in psychopharmacology. That I think has been

the strength because I think the BAP as always been a broad church and I'm just hoping it's not going to change.

But increasingly we are getting to the stage of having symposia which aren't constructed so that people make links between areas or else we seem to have much fewer people who have the broad understanding in the field that would enable them to say look you are going to just re-invent the wheel if you keep going down this route.
Well yes. I think it's complex. Where are the grand old men with the vision - this is basically what it comes down to. You want people with both experience and fantasy and that's bloody hard to find now. I think that that is the way in which scientific research and certainly academic research has gone. That people have been almost forced to over-specialise. One must always specialise in a specific area, obviously to do anything worth while, but to over-specialise and thereby exclude things that are not directly relevant to the problem which you're looking at at the present time! If you don't do it, they say you can't produce the papers, which means that you can't justify the grants, which means that ..

you won't get the next grant
And the University therefore starts looking very carefully at your performance during the year and your support from the University goes down and so on and so forth. I think it's an extremely dangerous way in which research is going in all academic institutions. I think that is impacting now on what's happening in societies like the BAP. People have not got time to really think in a broad constructive way about what's going on. When this happens at a senior level it has an even bigger impact for the junior level. Because the juniors are not being brought up in an environment of enquiry, of fantasy, of chancing a hunch. You've got a project to complete and by God it better work because the grant depends upon it and indeed your grant may depend upon it, your PhD may ultimately depend upon it. Don't take any chances for God's sake. Just play safe. Now this is bad for science and its being increasingly reflected in organisations like the BAP, which is extremely sad for the future.

You've recently become treasurer of CINP. Had you links there before?
Well I have been a member of CINP since 1968 and I have been a regular attender at their meetings because I see it as the major international body representing psychopharmacology. It's been a broad church with both clinical and basic psychopharmacology working together for symposia with appeal to both. So to me it was a logical extension. My involvement at a bureacratic level came about six years ago, at the time of the Kyoto meeting when Alec Coppen was President. The CINP is quite unlike the BAP in that it's very much a Presidential organisation. It is the President who appoints the Chairpersons of the different committees and so the whole thing can change from a one two-year Presidential period to the next. I think that's a big weakness. It means that continuity need not necessarily occur.

Anyway when Alec was appointed, he knew that I had been involved for many years in Africa, in Tanzania and Uganda and Zimbabwe, with third world education. I had raised this at members meetings, on a number of occasions, that CINP was an organisation dominated largely by North America, to a lesser extent by Northern Europe, which was not taking cognizance at all of the major problems in third world countries. It was basically a rich man's club. There are all sorts of reasons given why nothing was done. One was that it's a relatively poor organisation. It was 50 US$ per two years until I became Treasurer which was absolutely ridiculous, considering that you are dealing with only very senior people - you are talking about people with approximately 20 years years research experience with a large number of publications before you can actually become a member. Anyway to cut a long story short, Alec

said okay I'm the President, now I want you to form an education committee - we didn't have one before - and you're the chairperson, you do what you want and I'll back you, which is basically what I did. I had no money - there was nothing in the budget for the committee - so for 3 years I funded this by talking to friends in the industry and getting a few thousand dollars and the first three workshops we ran were in Harare in Zimbabwe. Ted Dinan and myself did them. We established a basic curriculum across all areas of psychopharmacology, aimed specifically at the needs of third world countries.

Aimed at who?
Well it depends on the country. In the case of Zimbabwe, there were only at that time four qualified psychiatrists in a population of 11.5 million and Zimbabwe was far ahead of most of the black African countries. So when you are actually talking about running courses, you are talking about running courses for mental health ancillary workers - very intelligent, highly motivated nurses, basically, a few general practitioners with an interest and one or two trained psychiatrists who were basically centred in a capital city. That's the level of your education. What should you be looking out for when you're using chlorpromazine, when you're using imipramine, when you're using diazepam? What are the real practical problems with these drugs and how should they be used ? What are the side effects and why do the side effects occur? We were trying to establish a rational basis for the drugs which are available on the WHO recommended list. On the basic WHO recommended list you've got something of the order I think it's about 130/140 drugs, that's all. Covering all therapeutic areas. Of those, the drugs in the CNS area are something of the order of 12 or 14 - you've got one or two drugs for the treatment of epilepsy, one or two for the treatment of anxiety disorders, which is basically the benzodiazepines, standard neuroleptics, which would be haloperidol and chlorpromazine, imipramine, basically as an antidepressant.

So you are really very limited and restricted to what can be done. Even that is a luxury in many places. You would get them in the major centres, but when you are really out on the sticks, although theoretically they should be available, half the drugs are not available. Now what the heck do you do when you've got patients going mad and all the rest of it. So Ted and myself found it a real education. I would deal with the basic pharmacology, side effects, drug interactions and Ted would deal with the clinical applications. It was very labour intensive. We ran these courses over a 5 day period and then we would try to get some of the clinicians together to talk about research. Research which is relevant to the country, research which doesn't require big aparatus and so forth. Get people thinking on how to use the material which is available. We did three years of this.

Julian Mendelwicz then took over from Alec Coppen and obviously this was producing some sort of waves within the CINP. So they said well perhaps we ought to give you a budget and that's basically what happened. So the committee has been extended and we've increased our coverage to South East Asia, Indonesia, Vietnam, Korea, to the Middle East, Yemen, Egypt, Iran this year, to Namibia and South Africa. We've got very big plans for training trainers in South Africa to help to cover the English speaking African countries. This has kept going under the new Presidency of Lew Judd. It's been quite anarchic. We've been working all the time with the mental health division of the WHO. Now we are trying to get a proper curriculum going and get printed material and so the whole thing is building up and hopefully we'll eventually have a course structure and all the main continents will be covered in terms of the training programme.

As a result of that I became known to the Committee. The Treasurer's position became vacant in 1992; it lasts 7 years. Its the worse position on the executive. For political reasons, geographical reasons, I was nominated as Treasurer and the rest, as they say, is history. The executive consists of 7 people - the President, 2 Vice-Presidents, the Treasurer, the Secretary, the Past-President - that's it. This group meets twice a year and sort of basically to guide the organisation.

The educational work you are doing is totally consistent with what I know about you but of course the other way to see is that you're spreading an Anglo-American cultural imperialism that is pharmaceutical company friendly and may not be relevant at all.
Oh well I disagree with that totally. The very fact that we're working with the WHO means that we work with drugs that are all generics and we have to be sensitive to the primary needs of third world countries, in terms of cost of drugs and all these sort of things. And secondly, we don't ask anyone they ask us through the WHO. So in other words a need is identified. We are asked to fill that need and we only go and fulfill that need. That's the way it always has to be with any of these educational programmes and I think we have to be very sensitive about any cultural imperialism of any sort.

Some of the things that we've seen in Africa and in Indonesia in terms of treatment of patients with mental health facilities and so forth are just unbelieveable. In Indonesia, we went to one of the State psychiatric hospital and it was sort of reasonable for a third world country in terms of the physical structure - very basic but reasonable and clear. But we went into an enormous male ward at 2 pm and all the patients were asleep. We thought this is very strange. These are disturbed, manic patients, acute schizophrenics and of course they had all had whacking great doses of haloperidol in the backside or something like that. They were zonked out and this was the way the whole thing was run and controlled. And then we were shown the ECT machine and we thought great, have you got an anaesthetist? Oh no. Raw ECT. Big men hold the patient down - it's One Flew Over the Cuckoo Nest stuff. This is the way things are done. So that's the level you're dealing with. In many cases, they don't even see a psychiatric nurse; if the patient goes a bit mad you tie him to a tree until he calms down.

So cultural imperialism may be a good thing.
No I'm not saying that at all that cultural imperialism is a good thing. No, you don't impose; you say well there are other ways of doing things. These are the other ways which can be used and they can be used in a relatively inexpensive way and in terms of the impact it has on the welfare of the patient, it may be much better for what you are doing. So you try and educate by example. What I would like to see, of course, is an extension of the educational programme so that we could have scholarships to take out some of the young trainee psychiatrists from these countries and train them in a really good environment somewhere and then send them back so that in fact you are enriching things. Now unfortunately the CINP doesn't have the money and WHO only has limited funds and they contribute nothing in terms of funding. And so this is what I would like to see done. Now whether we would be able to do it by gettin funds from charities like the Ford Foundation is something that we are now looking into. I see the programmes and workshops as showing that we are willing to help and that we are cognizant of the problems but it is scratching at the surface and we need to be doing a lot lot more in terms of really training young psychiatrists, first and foremost.

Can I put it to you that the engine that drives a lot of psychopharmacology, the goose that lays the golden egg, has been the pharmaceutical industry. I'm interested to explore your attitude to the industry given that you're Marxist in orientation.

Well the world we live in is a capitalist world and the countries that I live in have been capitalist countries, so what do you do. You either look at the reality of the situation or you pretend it doesn't exist. One of the fundamentals of Marxism is you always look at the reality of the situation. That applies to the industry. When we're thinking of psychopharmacology where do we get our money for research from... in an ideal world I don't think a single penny should come from private concerns for the sort of research that we want to do - it should be state funded ..

State funded? What about co-operatively funded... the BAP for instance should raise it's own funds or the psychiatric profession could?
No I don't even think that. To my mind, the hallmark of a civilised country is it values - its education programmes, its health service and so forth. It sees the need of enriching the intellectual life of the country. This, therefore, means that all basic research be it medical or non-medical, is funded through the appropriate organisation such as the Medical Research Council, the Science Research Councils and so on. In other words projects are peer-reviewed etc but this framework does guarantee the total independance of the scientist to carry out work for a reasonable period of time on projects that would otherwise never be funded if you relied purely on funding of the private applied type, where research has to have an immediate pay off in terms of the person funding it. That's what I mean by state funded research. To some extent that was the case in Britian in the good old days before the ghastly Thatcher. Even in Ireland when I first came 20 years ago, restricted though the funding was proportionately it was higher than it has been in recent years. That is not the situation now and I don't think in the foreseeable future that will ever be the situation in any industrialised country. What are we left with? We are left with universities which are becoming primarily teaching institutions, conveyer belts for turning out half educated graduates and technicians - not scientists, not intellecutals, whether it be in the arts or in science and I think this is an extremely dangerous situation.

Anyone working in the university is expected to raise funds to support basic research. In pharmacology we are very fortunate in that the industry needs us and the reason they need us that we can do some fundamental research project or long term research projects cheaply. And the reason we can do it cheaply is of course that we've got highly motivated PhD students, who have within 3 years to get a PhD and ultimately get a job. So they are highly motivated and reasonably well trained and they only have to be paid a pittance and so you can get work done in a university which you would never get done in industry for that cost. So, therefore, its not even a symbiotic relationship, its a parasitic relationship. Now that doesn't mean we're not grateful. Of course we're grateful and if we don't have that money coming in from private resources we would have no money at all for research and we might as well pack up and go home and just teach. The reality is that without the industry, there would be no basic research of any sort in psychopharmacology because all the other sources of funding by and large have dried up.

Right now let me be as awkward as I can. On the one hand, you do your work in Africa for WHO and your orientation as a Marxist seems to fit into this quite well. However, on the other hand you are very publically seen defending for instance the latest group of antidepressants, the SSRIs, vigorously, even though the evidence that they are really much better than the older generation of antidepressants doesn't appear to convince most clinicians. For instance take the question of long term efficacy of antidepressants. This is important but studies on the longterm efficacy of the SSRIs becomes for the Marketing Department of a drug company just the way to sell their drug rather than the answer to a scientific question and people like you get used to put forward an industry

friendly point of view. What this leads to among many practicing psychiatrists is a perception that your doing the marketing of these drugs for companies better than they can do them themselves. It's an ironic and ambiguous position it seems to me.
Well yes I don't see it that way of course. I would never do anything which would prevent me from sleeping comfortably in my bed at night. Knowing the drug industry pretty well, having worked in it and having worked closely with it for well over 20 years, the reputable international companies have no time for the so-called academic psychopharmacologist that can be easily bought and will say exactly what they want him or her to say about a particular drug. Since minaserin we've had lofepramine, we've had selective monoamine oxidase inhibitors, we've got this plethora of SSRI's, so the industry realises that what is flavour of the month this month is going to be changed next month and if you've got somebody who is constantly changing and saying exactly what the Marketing Departments want their objectivity is lost. The shelf life of this kind of person is extremely short. And what the reputable drug industry wants, I think, is people who are independent and who will say what they genuinely think about the compound. And it works in their favour just as much, to protect the integrity and independence of the individual.

But with the debate about the SSRIs, you get statements being made by people, even within the BAP, who say that the average clinician shouldn't be using new compounds and if they don't switch over they will start getting sued. This is not the way for debate to happen. It seems like debate in soundbites. We get you on national radio saying that your average jobbing clinician isn't prescribing the SSRIs, which are a much safer group of drugs, because of the price. But this is not the way they are perceived clinically
My argument would be, and I put this at more length in fact on some of the other radio programmes this week, is one that I've always said which is that there's no improvement on efficacy in the last 30 years in the area of treating depression - we're all agreed on that - what is new I think is the side effect profile and toxicity. Now I happen to think that's an extremely important issue to be getting across.

The other big problem is that of suicide. My argument there is an ethical one. I think we should always, as far as possible, consider the needs of the patient first. We can never predict which patient is going to attempt suicide and how they are going to attempt suicide. What we do know is that drug A, a cheap drug, if they do attempt on that there's a higher probability that they're going to harm themselves than if they drug B, which is equally effective as an antidepressant. So leaving everything else aside from a purely moral point of view I feel we should be prescribing drug B.

All of this came out of a long article I wrote in the Irish Doctor, where I was specifically asked as a pharmacologist to write about SSRI's for the simple reason there are four of them in Ireland and they're expensive drugs. The media issue has come out of that but in every programme I've said look there are 2 types of drugs. There's basically the old ones, the tricyclics and basically different groups of new ones of which the SSRI's have received some prominence but there are others. So, to my mind it's all totally consistent with my philosophy. I want to see drugs used appropriately. I want to see the best drugs being used. I think it comes back to my view in a civilised society we look at cost in the real sense and the cost means taking into account the quality of life of the patient.

But the average clinician doesn't perceive a major advantage to the new drugs. A lot of people will take the Pope maxim, "Be not the first to take up the untried, nor yet the last

to cast the old aside". Then you have the argument that the studies that lead to drugs being licensed are not independent science. They are constructed to allow the FDA to legitimise certain claims rather than constructed from the point of view of trying to do independent science. So from that point of view, it seems reasonable to try these drugs out on some patients and chat to colleagues rather than go by the so-called evidence. Any powerful lobby otherwise is going to look like its orchestrated by one of the companies to do the marketing for them.

Yes well of course that's an interpretation. I can't to anything about the way people interpret what my motives are. All I can say is what they are, what the reality is. I'm associated with the National Drugs Advisory Board - and when you actually look objectively with the data, most people would independently come to the same conclusion that these drugs are equally effective as the older tricylics and they have the major benefit of being less toxic, and therefore better able to fit in with the new concepts of the long term treatment of depression. You cannot persuade me, as a pharmacologist with the knowledge of toxicology, that a drug which produces a constant tachycardia, for which no tolerance develops is beneficial for the cardiovascular system of that patient. And that is precisely what happens with any tricyclic given at the appropriate therapeutic dose. Leaving aside everything else, from the toxicological point of view, that is bad news. And I stand on that. I'm not advocating any particular new second generation antidepressant. I refuse ever to speak for a particular company or particular drug. I would just talk about a group of drugs. So if you want to ascribe to me motives which I don't have that's fine. I think that the worst thing we could do is to shut ourselves away in a laboratory, talk to rats and write obscure papers which nobody reads. If you're going to appear in the public domain you are going to have people who are going to doubt your motives and say well of course that's the way Leonard goes on and has expensive holidays and big cars, neither which of course is true.

But on the other hand if the SSRIs went under or if they hadn't impacted at all, an awful lot of companies might have been tempted to pull out of CNS and as a consequence Alzheimer's research programmes wouldn't be as likely to be happening. Do you not think that people like you and me have to be prepared to be compromised slightly to try and make sure that industry don't find CNS an area that they don't want to be in.

No, I am convinced that the industry looks very carefully at all this and they realise there is so much that still needs to be done to find new drugs for the treatments of different types of mental illness. If they can find anything for Alzheimer's disease, then this would be an enormous breakthrough, from a medical and a financial point of view which is why all the money is going into memory research. Every company of any size has got Alzheimer's research programmes going on. The consequence of that to neuroscience, both clinical and basic, is very considerable. That is a positive side, if you like, of the industry. Okay, they're motivated by greed, it makes no difference whether you're selling bombs, soap power or drugs, the motivation is the same. However, from the scientific point of view, of course, it is extremely beneficial and with the sort of society we are living in, it is the only way that those of us who are basic researchers in the universities can exist. Its a very complex issue, but that's the world we're in. I don't feel compromised by it. I wish it were not that way but changing it means changing society.