NEUROSCIENCE & DRUG DEVELOPMENT
LES IVERSEN

You went to Julie Axelrod's lab in the mid-60s, what was it like to go from Britain to the NIMH in the 60s.

It was a completely mind-blowing experience for a young English scientist, brought up to be very economical with running expenses and not having all that much access to equipment, although in Cambridge, when I was doing my PhD, I was very lucky in a number of respects. I had absolutely committed myself to doing brain research by the time I graduated in biochemistry in Cambridge. I was obsessed with plants and botany as a sixth former and got a scholarship to come to Cambridge on the grounds of my performance in botany. But the classical botany taught in Cambridge in the late 1950's soon proved boring, and I rapidly became enthused by biochemistry, which was a much more glamorous subject. I ended up specialising in biochemistry at an enormously exciting time for biochemistry in general and biochemistry in Cambridge in particular, because this was only a few years after Crick and Watson had made their dramatic discovery about DNA. I became fascinated by brain research, largely because I read a couple of books by Aldous Huxley called "The Doors of Perception" and "Heaven and Hell", which related his experiences of taking mescaline and then later taking lysergic acid. These books were absolutely fascinating, among the most influential I ever read. The mystery which Huxley describes so beautifully was how is it that taking a minute amount of chemical substance can so totally alter your perception, your consciouness and your view of the world even to the extent of believing that you have had a visonary experience. I found that absolutely fascinating - and I still do. It's a mystery that still hasn't been solved. But that's what triggered my interest and also brain research at the time was beginning to take off as a growth area in biology.

My problem in Cambridge was that there was no-one in the Biochemistry Department doing anything remotely concerned with brain research and I wanted to be a biochemist and to do brain research. My great stroke of luck was to find a supervisor in Gordon Whitby when I was about to start my PhD. He had just come back to Biochemistry in Cambridge from a year in Axelrod's lab at the NIH and he had been among the first to use radioactively labelled noradrenaline to demonstrate the concept that noradrenaline was disposed of in the body not only by metabolism but also by an uptake mechanism mediating recapture into sympathetic nerves, which was then a totally novel concept. So I was extremely fortunate in having Gordon Whitby, as a supervisor which allowed me to do neurochemistry research in a very early stage of what proved to be an exciting branch of neurochemistry and neuropharmacology, and to use the techniques that he had just learnt in one of the world's top laboratories[1].

The other stroke of good luck was that we had one of the first radioactive scintillation counters in Cambridge, although in those days we had to re-use the glass bottles that we put each sample in, wash them out at night and re-use them the next day. One of the things about going to the National Institute of Health was that you didn't have to be quite that economical! I went to the Axelrod Lab, of course, because my

[1] Axelrod J (1996). The discovery of amine reuptake in The Psychopharmacologists Vol 1, pp 29-50.

mentor in Cambridge had trained there and I had that introduction. I was very fortunate to be there at a fairly early stage of the Axelrod Lab, as you know from your interview with Julie. He was what you might call a late starter. He didn't get his PhD until he was in his 40's and he was in his late 40s before he was put in charge of his own laboratory for the first time. Since then he has never looked back. He was enormously productive but when I went there he was still at a relatively early stage. He had had a number of foreign visitors and Post-docs but we were still among the first generation of those.

It was a great time. From the point of view of the area I was in, catecholamine research, things were booming. There were so many things to be discovered still with radioactively labelled noradrenaline and other catecholamines. It was like ripe fruit ready to be picked. Jacques Glowinski, a French visitor, and I worked together very closely during that year in Julie's lab, capitalising on work that he had already started before I came. The project was based on the idea that you could study catecholamine metabolism and drug effects in the brain by using radioactive catecholamines. But they had to be injected directly into the brain because they wouldn't pass the blood brain barrier. Jacques had devised a technique of injecting radioactive amine into the ventricular system in the rat brain and we did hundreds of experiments. Thousands of scintillation vials were stacked up outside the door each day and we worked from morning to night. It was a really intense period with great encouragement from Julie Axelrod, who was, on the one hand, a source of more ideas than you could possibly handle, and on the other hand, he let young people do their own thing with an extraordinary degree of freedom. He was a wonderful teacher.

During that time the National Institute of Health was in an enormous boom period. One reason for this was that the best of the output of American Medical Schools had decided quite reasonably that a couple of years research at the NIH was probably preferable to going to the jungles of Vietnam and being a soldier doctor. Instead they fought each other to get into the NIH to do their military service in that way and the NIH, had the pick of the most talented young doctors. There were some extraordinarily bright people, who stayed for a short time and left. Unfortunately I think the NIH has since become much more ossified and is no longer the intellectual powerhouse that it used to be.

So even something like the Vietnam War can in some respects be a good thing!

I think that's right! But it was a period in any case, despite the Vietnam War, of immense optimism about medical research and its ability to discover the secrets of human disease and eventually to treat them. All of us had that naive optimism that we could understand even mental illnesses and treat them far better than had been done previously. Remember at that time, in the early 1960s, we were seeing the enormous benefits to mentally ill people that had come from the introduction in rapid succession of new drugs for treating psychiatric disease, monoamine oxidase inhibitors, tricyclic antidepressants, the neuroleptics, chlorpromazine and all the others after it, for treating schizophrenic illness and the benzodiazepine tranquillizers. That all happened in a remarkably short space of time and I suppose we felt that it was going to go on happening like that and we would understand more

and more and have rational grounds for developing centrally acting drugs. In retrospect we didn't realise that those were the big CNS drugs of the 20th Century. What's happened since has been far less spectacular on the whole. But anyway it was great and it was in a log-growth period, and it's always fun to be in a lab which is in a growth phase and in a field that's optimistic and full of ideas, so that was a very influential time for me.

What about the other people. Some of the older stars who were still there, people like Brodie, but his star was probably starting to wane..
Well Bernard Brodie was there but for some reason, which I never really understood at that time, the Axelrod lab were not really on speaking terms with the Brodie lab. Perhaps because Brodie resented the fact that his pupil, Axelrod had become so spectacularly successful. I don't know why but we were not really close to them at all so we never got to see people like Costa, Udenfriend and Brodie. We knew that they were somewhere in the same building we just never visited. We saw them at seminars but we really didn't have much relationship and that's something I regret. I came to know some of those people later. Mimo Costa, for example, is someone I have grown to respect and like as the years went by. At that time, particularly Jacques Glowinski would have stand up debates with Mimo Costa who was famous for his Latin temperament and was prone to get carried away in public debate. Jacques Glowinski also has something of the Latin in him and they would sometimes have very spectacular arguments at public conferences.

So we first got to know Costa in that way, but I have got to know him since as a friend and a colleague and admire his continuing ability to come up with original ideas, some of which don't work out but some of which do. He's that sort of person - he has no inhibitions about telling you what his latest idea is and why it's important. On the other hand he's a very intelligent, ingenious and inventive person and has contributed a great deal to the field of neurochemistry and neuropharmacology and still does. In his 70s, he lost his job with the Fidia Research Laboratory in Georgetown, Washington, because the company went bankrupt but Mimo, then got himself a new job and a new career in Chicago. Even though he is in his 70s he was recently appointed as a full tenure Professor in the University of Illinois. You have to admire someone who can keep going like that and keep wanting to do research and having good ideas.

At the other end, there were people who were just beginning to come into the system, people like Sol Snyder.
Sol was beginning his research career as you say in the Axelrod lab. We didn't actually work together. Sol was doing his own thing, which was somewhat different from the catecholamine research that Jacques and I were doing. But Sol and I were very close then and have been close friends ever since and I've followed his subsequent research in great detail and with great admiration. Again a person of extraordinary intellect and originality, with the ability to know when to jump into a field and when to move on also, which is equally important. He would tell you, I think, that he owes a great deal of that way of doing research to Julie Axelrod who also is a fountain of sheer creativity and originality. As you know, Julie's saying was "don't read the literature because it will only confuse you". You should just get on and do your own thing and have your own ideas about what the problem is and how to solve

it. That's very much been Sol's way of doing things. With great success. He has not only contributed enormously through his own ideas but he's trained a whole group of people in the United States who have gone into American Academic life and many of them occupy important and senior positions. So he has been very much a mentor also in his way teaching that way of doing research.

After the NIH ?

I had a year in Harvard, which is also a very influential to me. The years I spent in America were enormously important, because I gained contacts in the North American research community which is so huge and productive and important. At Harvard I met a different sort of scientist. They were much more neurobiology and cell biology oriented and less biochemistry and pharmacology oriented than the Axelrod group. To be in Steve Kuffler's Department of Neurobiology for a year was a great privillege and a joy. I worked with the biochemist in that lab, Ed Kravitz. I was the first post-doc that he had ever had, and he and I got on very well and I got introduced to many new areas of neurochemistry and neurobiology.

In particular I got to work on the amino-acid inhibitory transmitter, GABA, for the first time. I was again lucky enough to be in the right place at the right time because the Harvard group had spent years of detailed, meticulous research pin-pointing the role of GABA as the inhibitory transmitter for nerve-muscle transmission in lobster and other crustacea. In such animals, the muscle fibres are innervated not only by excitatory motor fibres that create contraction in the muscle but each muscle also receives an inhibitory fibre. This is quite unlike what goes on in mammals where all the inhibition takes place in the central nervous system. So you had these two rather large axons innervating each bundle of muscle fibres and they had very good circumstantial evidence for the role of GABA as the inhibitory transmitter.

We developed a project to demonstrate finally that it was GABA by showing that when you stimulated the inhibitory nerve electrically, you could demonstrate the release of GABA into the surrounding fluid. A classic Otto Loewi type experiment if you like. There was every reason to think that it would work if only we could work out how to do it. The problem we faced, Ed Kravitz and I and Masanori Otsuka, the Japanese neurophysiologist who was responsible for that side of the work, was how to do the experiment on a suitable muscle. One of the unwritten rules of the lab was that you shouldn't work on edible parts of the lobster, so preferably you worked on the walking leg or something like that. And secondly, more importantly, was how to measure the minute amount of GABA that was likely to be released from nerves. This came out in seawater which is 0.5 molar sodium chloride, so we had to pick up this minute trace of amino acid in a highly saline fluid. Those were just technical problems but they took almost a year to solve and we ended up violating the lab rule - by using one of the large crusher claws of the animal. The whole muscle weighing several grammes is innervated by a single nerve fibre and Otsuka could find it, pick it up and stimulate it and Ed Kravitz and I collected the seawater that was dripping over it. Lo and behold, in the last few weeks before I had to go back to England, we did show GABA release from that preparation. It was a first ever demonstration and it nailed down the idea that GABA was a neurotransmitter, which I then went on to work on in mammalian CNS. Now everybody believes that GABA is the main inhibitory transmitter in the brain. But those were heady days because this was

pioneering in a relatively new field at the time and in a great lab. I was exposed not just to biochemistry but to all the other disciplines in neurobiology. At that time the Harvard Neurobiology Department was one of the first Neuroscience Departments anywhere, the idea, which subsequently really took off, that neuroscience is a discipline in its own right but it embraces all sort of methodologies and principles.

Was this anything to do with Francis Schmitt.
He was also a great influence on me later when I became an Associate of the Neuroscience Research Programme at MIT but not at the time. I didn't know Frank Schmitt when I was in Harvard at all, although he was at MIT. He had already started his remarkable, “Invisible University of the Brain”, as it was sometimes called, the Neuroscience Research Programme at MIT, which was funded by NIH money. It brought together groups of experts in many disciplines from crystallography through to psychology and made them sit in a small room and talk about brain research problems. But Steve Kuffler was the moving force behind the Harvard lab.

Who was Steve Kuffler?
He was a neurophysiologist of extraordinary talent, technically and intellectually, who had brought together a group of very able people in Harvard. He had this genius for choosing the right people and knowing the right sort of preparation to work on to solve a particular problem. He would come up with some extraordinary organisms and extraordinary preparations to look at problems.

At the time I was there, for example he was interested in glial cells and he came up with the optic nerve of the mud-puppy as a suitable preparation. It's a sort of amphibian, a very exotic thing and it just happens that the optic nerves have these giant glial cells that are big enough for a neurophysiologist to impale and record from directly and then stimulate the optic nerve and see what happens. Everyone at the time saw the glial cells as non-functional, just a supporting cell that held the nervous system together somehow. But Kuffler and his colleagues were among the first to show that if you did record from them they undergo potential changes as the nerves are active and subsequently of course we now know that glial cells have all sorts of pharmacology, they have receptors for a variety of neurotransmitters and peptides. But none of that was known at the time.

Kuffler had this gift of going out into the animal kingdom and finding the most suitable prep and then finding brilliant people. At the time I was there, for example, had Hubel and Wiesel were working in the visual system and making their dramatic discoveries about single cells in visual cortex that recognise direction of the stimulus and orientation and so on, which blossomed later into a hugely important area of neuroscience research. So those were exciting times and for me a great experience. An entry into the neuroscience world which I wasn't really familiar with and entry into a new area of neuropharmacology which I subsequently continued to be involved in.

You returned to Cambridge and later joined the MRC in Cambridge. For most of us the MRC/LMB complex is the closest thing outside the US to what the NIH must have been when you went to it.
That's an interesting perception yes. The MRC labs on the hospital site in Cambridge were a very important set of resources for the Medical Research Council.

I must say my own Unit, the Neurochemical Pharmacology Unit, didn't have that much contact with the Laboratory for Molecular Biology. We were fairly self-contained in the Department of Pharmacology next door to the LMB but not actually part of it.

I worked for the MRC for 12 years and it was a terrific time. I have been lucky throughout my career in being in places where there was a growth phase of development and the MRC was in such a phase in the 1970s. It wasn't exactly an era when money grew on trees, but the MRC budget was growing at a healthy rate, about 10% a year and they were setting up new Units and the neuroscience area was flourishing. I was lucky to get my own Unit at quite a young age. And the MRC in those days had a wonderful policy of letting you do your own thing. I can hardly believe in retrospect how much freedom we had. We had, of course to talk to people in Head Office in MRC but we had friendly relations with them. One had to write a progress report but only once every 3 years; there was a site visit once every 6 years. When I think what it was like subsequently working in a company, where you had to write a report every week of the year, this was really a luxury. We didn't have an enormous budget but we had enough to do most of the things we wanted to do and I was lucky to have a constant stream of wonderful young people as graduate students and post-doctoral visitors from all over the world. We had a really fantastic time during the 1970s and the science was also developing apace. We were still very optimistic at that time about the ability of neurochemistry and neuroscience to crack some of the remaining problems like schizophrenia, which is just one of the areas that we concentrated a good deal of effort on.

You moved into the dopamine field. Do you want to take me through that.
I was very much influenced by a particular event. It was at a meeting organised by the Neuroscience Research Program at MIT. By which time I was an Associate of that and a regular attender at his meetings. It was a great opportunity for me to go to the States 2 or 3 times a year and meet top neuroscientists and maintain contacts. One of the things the Neuroscience Research Program used to do was to have large summer school meetings in the Rocky Mountains in Boulder, Colorado that used to last 3 weeks at a time. They would invite students from all over the world and have a high level faculty teaching. The whole of neuroscience in 3 weeks basically. A very grand concept, nobody would ever find the money to do it now.

At one of those events in 1972 Sol Snyder gave a lecture on the dopamine theory of schizophrenia and reviewed the evidence which was coming together at that time, which said "dopamine release is how amphetamines cause psychosis, anti-psychotic drugs work by blocking dopamine, and this is what it's all about". Sol's lecture was a wonderful synthesis and it really triggered my enthusiasm for that area. I was lucky, shortly after that to get into dopamine research through the discovery made originally by Paul Greengard in Yale and John Kebabian, his graduate student, of a biochemical model for the dopamine receptor in brain, which relied on the measurement of dopamine stimulated cyclic AMP formation in brain homogenate.

This was before radio-labelling?
Yes this was before anybody had a way of labelling the receptors. Many people believed that the dopamine receptor in brain was the target for anti-schizophrenic

drugs but nobody had the biochemical tools to prove that. Richard Miller, who was an outstanding graduate student, started his thesis work with me in Cambridge on the dopamine-stimulated cyclic AMP system that Greengard had described originally in retina. We were able to show in the brain, much to our delight, that a number of anti-schizophrenic drugs inhibited responses to dopamine in this system and they did so in a rank order of potency which fitted their clinical effects. For example, compounds in the phenothiazine series that were not clinically active did not block, so we thought we had discovered the target for anti-schizophrenic drugs, although there were some warning signs that should have told us that we were wrong. A whole group of drugs, the butyrophenones, haloperidol-type drugs, simply did not work in this system and we knew of course that they were very powerful anti-schizophrenic drugs. Shortly after that it became apparent, when Sol Snyder's lab in Baltimore and Phil Seeman's lab in Canada finally got the right radioligand to label the dopamine receptor, that what they were labelling was a different dopamine receptor from the one that we had been studying. We had been studying what is now known as the D-1 receptor and the key target for anti-psychotic drugs act is the D-2. Of course we didn't know that at the time.

When the Snyder work developed did you make the jump to the idea that there must be a D-1 receptor there or how did the D-1 receptor ..
Well I guess at the time the Snyder and Seaman work came out, we were out of that field. Richard Miller had gone on to do other things in the US. But we had actually come to the conclusion that there must be more than one dopamine receptor because the butyrophenones didn't work on the adenylate cyclase model.

Instead of further work on dopamine receptors I decided to pursue the dopamine hypothesis by trying to collect post mortem brain from patients dying of schizophrenic illness. I developed a major project with Angus MacKay, who was a young psychiatrist training in research in my laboratory and with Ted Bird an enormously enthusiastic and energetic American visitor who had the idea of setting up a Brain Tissue Bank in the MRC Unit in Cambridge. I think we were one of the first anywhere in the world to start a systematic collection of frozen postmortem human brain, carefully dissected into particular regions and stored and made available to the academic researchers around the world. Ted Bird and I were surprised really at how many things you could do with such tissue specimens. Biochemists are brought up to believe that you have got to remove tissue from the organism as soon as the animal is dead, and you have got to freeze it quickly otherwise it is not going to be of any value. It turns out that that isn't true for neurotransmitters and neuropeptide systems in brain. The biochemical systems associated with neurotransmitters, the enzymes, the uptake sites, the various receptor proteins are remarkably stable post-mortem and can be measured even under the normal conditions of post-mortem collection and storage.

So we set up, among other things, to test the dopamine hypothesis of schizophrenia, which at first sight might seem quite straightforward. But of course, we hit many problems en route. The results, were initially encouraging because we were able to show that you can indeed measure increased levels of dopamine and increased densities of dopamine receptors using the then available radio-ligand binding assays. But of course, the interpretation of these data was not simple because it was

becoming apparent from animal studies that treatment with anti-schizophrenic drugs for any length of time leads to adaptive changes in brain chemistry - including increased dopamine levels and increased densities of dopamine receptors - as some sort of compensation to the receptor blockage. So the results remained ambiguous and I think to this day it is unclear whether the post-mortem findings mean anything in terms of the dopamine hypothesis. Like others we tried to find drug naive subjects, but they are few and far between in developed countries. So this remains a set of findings which we were quite pleased with but really in the long run I don't think they helped understand the illness all that much.

This area has I suppose been taken over by the in-vivo brain imaging people but while it lasted one or two of the key figures trained with you - Gavin Reynolds.

Yes, although brain imaging of dopamine receptors in schizophrenic has also given conflicting results. Gavin was in Cambridge as a visitor and he has continued with great dedication to work in this area in which he continues to make important contributions, but I think he would admit like anyone else that this field of study is fraught with many problems of interpretation. The finding that he has made which I find very intriguing is the observation of increased dopamine levels on one side of the brain in schizophrenia, in the amygdala. That is important for some of the other neurobiological ideas about the nature of schizophrenic illness, what goes wrong in the brain. Maybe some day, we will put our finger on a neurochemical abnormality in the dopamine system in schizophrenia, but so far I think we have to admit that it's eluded us.

One of the other things we did on catecholamines was to pursue the use of 6-hydroxydopamine as a tool for probing catecholamine systems in the brain. This was around 1970, and a young American post -doctoral fellow, Norman Uretsky, from Chicago got onto this project. Hans Thoenen and his colleagues in Switzerland had shown the remarkable ability of 6-hydroxydopamine to destroy selectively sympathetic nerve endings in the periphery. It is a remarkably selective neurotoxin, a catecholamine derivative that is taken up and concentrated by the uptake mechanism in sympathetic nerves and then by means of a cytotoxic free radical mechanism it kills the nerve. Nobody had used it at that time in the brain and Norman Uretsky was able to show that if you gave the compound directly into the brain - you can't deliver it by other routes because it doesn't get through the blood brain barrier - it causes a very selective distruction of both noradrenergic and dopamine systems. Later on that became refined by us and by many others to show that if one administered minute local micro-injections of 6-hydroxydopamine into one area of the brain, it would cause selective damage to one particular dopamine adrenergic system. You could if you injected into just one side of the basal ganglia, for example, as Ungerstedt and his colleagues showed, produce an animal with a hemi-Parkinsonism syndrome. such animals when stimulated with dopaminergic drugs would rotate in one particular direction or another. That became a whole industry of its own in neuropharmacology - the rotating rat. This was exciting stuff and again we were lucky enough to be in at the very early stages of it.

Personally the most rewarding area to get into during that period in the 1970's was to get involved in neuropeptide research which was for me an entirely new area. We

started quite early in the 1970s with research on substance P, which I continue to be fascinated by as a neuropeptide. The structure of the peptide had only just been announced by Susan Lehman in 1970 as an 11 amino-acid peptide. In those days it wasn't that easy to make peptides synthetically but a lab at the Merck Institute in the US had made large amounts of substance P. Ralph Hirschman, the head of the chemistry group there at that time generously enough gave me a substantial amount (50mg) of the peptide, which kept us going for years. We started a whole programme of research around that 50 mg of synthetic peptide. It was enough to make antibodies with, and an Argentinian visitor, Claudio Coello used the antibodies to immuno-histochemically map substance P systems in the brain. We were also able to measure substance P release from isolated fragments of brain or spinal cord using a radioimmunoassay. Tom Jessell did some of that work and was able to show for the first time that the release of substance P from the sensory endings in the brain stem was inhibited by morphine and other opiates. That suggested a mechanism to explain one of the ways in which morphine controls the input of pain information into the CNS, an idea which became quite widely accepted.

In the mid 1970s, there was something of a sea-change happening with research - it became less inclined to be seen as pure research. There was a very famous LMB episode with Caesar Milstein where they discovered monoclonal antibodies and hinted that there might be quite a lot of money to be made out of all this, but the MRC failed to get a patent on it. This is often seen since as a key episode where the old attitudes were seen as being wonderful but not suited to the modern world. You were in there when all of this was going on. Did things seem to be changing to you?
Not then, although it certainly has since. I think you are right to say that the particular episode, when the MRC failed to recognise the importance of monoclonal antibodies was one of the events that later helped to crystallise thinking in this area, and explains why attitudes now are so different 20 years on.

There has been a sea-change in the attitude of University people. Academic people and MRC scientists now think about their work in commercial terms whereas we never paid any attention to that whatsoever. During the entire period that I worked for the MRC it never crossed our mind at all that anything we were doing might have any commercial value, nor did it the cross the mind of any of our administrators at the MRC Head Office, as far as I could see. It wasn't the way we thought about science. Now I think the pendulum has swung almost too far the other way. Scientists are looking over their shoulder at their lawyer to ask whether they are allowed to talk about what they are doing and this is one of the frustrating aspects of modern science, this requirement for confidentiality, imposed on scientists by the pressure for commercialisation. I think it's had a lot more effect in the United States than it has in Britain. In the US it's almost the norm for my academic colleagues to be involved somehow in one or other small company, whereas that's still very uncommon here.

When I came to Cambridge at the end of 1985, the impact of your leaving was still quite substantial. There was a remarkable amount of surprise but on the other hand both you and John Hughes for instance in the early 80s were making a move from academia to industry

I can't understand to this day, why people were so surprised. It's not as if I or Humphrey Rang (going to Sandoz) or John Hughes (to Parke Davies)[2], were the first academics ever to move to the pharmaceutical industry . There is a long tradition in Britain, starting with Sir Henry Dale who went to the Wellcome Labs at the turn of the century and revolutionised their research programmes. Then he went back to academia. John Vane went to Wellcome and came back to academia. Sir James Black went from industry to academia and then back to industry. There has been a fairly healthy interchange in Britian and this is one of the reasons I think why Britain has done so well in the pharmaceutical research area. We have, for example, in the British Pharmacological Society, as many members from industry as we do from academia.

During the 60s and 70s was it as respectable as it is now.
Well I suppose it's become more so. Attitudes have changed greatly in the last 50 years. In America, it was only after the Second World War that pharmacologists working in industry were allowed to join the American Pharmacological Society. They were taboo; they were not allowed in because what they were doing in industry wasn't good science. So the US had similar snooty attitudes.

Why did I become involved with the Merck project? Merck came to Britain as part of it's global expansion plan. The company was expanding in all directions and quite rightly felt that they should expand their research and make it more international. They picked on Britain as one of their European centres and they picked on neuroscience as an area that was blossoming in Britain and they were looking for someone to direct their new laboratory. I was initially involved with this project as an advisor and as I got more involved I could see what an exciting large project it was. I could see that the people from Merck were serious about what they intended to do. They were willing to spend money, they were willing to take a long term view of what came out of the lab and I liked the people I was dealing with.

When they set this up, it was probably the strongest neuroscience research facility in the UK, stronger than any university departments
Well it flourished. We were treated very generously and were able to construct a wonderful modern building which is one of the most delightful places I have ever worked in. I think people's work is influenced by the surroundings they work in and this was a wonderful place, done with great care and quality down to the last detail. There was an opportunity to start completely from scratch because Merck had no research operation in neuroscience in Europe at all. We were able to go out and recruit the best people we could find and at that time there were fortunately for us quite a number of good people around looking for jobs. We hired some very talented people in pharmacology, chemistry, biochemistry and behavioural science and built up to somewhere around 200 scientists when we got to our peak capacity with another 100 support staff. So it was another period of log-growth which I enjoyed being in. It was a terrific privilege to have that opportunity.

[2] Hughes J (1996). The discovery of the opioid peptides. in The Psychopharmacologists Vol 1, pp 539-564.

Partly by serendipity, partly by opportunism, we got into some very exciting areas of science quite quickly. Most notably into the glutamate area of pharmacology which was a completely new one for me, although it was expanding during the 1980's quite rapidly. We got into this through a Merck compound, which is called MK-801.

This is one of those compounds like 3-PPP, or 8-OH-DPAT, whose codes are highly significant for psychopharmacologists but which aren't known by the public at large.

Yes, this is one of those code numbers that are well known to scientists all around the world. MK-801 was developed by Merck in a sort of old fashioned way. It was picked up through random screening of organic chemicals as a powerful anti-convulsant. It has extraordinary effectiveness at very low doses in animal models of epilepsy. It was orally active and brain penetrant - so active that Merck decided to develop it as a potential anti-epileptic drug. They had got quite far into development by the time I joined the Company and started the Harlow Neuroscience Research Centre. Indeed Merck was about ready to go into the clinic with this new chemical but they didn't have the faintest idea how it worked. It was simply an anti-convulsant with an unknown mechanism, and they thought quite rightly, we should try and find out how it worked and determine whether we could build a better second generation compound.

We took that challenge on and fortunately we made very quick progress, following the Sol Snyder paradigm, which by then, thanks to his pioneering work, was the obvious thing to do, i.e. to radiolabel MK-801 and then see if we could find a binding site for the drug in brain homogenates. Eric Wong, who had just joined the lab as a PhD scientist was rapidly able to do this. He found a nanomolar afinity binding site which had a unique distribution in brain, which was displaced by various analogues of MK-801 with the right rank order of potency according to their anticonvulsant activities. We knew that we had the pharmacologically relevant site but we still didn't know what it was. So we again used the Sol Snyder technique, which is to grab hold of the Sigma catalogue and tick off all the things you can think of and throw them into your binding assay to see if they interfere. But we still didn't find the answer. Even though we put in glutamate and N-methyl-aspartic acid, nothing happened. In retrospect we know why that had happened - because there is so much glutamate present in the brain homogenate that adding a bit more doesn't make any difference, it's already occupying the sites and doesn't have any further effects. In any case the drug doesn't bind to the glutamate recognition site; it binds to some other part of the receptor. So that didn't work.

The only compounds that Eric Wong found that worked in displacing radio-labelled MK-801 were phencyclidine and ketamine. Were it not for another piece of good luck, that wouldn't have helped us either, because nobody really knew how they worked. They were anaesthetics of unknown mechanisms and that didn't help. However, David Lodge, a neurophysiologist and neuropharmacologist, fortunately for us had just published at this time some observations on phencyclidine and ketamine, involving classical neurophysiology-type experiments, recording from single neurones in the brain of an anaesthetised animal then applying glutamate, phencyclidine or ketamine and finding that these anaesthetics were quite good glutamate antagonists. Not only that but they appeared to be NMDA subtype

selective. So that gave us a clue and then John Kemp, who ran the neurophysiology lab in the Merck Neuroscience Research Centre, went on to show in brain slices, and later in brain cells in culture, that indeed MK-801 was an extraordinarily potent non-competitive NMDA receptor blocker.

So that gave us a mechanism and we were, almost unwittingly, plunged into a rapidly expanding area of neuropharmacology with an extraordinary tool. We did a lot of work on MK-801. Epilepsy wasn't the big indication. The big prize was neuroprotection: the idea that you could protect the brain against damage after a stroke or a head injury where there is a lot of free glutamate floating around doing damage. The NMDA receptor, which MK-801 targeted, seemed to be the key toxic mechanism. We were able to show, thanks to good work done with Jim McCulloch in Glasgow, who is a real expert on animal models of stroke, that MK-801 was highly protective. It reduced the volume of damage in animal models of stroke by a quite spectacular degree. Not only that, it was effective even when given some time after the initial insult to the brain. We thought we were really onto something quite exciting. Many other companies rushed into that field all with the same objective. Even now we don't know the answer as to whether this is going to work in the clinic, although some companies are now quite well advanced into clinical studies.

Merck, however, much to my disappointment at the time, decided to pull out of the area for a number of commercially sound reaons. MK-801 had a number of grey clouds floating over it. Apart from the very positive results that we had in animal models of neuroprotection, there was also the question of whether it might not be a psychotomimetic drug like phencyclidine, and indeed clinical experience now with other compounds does indeed show that it is very likely that most NMDA blockers will be phencyclidine-like psychotomimetics, when given to people. Whether that is a sufficient no-go area to prevent you using it, especially after strokes. I think is still debatable.

There is a curious ethical issue there - do you stop the production of these kinds of drugs because they will leak out on to the street.
That was one of the worries of course. Merck is a highly successful company and very much aware of not doing anything that might damage it's excellent image in the medical community. That's one of the reasons why it behaves somewhat cautiously and conservatively. That was only one of the issues. There were a number of other question marks. One was a very practical one. MK-801 causes, among other things, an increased autonomic outflow which leads to a quite substanial rise in blood pressure and heart rate both in animals and in people. This, we knew from volunteer studies was likely to occur within the range of doses that we were going to have to use. So if you think about that - there’s a patient who has had a stroke and you are about to give a drug that's likely to give a surge in blood pressure, a normal thrombo-embolic stroke might be converted into a haemorrhagic one, which you can't do anything about. This was regarded as a rather high risk side effect, even though it was probably one that could be controlled by suitable co-medication.

But its that kind of situation, where high risks are worth taking.
Well, there's a balance of risk and reward in most drug development projects. But really the final straw that led to the company's withdrawal was a paper published by

John Olney in Science in 1989. He made the surprising observation that when you give a single dose of MK-801 or phencyclidine to animals and look carefully in the brain for histological changes, in some areas of the cortex most of the large neurones became honeycombed - full of fluid-filled vesicles. The neurones became swollen and they looked like Swiss cheese. He described this as a neuropathology associated with these drugs, although even in the first paper he showed it was reversible - within a few hours it disappeared again. And he also showed that if you gave a second dose of MK-801 you didn't get the reaction a second time around. Nevertheless, it created a large problem because, if Merck is cautious, the FDA in America are even more cautious.

They convened a special meeting of experts to discuss this new set of findings. I had to go there as an expert witness for Merck and make our submission. We ourselves, of course, began to study this phenomenon intensely. We found that this was very largely a reversible pathology. On the other hand, if you gave a very large dose of MK-801 you did show a tiny percentage of neurones dying in these areas of brain. We were faced with this problem - here we had a drug that under extreme conditions of dosage might conceivably cause the death of a very small number of brain cells, while on the other hand it could potentially rescue a thousand million other brain cells. After some years have passed the balance of opinion now is that this isn't a no-go issue - drug companies are being allowed to develop NMDA antagonists which have similar pathology. We understand the phenomenon and that makes the FDA more comfortable with it, but at the time they set a number of rather stringent conditions for Merck and the other companies involved. Merck decided not to proceed with the development of MK-801. It was a commercial decision, probably correct at the time, but obviously disappointing to me and to the other scientists involved.

We continued to work in the area, trying to get a better version of MK-801 and trying to target another aspect of the NMDA receptor, the glycine modulatory site. But so far that hasn't come to fruition, although there are now compounds around from a number of companies in trial for the acute treatment of stroke, using this NMDA mechanism and we are all waiting to see how it's going to develop.

One of the other areas you moved into in this period was the neuropeptide area. Now you recently wrote a piece called "Neuropeptides - promise unfulfilled?".

Right. That proved to be a field again like the dopamine theory of schizophrenia, if you like, of great optimism, which somehow wasn't fulfilled in the sense that we still don't understand the basis of schizophrenia even though I think we now understand how anti-schizophrenic drugs work, which is a step forward. With peptides, we understand a great deal about how they are made, where they are and how they are released. We are now beginning in the 1990s to have a whole pharmacology based on a series of novel non-peptide organic drug molecules that target peptide receptors, which is a tremendous step forward. But we still don't understand what the neuropeptides are all about and why they are there. It remains as good a mystery as it was when we started working in the area. That doesn't mean that we didn't have a lot of fun on the way and make some interesting discoveries.

Substance P was the focus of that activity in the Merck Labs as it was in my Cambridge Lab. We had a substantial chemistry programme aimed at the rational design of an antagonist, based on looking at substance P and trying to make confirmationally restrained analogues of it. Brian Williams and others in the Chemistry Department at Merck did a wonderful job in making such compounds. We also tried the other Merck traditional approach which is natural product screening. Merck had a large programme of screening micro-organism fermentation products and looking for, not just antibiotics, but for all sorts of drugs. That programme over the years has been very successful.

For another neuropeptide, for example, cholecystokinin, Merck in the States discovered the first non-peptide drugs that antagonised CCK receptors from a natural product lead, asperlicin. We did quite a lot of work on the CCK antagonists to try and support the idea that they might have some therapeutic utility in the treatment of panic and anxiety states. That actually never came to anything. If you inject CCK peptide into people it induces a panic state that lasts for a few minutes. It's very unpleasant and you can obtain a dose response curve for panic vs dose of CCK and that could be blocked with the Merck antagonist so we thought we were really onto something quite interesting. But when the antagonist drug was given to patients who normally experienced panic attacks at regular intervals, it didn't do anything. They continued to have their panic attacks with the same frequency and the same severity. So all we ended up proving was that we didn't understand the basic rules of logic. The premise was that “CCK causes panic” but you can see that the implication that therefore “panic is caused by CCK” is a non-sequitur.

We spent a lot of effort on substance P without getting very far. We didn't find anythying in the natural product screening programme and we gave up on the programme for a few years until 1991, when scientists from Pfizer, published the first paper on a non-peptide drug that targetted substance P receptors. This was a very important discovery and got us back into the area. That one discovery was enough to trigger drug companies all over the world to create a multiplicity of new substance P receptor antagonists all based on the original starting point from Pfizer.

There's a public perception that being natural has to be better but in actual fact when you compare for instance, TPA vs streptokinase, the artificial compound comes out superior to the natural one. It's curious isn't it.
Well I don't go along with this natural approach. Certainly for brain peptides you're not going to make much progress that way because the peptides don't get across the blood-brain barrier. In retrospect we would never have found a substance P antagonist by using substance P as the starting point for our chemistry, which is what we were trying to do. The newly discovered antagonist drugs actually bind to a different part of the receptor from the site where substance P binds and they bear little structural resemblance to substance P. It's not like another key that fits the same lock, it's a different key that fits a different part of the lock. We could have spent a hundred years modelling substance P and you would never have discovered these new drug molecules. But now you have got one agent and you can model from that with computer modelling techniques and come up with 101 other antagonists.

I am looking forward to seeing how some of these stories play out. The NMDA story is still wide open in terms of whether it is going to have any therapeutic utility, and the substance P story is coming to that stage now. There are a number of very powerful Substance P antagonists drugs from different companies in different stages of development for a variety of indications. For example substance P is involved in the vagal emesis reflex circuit and substance P antagonists have proved to be broad spectrum anti-emetics in animals. They work against a wider range of emetic stimuli than the recently introduced 5HT-3 blocking drugs which have proved very succesful both medically and commercial.

Shortly after you moved over to the industry, I was aware that a few of your colleagues such as Roger Pinder and Brian Leonard saw a potential clash ahead, which was you were going to Merck for the opportunity to move science forward while Merck made drugs - there was a clash potentially there they felt and they weren't sure how it would play out. How did it play?
Well, when I moved to Merck, certainly one of the attractions was having a brand new lab, the ability to recruit a whole cohort of talented scientists, a lot of freedom to choose what sort of scientists we felt we needed and the ability to choose more or less what we wanted to do as targets, although we knew right from day one that this was a drug discovery lab. It wasn't like some of the research labs that had been set up by companies, which were essentially public relations exercises, like the Roche Institute for Molecular Biology in Nutley New Jersey, for example, or The Roche Institute for Immunology in Basel - pure blue sky science and not related to the company. The Merck Neuroscience Research Centre was never like that, and I knew it was not going to be. It had, right from Day One, taken over the responsibility of inventing new drugs in the CNS area for the company world wide. Merck dispersed the small CNS group they had previously had in the States. So we were out there on our own and if we didn't get CNS drugs we knew that the company only had one set of people to blame and that was us.

Fortunately for us, the company was going through an extremely successful period commercially and they could afford to take a long term view, which they did. I have got no complaints at all about the way that Merck treated me or the other scientists at the Neuroscience Research Centre. They gave us very generous support and we had a great deal of freedom in choosing projects to work on. We wanted as badly as anyone else to make drugs for the company. On the whole I think our track record was not bad in that respect. Discovering drugs and developing them is a highly risky business. Not more than 1 in 10 of the ones that are recommended by the basic research lab actually make it all the way through development and into the clinic and get registered. There are many many ways of losing compounds and, over the years, we discovered several of them!

So we did achieve some of the things that we set out to do but we also lost some good looking projects and some good looking compounds. You've heard about MK-801. We also got, into a very fruitful collaboration very early on with a small Danish company called Ferrosan and a very talented group of drug discovery scientists from whom we learnt a great deal. We worked with them on partial agonist benzodiazepines with the idea that a benzodiazepine that didn't have the full agonist profile of diazepam might have some advantages as an anti-anxiety compound but

lacking the sedation and lacking the dependence properties of some of the classical benzodiazepines. That was a good idea, although nobody has actually pulled it off successfully in the clinic as yet, despite many attempts. Abecarnil is on the market now and its the closest to a partial BZ agonist but not a perfect one. Anyway, we got into this collaboration and within a few years of starting the Neuroscience Research Centre we had development compounds from that, which looked very promising in animals. Unfortunately all the development compounds were lost through toxicology in animals for various reasons and never got through to being given to patients.

At the time, Merck and Glaxo were the 2 largest players and both were making a big deal about the fact that they were science driven. It had become the respectable thing to be into "rational drug development". How much is that mythology.

That was not mythology from Merck's point of view. Merck is a very unusual company in being science led. I think it has been since the time of George Merck in the 1930s who was among the first to recognise that if you want to be successfull in pharmaceutical research you have got to go out and attract top quality scientists and give them a working environment that they find attractive. You have got to allow them to publish. Merck did that at an early period, before the Second World War, when other companies weren't behaving like that and Merck continues to have science as its driving force. After all Roy Vagelos went from being an academic research scientist, to Head of Research and Development in Merck and then to being Chief Executive Officer of the Company and one of the American business community's hero figures of the 1980's and 90's.

What was he like?

As you'd expect, he's a charismatic figure. He drove the cholestrol-lowering programme and also the angiotensin converting enzyme inhibitor programme at Merck, both of which when the company started on them, were speculative. Nobody could have predicted that blocking angiotensin synthesis would prove to be of universal benefit in all people with high blood pressure, and of enormous benefit to people with heart failure. But Roy Vagelos drove that programme with enormous energy and of course, he brought in the idea of a cholestrol lowering programme and led that. It was a long programme that took nearly 20 years to reach fruition. So yes, he deserves all the credit.

Did you encounter any problems at Merck?

I think one disadvantage we had in the Neuroscience Research Centre was not being on the Headquarter site, so we lacked that day to day contact with the rest of the company. Another disadvantage was that Merck had nothing else going in the CNS area. The only major CNS product when I joined the company was Sinemet, a combination of L-DOPA and carbidopa for Parkinson's disease, which was a very successful product. It dominated the world market for Parkinson's disease for many years. But the research on Sinemet had been done long before I joined. None of the development people had had any experience of developing a CNS drug. Nor had any of the senior management, who sit around the High Table in Merck and make the decisions about what goes forward and what doesn't.

Merck had hit the doldrums in the CNS for a number of years. That was one of the reasons why they set up the Neuroscience Centre. So we had the disadvantage that we were talking to people to whom you had to explain everything from the beginning and that wasn't so easy sometimes in a company that deals with anti-infective agents, cholesterol lowering agents and cardio-vascular agents, where you've got nice clear end points. You can measure blood pressure, that's easy; you can measure whether you treat the bacterial infection; you can measure cholesterol, but if you go into the development of CNS drugs you're talking about clinical trials where many of the patients get better on placebo anyway and you are looking for some small change on top of that, and how do you measure depression or anxiety?

One of the interviews I read with great interest in your first volume was by Peter Waldmeier at Ciba-Geigy[3]. I share some of the obvious agonies that he went through in a long career, of having what he thought were really excellent projects turned down by senior management or if not turned down, at least not supported, which is almost the same thing. In order to get something through to the end in a drug company, you have to have people who really believe in it and champion it, otherwise, they just look for reasons to stop it, which is what you could see from that account that he gave you. I knew Peter Waldemeir very well and Laurent Maitre, his boss from a period in the 1970's when I acted as a consultant to that group. They had what appeared to me very good ideas. They were working on 5-HT uptake inhibitors long before anybody had thought about them, at least at the same time as Arvid Carlsson was, but this was never followed up by the company.

Talking about 5-HT uptake inhibitors, I can tell you a little about zimelidene. One of my first exposures to drug development and how complicated the whole process is, was within a few weeks after joining Merck, in 1983. I went to visit the clinical research group in the US, a large group, headed by Marv Jaffe. They had a small CNS team there which had been working with Astra on zimelidine, because Merck has a deal with Astra which gives them access to any Astra product for development in North America. They had completed the Phase III trials for zimelidine in the USA and Canada and they were overjoyed because clearly the drug was working as well as amitriptyline, and it was far less toxic. They were over the moon. They were having a party to celebrate the loading of the truck that was going to go down to Washington with the registration file in it. I saw it in this room and it impacted on me just how complicated it all was - to see a room full of volumes of data going from floor to ceiling in several large piles, 200 or more volumes of data. If it had gone through, zimelidine would have been registered probably a year before Prozac in the States. It was already on the market in Europe, by Astra. But no sooner did the truck get to Washington, than serious adverse effects began to crop up in Europe, at a rate of about 1 in 100,000. This is the nightmare that any drug company has. It doesn't matter how well you have done the clinical research. You can have 3,000 patients in a Phase III trial and never pick up a rare serious complication.

[3]Waldmeier P (1996). From mental illness to neurodegeneration. in The Psychopharmacologists, vol 1 pp .

Of course Prozac has done so well to some extent has been because Lilly are a US company and the Americans are going to home-buy but if Merck had been pushing Zimelidine, would Prozac have ever been heard of...
We could have had a part of that market. From my point of view the story has some extra appeal because I started in reseach working on amine uptake. We knew how antidepressants worked very early on. As soon as the uptake mechanisms for 5-HT and noradrenaline were characterised, it was apparent that the conventional tricyclic antidepressants acted as amine uptake inhibitors. One could ask why didn't the major companies like Merck and Ciba-Geigy get right back in there and make better uptake inhibitors as soon as they knew about it? Merck had amitriptyline but the main thing wrong with amitripytline was its powerful cholinergic effects which makes it toxic. We could have had a “son of amitriptyline” but we didn't get there. We didn't even think about working on zimelidine in the Neuroscience Lab in Merck because we thought that story was all over. But it's strange to think how a mechanism that we already knew about for the conventional antidepressants could suddenly become overnight a block-buster with Prozac selling $2,000 million a year and portrayed as a totally new development in psychopharmacology, which basically it isn't. The 5-HT uptake inhibitors have some advantages but their main one is that you cannot commit suicide by overdosing because they are not that toxic.

Let me hop to another emblematic scene in which you have had connections with all the players. Another Merck drug, a D4 antagonist failed. Merck put a lot of money into trying to test this out clinically - on the back I guess of claims by Phil Seeman. Now, often claims made on the back of sometimes flimsy data or thin arguments seem to catch the field and one of those who are caught are the drug companies. You could say they're possibly naive to move so fast on the back of these claims but on the other hand companies are the only people who can actually test some of these claims out. Another player in all this, who worked with you previously, Gavin Reynolds, did perhaps more than anyone else to kill the D4 story.
Well the dopamine D4 antagonist as a novel CNS drug discovery target is a beautiful example of how powerful the techniques of molecular biology are and what impact they now have on drug discovery in CNS, as in every other area. What motivated us to start a project for D4 wasn't really the Phil Seeman paper claiming large increases in D4 receptors in the brains of schizophrenics, it was the original paper published in Nature by Seeman's group - by van Tol et al, who first described the discovery of this dopamine receptor. It was not only novel but it also had unusual pharmacology in the sense that clozapine had a preferential affinity for this site. Now clozapine somehow holds the clue about how to make better antipsychotics. If you could only understand how clozapine worked, you might have a way of making “son of clozapine”, which would be the next generation of anti-schizophrenic drugs. So we were always alert to anything that had to do with clozapine and we came across this paper. My boss in Merck, Ed Scolnick who is very molecular biology-oriented in his thinking, said "this is it, go for it". And that was all it took, that one letter in Nature and we went for it. The Merck chemistry team in Harlow did a magnificent job in coming up with a highly selective, high affinity dopamine D4 antagonist in a very short space of time. We got a development project in place and we carried it right through and it was completed after I left, but we now know that in the clinical trial the patients didn't show any improvement, in fact there was a tendency for them to get

worse (Kramer et al 1996, Psychopharmacology Bulletin, 32:467). They couldn't tell whether they had the active drug or the placebo. But this was a nice example, I think, of what a big company can do. You can have an idea, but to put it into practice is quite another thing and to put it into practice quickly, so you could have some competitive commercial advantage, you have got to move quite fast and you have to be willing to put in a significant resource. I couldn't tell you how many dollars or pounds were spent on that particular project but it was a significant effort. Not just one chemist in a back room but a whole team.

At first sight it was very good news for us that having chosen to do a D4 antagonist project and put all this effort in, a paper comes out almost the next day from Phil Seeman claiming a seven fold increase in this receptor in schizophrenia. We thought this was great, but then we looked at the paper more closely and tried to replicate it and I talked to Gavin Reynolds and we realised clearly that it was a very contentious claim. There's something about schizophrenia research that impels people to make extraordinary claims. If you look over the history of schizophrenia research, it is littered with the skeletons of chemical hypotheses.

There's an art to these claims. There has to be good marketing copy to the claim. One person who has been able to do this awfully well whom you liaised with in Cambridge was Tim Crow. The idea of type 1 and type 2 or positive and negative schizophrenia and the progression from one to the other was an extraordinarily influential claim, which in some respects ran in the face of all the evidence, but it was a good marketing concept and I think marketing plays more of a part in academia than many people would like to concede
Like other aspects of life, it's one thing to have an idea, it's another thing whether you can convince other people that your idea has any merit and some people are better at this than others. Sol Synder is a very good exponent of this art. Merton Sandler is a wonderfully persuasive talker. Mimo Costa is another person who could get up and give you an outrageous hypothesis and you would find it very plausible because of the way he delivered it. I don't think I'd put myself in that category of being a proponent of hypotheses. My way of doing things is usually more opportunistic. If something looks good I am willing to take it up and run with it at a very early stage if I have the feeling that it's ready for development.

In addition to having worked with Sol Snyder you also did some work with what at the time must have been a fairly young Sol Langer..
Sol Langer and I worked together briefly in the 1960's in Cambridge when he came as a visiting scientist to Marthe Vogt. We were not in the same department. Marthe Vogt worked with Gaddum at Babraham. She was the first person to describe the existence of noradrenaline in the brain in the 1950's. It took some effort to persuade people to think about chemical transmitters in the brain in those days. She was one of that generation of scientists who basically never give up research and just go on going into the lab every day. Feldberg was another example, who should perhaps have been stopped but nobody had the temerity to tell him so. Actually, when I was planning to do a PhD in Cambridge in 1961 one of the people I had talked to was Marthe Vogt and I had seriously thought about going there to do a PhD with her.

What was she like then?

She was a fairly austere lady in many ways. It was quite difficult to get on friendly terms with her although eventually I did. She was very open, always willing to tell you about her research. She was trained in a classical mode of pharmacology, which I don't think would have suited me very much as I was trained in biochemical techniques. But she did what she did with great ability and continued to make contributions for many years. So that's how I got to know Sol Langer. Sol and I had been friends before that because when I was a post-doc in the Neurobiology Lab at Harvard he was a post-doc in the Department of Pharmacology, just a few floors up in the same building and we used to see each other there. He is one of those people who went into industry and continued to do original research of his own. I don't know how he managed it.

If you had stayed with reuptake mechanisms when you were working on it and wrote the monograph on it, you would have had the chance to market yourself as the creator of this generation of drugs to some extent...
It would have been incredibly boring scientifically. I suppose it's a weakness but I can't stick with one area of science for ever. There are so many exciting things happening all the time in our field that you'd like to be part of. Right now if I was given the chance to do new research, a lab and new work, I would learn about molecular genetics and get into research on the genetic risk factors in psychiatric illness, which I think is the big project for the future in psychiatry. It's where we are going to see, hopefully, very soon, the really big discoveries being made, whereas you could say psychopharmacology research has been spinning its wheels for the last 30 or 40 years, since the really major discoveries were made in the 50s and 60s.

But are the molecular genetic projects not going to spell trouble for the industry in that they are going to break down the monolithic concepts like schizophrenia, which means the market is not going to look out as attractive.
That's a very perceptive comment I think. It's true not just for psychiatry but for any illness with a polygenic basis. You can see it happening in diabetes research, for example. There won't be a single gene for diabetes, there will be 10 or 12 risk factor genes for diabetes. And then you have a single disease turned into 12 different genetically based entities and how you are going to treat each one of those fragments, whereas you can treat them all with insulin and you can treat all schizophrenics with chlorpromazine? So, you're right but we don’t have to think about everything in terms of whether it's good for the pharmaceutical industry, we have to take a broader picture. Whether it's good for us as a species to understand schizophrenic illnesses, I have no doubt at all. It's going to be probably by small advances that we will suddenly realise that we have made a major insight. You can see it happening already in Alzheimer's disease in the last 5 years. There are now 4 different genes identified as risk factors and many more no doubt will be coming. It will give us a totally new way of looking at these diseases and in the long run it must give us a totally new way of thinking about how you might prescribe therapy.

Was there ever at any point, working within the industry when you felt that people just aren't grateful for what the industry do. You find the drugs which cure the infections diseases that kill their children and they’re very grateful for a short time but then everybody forgets about that pretty quickly and just thinks about the nasty pharmaceutical industry again

That was one of the striking things about moving from academia to industry. You go from a profession in academic research which isn't particularly liked by the community at large but it isn't particularly disliked either, it's sort of neutral. People think about scientists as some strange creatures but they don't necessarily hate them. Then you go to be a scientist in industry and you are universally hated and reviled.

It's curious isn't it when you think of all the benefits that derive from pharmaceutical research. Just look at the reduced risk now for cardiovascular disease, which is seen because of the new pharmacological treatments but somehow it goes over people's heads. The other thing in the pharmaceutical industry that I find very strange is that you are always being asked for perfection - you have to have a drug which is totally safe and totally effective with no side effects . This is what is expected of you, whereas as surgeon if I wanted to invent a new surgical procedure which had a mortality rate of 10%, I could go ahead and do that. I might even say that my operation was wonderful because it had a 90% success rate! Look at the early history of heart transplant surgery where everyone died quite soon after the operation, but everybody thought that this was a great advance and the surgeon a great hero. It's very difficult to understand.

I suppose at the back of it, is the fact that drug companies make a lot of money. Maybe surgeons make a lot of money too but not on the same scale. It's the idea that you can profit from the sick that sticks in the gullet of many people. Personally, I don't have any problem with that. I think that the pharmaceutical industry may have been guilty of considerable excesses in the last few decades, finding it too easy to make money and having too high a profit margin and being somewhat self-indulgent about the way that it spent money. But, on the whole the free enterprise system has created far more drugs than any other system that you could think of. Look at the Soviet system, producing virtually no new pharmaceutical discoveries at all in the last 50 odd years. Here we are in the capitalist system with companies competing against each other for commercial advantage and that's one of the ways of getting things done and getting them done in a hurry. But there are limits to this. You might ask why do we need 7 different angiotensin converting enzyme inhibitors, wouldn't 2 be enough? And the industry is thinning itself out on these lines. You wont have 7 drugs of the same type any more because it won't be commercially viable to do it.

You left Merck and moved back into academia. How's that going?
To go out on Monday morning and not to have to think about getting on the airplane to Rahway New Jersey has some attractions! I've got some new interests now. I'm interested in positron emission temography, or PET imaging and I have a link with the MRC Cyclotron Unit at the Hammersmith Hospital - one of the pioneering labs in this area. The reason I find it fascinating as a pharmacologist is that this is the only way in which you can look at drug receptor binding phenomena in the living patient. You can look inside the brain and you can even see dopamine receptor ligands binding dopamine receptors in the brain and you can do all sorts of things with that. I find that very exciting, so I am working with them to help inject more pharmacology into the way they do things.

Do you see yourself as a neuroscientist or a psychopharmacologist?

I think of myself really more as a neuroscientist than a psychopharmacologist. Clinical psychopharmacology has never really excited me much, I am sorry to say. If I have a choice of meetings to go to, I will go to the Society of Neuroscience in the USA rather than to the ACNP, although I have been many times to the ACNP and CINP meetings. I find the ACNP and even more so the CINP have a sort of old boys club feeling about them. They tend to be dominated by cohorts of people who have been around for a long time and they have this special relationship with one another and with certain pharmaceutical companies, and it's all very cosy. I don't find it particularly attractive.

Wouldn't you get any of that in the Society of Neuroscience?
No its not like that. It's a very democratically run and dynamic society. They've had a remarkable success in building a society in only 20 years. The Neuroscience Research Programme had a great deal to do with that. A lot of people who were in the NRP ended up as Presidents of the Society for Neuroscience. Frank Schmitt's NRP group was not a fixed group of people, there was turnover there, and a lot of people went through the NRP in that way . I was an Associate for about 10 years. NRP had a great influence on the development of American neuroscience in the 1960s and 70s. The Society grew out of that and has become phenomenally successful. Too successful some would say. There are more than 25,000 members and I am going to a meeting next month (November 1996) where 24,000 people will register.

And will they all be there for serious business, as opposed to people who go to the APA meetings where most people are there on a junket.....
They're not going to be out on the beach in Washington in November. They are there to listen to science and it's on a big scale and very efficiently run. Maybe a little bit overpowering; it takes you a few days to recover from an event like that. I find the depressing thing about going to a big meeting like that is that you realise just how insignificant you are. I gave a lecture there a few years ago on MK-801 and you go into auditorium built like an aircraft hanger and you can't even see the back row of seats from the stage. It was an intimidating experience. The experience of attending these mega meetings is like going out into a field on a dark winter night and looking up at the stars in the sky. If you do that for a few minutes you realise how utterly insignificant you are. If you fell under a bus tomorrow it wouldn't make the slightest bit of difference.

What about Frank Schmitt?
Frank was very much the guru figure of the NRP. He was a very forceful person. I grew to like him more over the years than I did initially. Initially to an English person who has been brought up to be fairly reticent, Frank was overwhelming. He was always telling you how wonderful things were and how important the contributions of NRP were. This was it, the NRP, in that little room was probably the centre of the entire brain research universe. And he had this almost grandiose vision of how this organisation ought to operate. On first exposure I found that a very un-European way of doing things. The NRP used to have meetings where they would have verbatim transcripts on a meeting that went for 2 days. Every word was harvested in case some gems of wisdom were uttered. But I got to like and respect Frank a lot more over the years. He had this knack of identifying an interesting subject and then

bringing in people who had never thought about it before. He brought in nuclear physicists or electrical engineers or people who write electronic circuit diagrams and made them think about the brain.

In the foreword to volume 1 of these interviews I mentioned that someone had put it to me that if I really wanted to find out about the history of the field, I should interview the wives of these eminent pharmacologists - but in your case your wife is an equally eminent psychopharmacologist
Yes, Susan was with me during the 2 years of post-doc in the States in the 1960s. In Harvard, when we were there, she worked in Peter Dew's lab in the Department of Pharmacology, the same building in which I was in Neurobiology. At that time she got involved in psychopharmacology and in behavioural studies and she got so enthusiastic about that field that she stayed with it and has done ever since in her research career. When I moved to the Merck Lab she moved shortly afterwards to become Head of the Behavioural group there and set up a Behavioural Psychopharmacology lab. She has made her own important contributions in the study of peptides in brain and particularly in the study of brain dopamine using 6-hydroxydopamine as a tool, which we developed as a way of lesioning the specific catecholamine pathways in brain. This allowed her to show conclusively that amphetamine owes most of its psychostimulant properties in animals to its ability to interact with the dopamine pathways. We have worked very closely on many projects.

It must have been an extraordinary marriage because she hasn't just been the quiet wife tagging along after her husband because she's been a President of the BAP and is now Prof of Psychology here in Oxford.
Yes, she is particularly enjoying her present job as Chairman of the Department of Experimental Psychology in Oxford. The person who had that job before, Larry Weiskrantz, was her PhD mentor in Cambridge in the 60s. She's been closely attached to the Department in Oxford for many years and is now enjoying her new role. She is, I think, the sixth woman Professor in Oxford against some 280 men Professors, so there is still a bit of gender bias in the selection process.

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