THE PLACE OF NEUROPHYSIOLOGY IN PSYCHOPHARMACOLOGY
FLOYD BLOOM

When I first went to do psychopharmacology research with Brian Leonard in Galway in 1980, pretty well the first thing he did was to give me a copy of your book the The Biochemical Basis of Neuropharmacology1 and said read this - this is all you need to know. More recently looking through bookshelves I've noticed your Brain Mind and Behaviour2 and been impressed by it. But the next encounter with you as it were was when you were invited to give the BAP guest lecture in 19873. The lecture included large amounts of neurophysiology, which I know nothing about, and dealt with alcoholism, which is not my area, but it still remains for me one of the best Guest Lectures I've ever heard in any forum - hence the interest for me to include you in this group of interviews; more than most people you seem aware of the need to reach out - to communicate to people outside your own area where things are at.

I could certainly understand how it must seem that way. There must be some of that in that book. Both of those books, however, were really not planned to do that when they began. The Biochemical Basis of Neuropharmacology was going to be project with a man who led the neuropharmacology course for graduate students at Yale University - one of my many Italian mentors in neuropharmacology, Dr. Nicholas Giarman. Unfortunately Dr. Giarman died as the book contract was being signed so Jack Cooper, Bob Roth and I agreed that we would do the book strictly to honour our departed friends' memory. We had no idea whether it would be a successful book or not but it encapsulated the lectures that we would have given in that course in that year and we wrote it strictly in the way we would have given it. Students seem to have liked the conversational tone of it all, so it's caught on and we have had a great deal of fun doing it together. It really started out not to become an icon of the field but really just to honour our dear friend's memory and that is the only dedication that the book has ever carried - to our friend, Nicholas Giarman.

The Brain, Mind and Behaviour Book came up because of the television series "The Brain" for which I was one of the science advisors. They had contracted for a book that would be used by junior colleges and community colleges to teach a course on the brain as viewed by modern scientific terms and the person who had agreed to write the book defaulted. With a relatively short amount of time they paid me a generous sum to try and take on this project. The first edition was not completely successful because it is like one of our US postage stamp things, we never got to see the galley proofs for the figure captions so many of them were just totally wrong. None of the reviewers picked up on that; the person who reviewed it for the New Scientist gave it such a thrilling review that I was so pleased to have had that review.

But it is the kind of book that will appeal across a wide range or interests and even to people not in the field at all...

That is exactly who it is written for, for people who were interested in the brain but had not had anything more than say a good high school course in biology. We had to speak in very plain terms and bootstrap our definitions as we got into it. But I have enjoyed it and I must say it has salved some of my feeling of responsibility for not being in an academic institution, for being in a research only institution.

Yes, that was one of the points I was going to make; it seems odd in a sense that one of the people I think of as being one of the best communicators in the field, who has the

capacity to communicate to people on the street is you and aren't in a university - Silvio Garattini is another such person

Yes, right. Well, you know it is a matter of how you parse your time. I find being at a research institution gives me more concentrated effort to focus on the research and I do these other things in my private time. I enjoy that but I don't necessarily have a lingering interaction with students the way you would if you were giving a course. You know, tastes are a matter of personal judgement and I find this quite acceptable. I am sure you have had the same thing; you go to some place that has read your book and people will comment as you did or bring their copy of it to have you sign it.

It isn't only those books though. A flyer for Psychopharmacology The Fourth Generation of Progress4 came in through the post about a week before I came over. This is at the opposite end of the spectrum. Far from for the man on the street this is the bible for most of us within the field.

This again is a matter of love more than it is a matter of desire because this College means a lot to me. It was a major maturation point when I was elected for membership in that College and then I became its president. The previous three versions of the text had very good reviews but they weren't organised so when David Kupfer and I took this on we tried to do it in a way that would provide a logical skeleton. No matter where you were in your life's education you could find an entry point and then navigate through the rest of the book - we are hoping for it to work out that way.

You've introduced the issue of your involvement with ACNP, do you want to tell me more about all that

Well, it was the same gentleman that I mentioned to you before, Nicholas Giarman, who was the person for whom we were doing the course and his close companion and collaborator in many years of research on serotonin, Daniel X Freedman, who became one of my closest mentors in my scientific career. Both of them invited me to go; the first year I was a post-doctoral fellow at Yale and that would have been 1965. I was elected to membership in 1968 and I had a chapter in that very first book, "The First Generation of Progress" so it goes back quite a way.

ACNP actually began if you look at the historical volume In The Beginning with a bunch of clinical investigators really concerned to get to grips with the issues raised by all these new drugs but its changed character a lot; do you want to pick that one up?

It was a very exciting time, probably a unique time in the history of brain research because we had drugs that seemed to cure mental illnesses and they produced very similar behavioural effects on animals and so that gave us an entry point. It was really the foundation of modern neuro-science because it gave us a way to connect the chemistry of the brain with the physiology of the brain in a way that you could now sort of think you had insight into the nature of mental illness. That was impossible before until the drugs provided the tools to do that. So studying the mechanisms of action of those tools became a very exciting opportunity and you could sense that in the field.

But its funny, at that inaugural meeting my mentor, Daniel X Freedman was a member of that audience and yet I cannot find a single word attributed to him. Another of my Italian mentors,

Erminio Costa, said a few things, he was associated with Dr. Brodie. But I mean in this text he is associated with Dr. Brodie quite a lot too. You really should interview Erminio too. He really is another pioneer. Erminio left Italy because the opportunities were here. He worked at the Himwich laboratory in Galesburg, Illinois which was one of the pioneering brain chemistry labs, in that era. He then moved from there to Dr. Brodie's Lab, all of which really put him in a place to see much of this in the happening.

Anyway to your question, ACNP from the time that I knew it was a relatively small organisation, 400 or 500 people. Non participating guests were relatively rare. What has happened through the years is that the guest proportions have risen and because there are just so many good people in the field, we have relented on our membership size. It used to be that it was sort of a fixed size, set of around 400, so somebody had to die before somebody else could get in. Now I think we have closer to 700 members and we elect on average about 20 a year depending upon the whims and choices of the council. So it has grown and now the meetings maybe have a 1000 people at them and you can't really feel that you know everything that is going on in all the nooks and crannies of the meeting the way you once did. But science has matured. I mean there was so little to talk about in the early days - the facts were so few that we could spread them out, now there are so many facts and so many specialised interest groups.

One of the things I have heard about ACNP, which is what you hear about BAP also is yes we have far more detail far more specialisation but that there is a problem, almost a crisis, in that a greater and greater number of people are coming along to meetings and finding less and less on the programmes that seems accessible to them - you sometimes hear people say they don't understand even titles of many of the lectures or posters when looking through the program.

Exactly. So what we have done for the last four years is have a teaching day specifically to provide - I don't like to use the word remedial education - but that is basically what it is. It still has not caught on to the degree and we still hear that complaint because in part we don't school our presenters enough. I think if we worked with the presenter so that they actually understood that they had to simplify their language because they are talking to people who are not active in the sport although in the audience there will be people who are very active in that sport so that's the kind of problem that arises. I think scientific societies in general have not paid enough attention to that. The teaching day is good but then there are going to be people who are either too busy or too proud to go to teaching day but who still would really welcome the thing and that's part of the motivation for Cooper, Bloom and Roth and for Brain, Mind and Behaviour - to say those things not in a demeaning way but I think really they are not that complicated if you really understand what you are talking about. Its just too easy to slip into codewords and buzz words that you forget what the origin is.

This is still a very clinically oriented college and if it doesn't connect back to mental illness in some way it seems to me that it could be any place. The years that I was there I tried to remind people that this was not the Society for Neuroscience. The Society for Neuroscience meets separately. This is the American College of Neuropsychopharmacology so good science is welcomed but it needs to be good science within the goals of this college.

There is a fear in recent years, in BAP, that it could break apart, the clinical people might feel that well there isn't anything left for us here, lets go back into the Royal College of Psychiatrists. Now you've recently had the American Society for Clinical Psychopharmacology formed by Don Kline for something like the same reason

Exactly. Two of the previous presidents. Don Klein from Colombia, and George Simpson from Philadelphia, both were founding members of that because they felt that there was not enough clinical. They still come to ACNP and I guess that there is enough people that it really won't destroy the College. The college under the Presidency of Roger Meyer did a very self critical examination of where it was going and it was decided that things really weren't so bad even if these people pulled out. Really what the feature of this is not clinical only but the clinical pre-clinical interface. And so in Psychopharmacology; The Fourth Generation of Progress, that's exactly what we tried to do. We tried to make it so that the pre-clinical scientists understood the nature of the diseases that they thought they were working on and the value of the drugs that they were using as tools and the Clinical Pharmacologists would understand the background at whatever level they chose to grapple with it. So we have introductory chapters and then we have more specialised chapters and very specialised chapters but they all are self referential. So if you want to know more about something or if you want to find out where something was introduced you can find the chapter where it began and hopefully that will keep that momentum going because I feel that's the real strong feature as it has been from the beginning of the discovery of these drugs.

I would just like to ask you about one or two more people that you've mentioned - Daniel Freedman. Why was his role in the field so important?

Well you can get a flavour of the man by reading some of the obituaries and by reading the wonderful article that was written about him when he was the president of the American Psychiatric Association. That would have been in about 1982 or 83. He was among the very first well trained psychiatrists to go to NIH, to learn modern methods of neurochemical analysis and apply them to the field of interest. His particular drug of interest was LSD. And the work that he and Nicholas Giarman collaborated on was the way in which LSD and other hallucinogens changed the brain's metabolism of serotonin and norepinephrin.

If you look around at who the major figures are in biological psychiatry on this side, they will often have one direct link to Daniel X Freedman or maybe two but everybody felt as though they were linked to him because in addition to his kind of wisdom and experience he was a delightful person. He was always nurturing. I learned more about organising people and being critical but gentle at the same time, when I was on the study section of which he was the chairman. Although we weren't so close when I was first at Yale he offered me my very first job, when he moved to the University of Chicago to be Chairman and it was a very difficult moment to say "no I didn't want to live in Chicago even though it would mean working with you". But he made Chicago a very respectable place in psychiatry.

Later we served together again and became even closer. He went to UCLA and I felt like he was sort of in my backyard. When I got married again he was my best man. But on top of this he was everybodys best man. If you'd been to his memorial service, well in fact we had an even more delightful occasion we had for his 70th birthday, when the American Psychiatric was here in Washington, a rather large festschrift and the people were organised to make presentations according to the eight lives of Daniel X Freedman as a scientist, as a teacher, as a mentor, as a philosopher, as a prophet, as a Government advisor, as an analyst because he was also trained in psychoanalysis as well as in biological psychiatry. His editorials for the Archives and his management of the Archives of Psychiatry had made it in our view the premier journal. And the person who took over the editorship Jack Barchass was a medical student who worked for him.

When I first came to Yale I worked with George Aghajanian and George was a direct lineage to Danny. And my co-editor of Psychopharmacology; The Fourth Generation of Progress, David Kupfer was a resident at Yale when I was a research member of the faculty and that's where our friendship began and he remembers those days as shaping his career. The rich texture of biology that was intermingled as a matter of logic and course with the presentation of psychiatric concepts was what made that area a unique area. And I would say that today Yale is still one of the strongest centres for biological psychiatry.

You're touching on a point which is of interest to me which is that in the UK, psychopharmacology generally happened outside Oxford, Cambridge and the Maudsley. The innovative centres were in Aberdeen, Birmingham, Bristol, Cardiff, Merton Sandler's unit, Alec Coppen's unit but not Oxford and Cambridge. Whereas here Yale and Harvard seem to have had much more say in the whole thing?

Although there is The Handbook of Psychopharmacology that Les & Sue Iversen edited, that was when they were still at Cambridge and before they went to Merck. And Marthe Vogt who was at Babraham in 1954 - she was really an originator.

That was in 1954 before the field actually took off

The psychiatry part was outside and I think that's what maybe flavours ours a little bit more conceptually was that the psychiatrists here wanted to learn neurochemistry and so they built around themselves these basic science units. And I don't know what the structure was at Oxford and Cambridge then. The man who has been the head of psychiatry at Cambridge Sir Martin Roth has certainly done for Alzheimers Disease what these other people did for psychopharmacology in the United States so it certainly can happen but I think it just takes the right leadership. It is a very interesting observation.

I have this theory though which may be at odds with some of what has actually happened in the US, which is that the drugs and techniques that we introduce in an area like psychopharmacology subvert an approach towards science which is theory driven - you have a drug like LSD and it blows most theories out of the water immediately. So if you take the approach that being scientific is all about having good theories and maybe you chuck your theories out if the observations don't support them that won't work in psychopharmacology. When you introduce PET scans for instance, people say well look we've got a new way to look at things, lets forget about the old theories and look and based on what we see we'll try and come up with some view that might fit the data.

I have no evidence that would say that that is an incorrect hypothesis. The people who I know, in my generation, in the UK are very much of the same kind of approach that I have but that's perhaps because they came to the NIH for post-doctoral training and so we all were sort of milled through the same process that said that tradition was okay but the unexpected was the thing to expect. And so even if you didn't have a hypothesis, since you knew you had a very incomplete description of the phenomena and there were multiple ways to look at it, the first thing was to sort of flush up what you really thought you were seeing when you saw this.

Before there was dopamine to look at, all of the actions of reserpine were explained in terms of norepinephrine and then serotonin and then dopamine. So then it became very complicated. Which neurotransmitter is really responsible, which depletion really counts for making them

depressed? So its been a time of constant surprises and constant regrouping of hypotheses and most hypotheses are taken with tongue in cheek or many grains of salt because..

Except by the industry who get hooked on the amine hypothesis for instance and build their drugs according to one hypothesis.. We have ended up with an awful lot of D2 blockers we don't get....

Clozapine is perhaps an example of a drug that breaks a little bit of ground and there are second generations of that one. But yes I mean it has been trial and error. In the day of that *In The Beginning* discussion, when the FDA requirements for testing drugs on humans were much less, then drugs moved pretty rapidly from a drug that did this in animals, without toxicity data, to lets see what it does to people. And if you read the original descriptions of the anti-psychotics they thought they were going to see something entirely different and it was the clever clinicians, who detected that there might be some place for this particular medication in that disease rather than this disease. Rather than treating battlefield shock it was really good for sedating disturbed people and that really led to a lot of rapid developments and modification of the drug molecule.

Let me just chase this further because again your work, in some respects, stands in contrast to how the field has developed. If you look back to the early meetings, for instance the one that was organised by Silvio Garattini in 1957 and you look through the programme, there was a lot of electrophysiology happening. Now that's very much classical science and its functionally oriented and behaviourally oriented. Electrophysiology has at least in the UK, except for one or two people, really been lost. By the end of the 60's there was very little work of that kind really happening. But you're one of the people here who has maintained that line of work, a more classical kind of approach - there's continuity in your work from Olds and Milner, Killam and Bradley through.

An interesting line. I started as a physiologist and my entry into the NIH system was as a physiologist and I think my training in internal medicine makes me sort of sensitised to functional questions. So it is not just knowing what the content of a particular biochemical is or the way in which its chemistry is changed I want to understand how cell communication has changed and how systems of interaction are changed and really I would like to be able to understand how its working in human brains. So yes I purposely have indeed tried to maintain a focus on functional questions.

That came through extremely strongly in your BAP Guest Lecture. The interest in it was that you actually talked about the effect of alcohol on the functioning of groups of neurones and through perhaps taking a more molar rather than a molecular view you seemed to be able to connect things in a way that was very exciting.

I have to. Maybe I don't call them hypotheses but I definitely have to construct scenarios in order to understand which experiments are really the most important one to do next. There are so many things that can be done. So being able to bring yourself back to some.. if I knew that then I could perhaps reframe orientation. I like to do an experiment that will really change things or at least tell me that I'm on the right track. If I do little experiments that don't really test the boundaries of the concept then I haven't really learned a great deal. Its busy work and its probably publishable and interesting to somebody but its not interesting to me if it doesn't help us advance where it is that we are going.

What about alcohol and alcoholism, where do you think its at?

I think it is at a very interesting time of departure because we have stopped focusing on what makes people intoxicated and started to focus on why do some people have difficulty controlling the termination of an alcohol consuming episode. What is it about individual differences that perhaps snookers people into becoming dependent on alcohol when others can walk away from it. And that same question I think pervades most of addictive drug research and maybe other behaviours that go under different titles like risk taking behaviours more generally.

For instance, take the work that is being done in France by Michel Le Moal who works at Bordeaux. He has just reported that animals will self administer corticosterone; that they like the feeling of having high plasma steroids. We don't understand how they sense those but they will self administer steroids to the level that their steroids would go when they are stressed as though there is something about what we call stress.. well you know the soccer game that we were talking about is a great example of that. If you watch human performance under times of war or times of sport and conflict, people perform at a level of physical and mental ability that they can't reach at other times. It seems that there is something about that. That to me is more interesting than why people are alcoholic. It seems to me that if I understood what it is about risk taking, what it is about apparently self destructive behaviour that has some mental rewarding, even though perverse, capacity to it that to me would be an interesting insight. I think that's where alcohol research is now turning the corner to asking. Our animal models are being shaped in such a way that we can understand the importance of environmental cues in shaping repetitive drug consuming behaviour and that layered onto the genetic basis, which for alcohol research is perhaps the strongest of all of the addictive phenomena - you can breed animals to readily become dependent on alcohol so in theory you can understand the biochemical nature of what's different about them from the starting line that they came from. Which genes had been enhanced, which new combinations and how did they emerge. All that's going to be Nobel in the next decade. And I think that is going to be a really splendid piece of mental construct on which to build on.

The whole alcohol, drug abuse areas is almost the murkiest of all in terms of the mad, bad kind of views of human nature.

I love to talk about substance abuse when I go to psychiatry departments. I think it is the current best set of biological data and animal models of direct relevance to human mental illness. And whether you call it a mental illness on the order of schizophrenia or depression, there is certainly a strong component of substance abuse layered onto schizophrenia. If you look at any group of addicts, you find a very high proportion of people who are schizophrenic. There is a very clear overlap with depression, particularly with alcohol; alcohol, depression and anxiety track together in serious ways. And maybe a route of insight into the real nature of those biological problems will come from studying the addiction part since we don't have any good clues to get into the other part.

Any ideas what the answers will be? What are your current ideas of what is it that is actually happening in the brain?

In addiction, I think its.. at one level its kind of simple. The brain is constructed with natural reinforcing mechanisms so that actions that are necessary to sustain the individual and the

species of that individual will happen - the probabilities become very high. So we have these rewarding circuits. And the drugs that we call the drugs of abuse - I mean broccoli is not a drug of abuse.

No but its got an awful lot of natural benzodiazepines in it. Maybe you've picked the one vegetable you shouldn't have!

Broccoli? I don't know. I was using it in a totally different way David. You remember President Bush made popular headlines by saying that now that he was President he didn't have to eat his broccoli. Because to many Americans broccoli, cooked the way mothers like to cook broccoli, is sort of like green library paste - it has no interesting features at all. I didn't know about the benzodiazepines, that's interesting but for the most part you don't catch a lot of people abusing broccoli because it doesn't have any immediate reinforcing value and it doesn't have any value that you can remember afterwards - I felt really good after I ate that green stuff. Whereas with really potent drugs that are abused there is both an immediate change which plays upon these chemicals which the natural reward circuits use and builds in an apparent feeling that that was really good, let's do that some more. I think its through trial and error that human history has evolved these ways of intoxicating ourselves. Crack Cocaine is new but the principle isn't and Opium goes back thousands of years. Every society on the planet that can distil something has made an alcoholic beverage. So that goes back a long way.

But a lot of other things don't catch on I mean you don't catch people abusing broccoli no matter what the time was. So I think that people have naturally selected by experimenting a lot and again its this interesting apparent correlation with the experimenters, the pioneers, the ones who are out looking for things - lets try this! Maybe it is because they got a special rush out of this in the same way that Michel Le Moal's mice now are getting a rush out of the natural hormone of stress. Putting yourself into a kind of predicament and bailing out is a unique learning experience.

Its the survivors that get to share their wisdom with the rest and that carries with it a kind of philosophic mastery of the situation, so they became the medicine men and the more powerful people. They prepared the concoctions. The early forms of these medications had religious connotations - they put you in a mood to communicate with God and so a belief in the consumption of something had magical qualities right from the beginning. So it has carried a place in our culture.

Some people would say that its been the pharmacodynamic aspects of the improvement of these natural social medications that led to the addictive state - that it wasn't until you could really distil a more powerful beer, that people had enough alcohol in the beer to make intoxication a problem. When it was low as in mead beer you didn't get enough out of it. So you got the very low threshold kind of stuff. A similar argument is that it was the discovery of the syringe that led morphine to be injected in a way that gave a rush that put the other rushes in the shade. In the same way when tobacco was used for cigars and for pipes you could only absorb it through your oral mucosa and so the amount of nicotine you got per puff was relatively low and it was long lasting. But the refinement of a different kind of tobacco leaf, with the process that makes it acid instead, led to the inhalation with cigarettes, which then gives a very powerful direct intra-arterial kind of injection to the head. So the pharmacodynamics have changed completely the use of what once was a more subtle form of pleasure. When you chew coca leaves, its not a whole lot different than chewing Wrigleys gum with a lot of sugar on

the outside. You got a little boost but it was slow and long lasting. But smoking it or injecting it gives something that is quite different and that's what leads to these powerful addictions.

So society as a group were of a mind to say that these roots have pleasant value but tampering and tinkering has refined the critical elements, in a way that is not much different to what we would do if we went to Indian or South American Folklore to look for drugs to treat cancer. We would find the roots and the poultices that they would make and then our chemists would try to extract the critical features out of it and make a pill that you could take. Except, here we have done it in a way that is not treating any obvious illness and so we call it self medication.

And that causes all sorts of problems

So I think anybody could be an addict. Some people might be addictable more than others because of their environmental situation. Yesterday we had a symposium that would strongly suggest that there has been a latent strong genetic theme in other forms of addiction that hasn't been recognised because we haven't followed people long enough to see it. But there is a strong concordance in monozygotic twins and in blood relatives of people who are addicted. So there maybe something there that hasn't been well recognised. And I think that plus environment gives us a large part of the apparent variability as to why people become addicted and how do you decide which ones they are.

Let me move back to things I probably should have asked you to begin with. You went to Yale and then you went to NIH and then to Scripps, can we go through what took you to each of these

I started really at Washington University in St Louis. As a medical student, I did neurophysiology research. I stayed there for my internship and first year of residency. As part of our residency programme, one of the criteria for advancement to the upper levels was to be the winner of a research associateship at the NIH and so I applied for that and got that kind of a job and that's what led me into CNS research. It was such a powerful and exciting time that I choose not to complete my residency.

NIH at the time had Julie Axelrod and Seymour Kety there.

Yes I was in the National Institute of Mental Health at the part that was at St Elizabeth's Hospital. Julie Axelrod was there and Seymour Kety. Costa was in the Heart and Lung Institute. In our part of mental health, we had a laboratory of neurophysiology that had in it Wade Marshall, who was a more classic macro-electrode neurophysiologist, and a lot of very hard core biophysics type people who were working mostly on spinal cord and didn't care very much about any neurone above the spinal cord.

Dr Brodie was in the Heart Lung Institute. Being at St Elizabeth's Hospital I was somewhat outside of that circle. I would come over for lectures three or four times a week. I guess of all those people, I worked the most closely with Ed Evarts who was the head of another laboratory in mental health. He was trained as a psychiatrist but was a very good neurophysiologist and interested in mechanisms of sleep and how the brain activity shifts during sleep. He devised some of the earliest methods for recording from animals that were awake, certainly with unanesthetized animals that were free to perform and do things. And he taught the research

associates basic modern neurophysiology. I had only taken physiology as a medical student five years before but even then things were taking off rather rapidly.

So you said that things were so interesting that you actually gave up clinical practice..

Yes I chose not to go back to finish my residency. I had been very interested in hypertension as a career and reserpine was a very interesting drug to me. So what I agreed with Dr SolMoirraghi, he comes back into my life many times, he was the person to whom I was assigned as a research associate. And he had taken into our labs a technique that started with David Curtis in Australia and John Eccles used a bit in his final days on the spinal cord, a technique called microiontophoresis, where the drugs were contained in one of the compartments of a multi-barrel micro- electrode and then you would use the electric current to essentially spritz small volumes out onto the surface of cells. It was a way to test the potential actions of drugs you thought might interfere with neuro-transmission.

There's a few people who claim they began microiontophoresis - Philip Bradley for instance was in there at the start

He was one of the first as well. I don't really know who was the first. Certainly Phil Bradley has a deserved pioneering role in the field. He started with Joel Elkes to look at actions of LSD and other drugs and Elkes was the organiser of the group at St Elizabeth's Hospital. He was recruited from Birmingham to do that by Seymour Kety. The group that I joined when I was a research associate was called the Clinical Neuro- psychopharmacology Research Centre and Salmoiraghi was the neurophysiologist of that group. The kinds of electrodes and the kinds of drivers that Dr Bradley's lab used were of a different quality and the kinds of answers they were able to derive were more limited because they were very coarse instruments. I mean they were maybe 5 times bigger - and the drivers that they were using couldn't generate the kinds of current you needed to get through high resistance small electrodes. So their results were somewhat confusing. David Curtis I think did it a bit more meticulously and by the time Salmoiraghi did it, he was certainly not the originator, but he was in the same way the Japanese didn't event the autocar but they sure made it a lot better, I think that's where he would see himself as. Trying to refine the controls and trying to refine the kinds of questions that you would ask.

Before then people would publish data that a third of the cells went faster, a third of the cells went slower and a third of the cells didn't do anything. In the first volume of the review of progress for the ACNP, I wrote the chapter on spritzing, you will see a lot of that kind of data .. but that was a transition point. From that point on we tried to get people to point their electrodes at places where it would make sense rather than just pointing at cells that were easy to record from. And it was that that drove me to do histochemistry because it was a way to put the chemistry at the level of the cells. So it wasn't just what did norepinephrine do on any old cell but what did norepinephrine do on the places where norepinephrine containing nerves provided the synaptic input.

So you moved from there to Yale in the 60's..

Well after I finished the first two years at NIH, it was to devise a method of bringing to the physiology chemical information that drove me to Yale to work with a man named Russell Barrnett who was recommended to me by my Dean at Washington University as somebody who really understood how to do histochemistry and understood the chemistry part of

histochemistry. So I went there to work with him to work out chemical reactions that would allow us to see where neurotransmitters were located in reference to these things. And I stayed there for 4 years, from 1964, ultimately joining the faculty.

So in essence to some extent trying to do some of the same things that Fuxe and Dahlstrom and people like that were doing over in Sweden.

Exactly '63 was when their papers started coming out - '62 was their very first one on the use of reserpine to deplete the catecholamine and serotonin content of the brain and this formaldehyde fluorescence idea was terrific. It was like light microscopy and it was not very good light microscopy and the freeze-thawing procedure caused the tissues to be severely disrupted. So a lot of us looked at those pictures thinking that there must be an awful lot of structural artefact up there. My question was a slightly different question. I wanted to see it with the electron microscope because synapses are really not identifiable at the light microscopic level. At least in those days they weren't. Now with antibodies against proteins that mark synapses specifically you can get pretty close to electron microscopic information at the light microscope level. My desire was electron microscopy.

I had spent 3 or 4 months in the final days of the NIH period working with Keith Richardson, who had been the Chief Technician for the EM Lab at University College London but couldn't get tenure because he didn't have a Phd, so he was essentially driven from England and found work at the NIH where he became the Chief of the Laboratory of Neurocytology. A wonderful wonderful man, who had such massive strong hands that he could do things that a very few people could do. Making his own glass knives. He taught me all these splendid primitive arts of electron microscopy and so I was very much convinced that electron microscopy held the answer to how to identify synaptic contacts with particular neurochemicals. And that was the approach I was taking with Barnett.

George Aghajanian and I worked together. He was a postdoc coming back from the army. His interest was in serotonin; mine was in norepinephrine and so together we worked out some of early methods to employ reuptake as a way of labelling nerve terminals with radioactive molecules. And that followed right on the heels of a paper that Axelrod and Potter did at NIH, when they gave it intravenously. They could see it taken up by the nerves of the pineal. That was the first demonstration of norepinephrine nerve terminals at the electron microscope level. So we said well if they can do that, we should be able to put it directly into the spinal fluid and see it in the brain and Les Iversen and Jacques Glowinski were doing that biochemically with Axelrod at exactly that same period of time. So it made perfect sense for us to try to exploit it for electron microscopy and it worked.

George Aghajanian has been another very influential figure.

That's right. George was sort of Danny's extension studying the physiology and the biochemistry of LSD. And they came up with some very interesting hypotheses. George also trained at Edgewood Arsenal during a time when many of the cholinesterase inhibitors were secret classified weapons and as part of that he worked out blood assay methods for LSD and was able to correlate the duration of the hallucinations with it. He has spent much of his career trying to work out the neurophysiology of LSD actions in the brain as well as morphine. He was the first to observe that the locus coeruleus neurones were hyperactive when addicts withdrew. And the whole line of treatment of drug addiction has been based upon that. A very quiet soft spoken man who has turned down many opportunities to leave Yale. He loves Yale.

He loves the New Haven environment and he loves to play golf on Wednesday afternoons on the New Haven Golf Course and that's a comfortable life for him.

So I stayed there for 4 years. While I was away the NIMH broke away from the NIH and became a separate and hierarchically equivalent thing. The first Director of the NIMH was Stan Yolles, who emphasised service and health care delivery as well as the research arm. And so everything moved up a ratchet and the old section of neurophysiology was now the laboratory of neurophamacology in the National Institutes of Mental Health. Salmoiraghi recruited me back to have a section on histochemistry because he understood the importance of that and then he immediately became the Director of the division and so I moved into his job as Chief of that laboratory and I was able to work there very effectively for the next 8 years.

So that took you through to..

The end of 75 is when I got tired of government life. Salmoiraghi had left to become commissioner of mental health research for the State of New York and unfortunately my performance as lab Chief gave me his job as division Director and the person with whom I worked in the hierarchy was the head of the whole programme wanted me to become the permanent Director and I didn't want to be an administrator. I wanted to do research.

People had been offering me jobs for many years. The Salk Institute had sort of ambivalent connections to brain research. They were working on nervous system research, trying to do molecular neurobiology at a time when molecular cloning techniques hadn't been invented yet. And so they were spending a lot of valuable time deriving cell lines and doing very meticulous things in cell culture but they weren't interested in the brain. They were interested in cellular and molecular phenomena. They didn't understand the importance of the brain.

Jacob Bronowski had come there and had done the Ascent of Man series and there was a reawakening of interest on the board's part to grapple with some of these more complex areas of neuroscience. So the President of the Salk Institute, Frederic de Hoffman came to me saying that the Institute were interested in having a laboratory and did I have any interest and what would it take if I did. My standard answer to people at that time was we needed a million dollars to buy the equipment and set up the labs. Everybody else would say well I understand what you need but we can't afford that. He said let me get back to you on that. Three days later he called me back and he said I don't have the whole thing but I've got commitments for nearly a third of that and if you would be willing to come with me on some visits to foundations and various places I think we could put this package together.

My wife had died and I had two kids and I wanted to change the environment. So this seemed like the right way to go. Within a year we had the package put together and I was accepted by the faculty as someone who could be appointed as a Professor and we brought the group.

It was an exciting introduction for me to science architecture because before then I had only every lived in labs that had been built by other people for other purposes. Now the Salk Institute itself is itself a piece of architectural splendour. Dr Salk himself, who had great interest in the brain and behavioural phenomenon, took great pride in the layout of this building and Louis Kahn had designed it for the maximum scientific flexibility. They wanted my labs to really meet the needs of what was going to go on. We didn't really have enough money to fill out the first 8,000 sq feet, so we only built up to about 6,000 of the 8,000 sq feet at the beginning. So they sent an architect, who had designed other labs at the Salk Institute, to the labs in

Washington and he spent two weeks photographing every step members of our group took, every hand movement that they did to try and get things together. He would draw up these plans and come back and I would say no this is not right because this needs to be closer to that and that needs to be closer to this and he did that 3 or 4 times and finally he threw up his hands in frustration and said what you need is a laboratory that's shaped like a Kodak Carrousel. I said what do you mean by that and he drew it - he said you need these things in the middle and everything else should fan out from there. I said fantastic, lets build that.

So we had a lab that had virtually no square walls in it at all. We had the computers which were very expensive in those days but the computers were the central tool to making neurophysiology expandable - so we could do it on a grander scale. At St Elizabeth's we had two rooms to do electrophysiology, in the new lab we were going to have six. And they were all going to run off of a central computer that would run the programme and batch it out to each of the rooms. It was a very efficient way of doing it. The rooms were all colour coded - it was fantastic. But first I had to get Dr Salk to agree because all the other labs at the Salk Institute were square labs and here was a lab that was essentially a big cigar box with a Kodax Carrousel at one end and everything else was a big wide open laboratory and it was magnif-icent. He looked at it for a while. He was a little resistant. In the end, he said well this just proves how great a design Louis Cahn did because it will accept even this so we were able to build it. It was exciting it really was.

How did it go trying to build up your own laboratory?

I went out 6 months ahead of time not really knowing how we were going to finance the continuing operations. I had dowry money that would keep us going for 3 years but I knew I had a ticking clock. In 3 years I had to make the thing self sufficient. And so I hit on Lithium as the thing to work on. This was because we knew how to evaluate sensitivity. We could look at changes in thresholds for neurotransmitters. We knew how to localise the best neurotransmitters and with Lithium you didn't have to worry about drug metabolism, you could just simply administer the Lithium in the food pellets. So we got the first two grants going in that way and it looked like such a nice formula that we then said well lets just substitute the word alcohol for the word Lithium - we can measure blood alcohol in exactly the same way and we can look at these other things and that one worked.

During the time I was coming across the country was when John Hughes and Hans Kosterlitz identified met-enkephalin. The first 6 months that I got to the Salk Institute, Roger Guillemin who was in the lab next door was also busy using his technology of peptide purification to look for other opioid like compounds and he had identified alpha-endorphin and later gamma-endorphin.

I didn't have a lab yet so I took his peptides and went to David Segal's lab at UCSD and we were looking at the behavioural effects of these on animals and that directly led to a strong interest in these opioid peptides. So the third grant that we did was on the opioid peptides. The grants all met with success and they were all funded and so we were able to get fully funded within a year after getting to the Salk Institute. And from then on other grants just sort of naturally spun off.

I had made an arrangement with George Koob, who I had met while he was still in Washington. He went to the Iversen's lab to do a postdoc, combining biochemistry and behavioural pharmacology, and we recruited him back and he filled up the behavioural part.

And we purposely picked a name for that group that was the Arthur Vining Davies Centre for Behavioural Neuroscience and the behaviour emphasis was there. The idea was that the cellular and molecular events should lead to understanding behaviour.

You've also had a range of strong people go through?

Well I have been very pleased, one of our very first people who was at St Elizabeth's, when I first came, Roger Nicoll was just elected to the National Academy of Sciences. Barry Hoffer is honorary Doctor of Science from the Karolinska for his work in brain transplants and explants. George Siggins is the editor of Neuroscience Letters and a very well recognised person. Bob Robinson is Chairman of Psychiatry at the University of Iowa. Efram Azmitia is Chairman of Neurosciences for the State University of New York in New York City. Gary Aston Jones is the Head of the Division at Hahneman University. So people of mine are all over the place.

One of the other key people in the field has been Erminio Costa

Yes, because he started at a time when all we could measure was norephinephrine and serotonin and a little bit of this or that. He has always maintained a desire to improve the skills for measuring things and the ways under which they are measured and he has continuously led the field into what the most important technologies are that we could bring to bear to make it more sensitive, more accurate and more rigorous. So mass- fragmentography is one example. High performance liquid chromatography, he was one of the very first to devise assay systems using that technique. He was one of the very first to use molecular biology in neuropharmacology and among the very first to use patch-clamp analyses in molecular biology. And his concepts of the allosteric interactions of excitatory amino-acids and his natural Benzodiazepine displacing peptide, those were novel concepts.

Have we gone too far down the cloning route. Up until recently there seemed to be some hanging together of the functional aspects of things and the biochemical aspects of things. But now with cloning, it seems to me we are producing all sorts of different receptors and the industry has gone down the route of saying well look lets just produce a drug that binds to this cloned receptor and to hell with any other way to produce drugs. Then move them as quickly as possible into man even without going through an animal model procedure. Are we entering a new reductionist era?

Well, you raise a lot of important and interesting questions. I mean the idea that you could build a drug properly to select for a receptor that has been cloned I think is a concept that hasn't been demonstrated. I don't know of any drugs that have been synthesised because we don't really have three dimensional understanding of the cloned receptors. We can make these nice models of 7 transmembrane domains and you can do a lot mutational studies that tell which parts recognise the transmitter and you can try to design drugs for them. But that's not really chiro-chemistry based on computerised reconstructions of enzymes that you can crystallise, where you can design for example in the case of the angiotensin converting enzyme inhibitors a drug that really fits into the pocket and sees the metal that's critical and blocks the activity.

There are a lot of companies who are trying to do that but really it is a very long and drawn out process. How do you decide which receptor you really want to invest your coins in. And that's where the lack of understanding of the pathology seems to me to come to the foreground. We have some feeling that we know which receptors are important because of the me-too drugs

we already have. So unless we want to have more of those drugs acting in the same kind of indirect ways, I mean they make mental health better but do they do it by fighting the disease or by assisting the natural reparative processes that the mind has? And I don't know that we know the answer to those kind of questions. Are they failures of the system or are they representatives of different kinds of diseases.

It would be interesting to ask that question to Herb Meltzer because he took Clozapine on when other people weren't willing to invest in it. It was a very peculiar drug and he has now shown that medication resistant schizophrenics actually can benefit from this drug despite its problems with bonemarrow abnormalities. So there are now 3 or 4 new Clozapine like drugs that are trying to reassemble the same mysterious combination of receptor features.

To an extent there seems to be some failure of nerve there at the moment in that we were going down the route having pure and purer drugs but the compounds that were being introduced weren't any superior. And what's happened with clozapine is that we've gone back to a dirtier drug which proves better

A dirtier compound which through its dirtiness may actually achieve what it is that we are looking for. Now maybe there is a Clozapine receptor for either norepinephrine, dopamine or serotonin but probably not. And probably this is some kind of combination and so you know the older style way of starting with the behaviour and trying to get drugs that would have... I mean Buspirone came that way. It was a drug that didn't look like a good anti-anxiety compound but somebody had the clever insight to follow it through and that's where the combination is. I am all for cloning but I think people need to be able to do behavioural pharmacology and we need to have a better understanding of the disease.

I'd rather invest my nickels in understanding the disease than in cloning more receptors and interestingly Les Iversen has taken that approach in his labs at Merck. I was on the committee that assessed the approach his unit took and I would say that he will get a splendid rating by our committee. It's true he hasn't come up with drugs but coming up with drugs is not easy.

I don't know if you read the stories in Nature or Science about the relationships that Scripps has had over its arrangement with the Sandoz Drug Company. It is an interesting feature of the field. A Congressman named Wyden, who is a Congressman from the State of Oregon, is in charge of a committee that was looking into drug pricing and at just about that time, we announced that in 1997 we were going to have a 10 year relationship with the Sandoz Corporation - that we would give them options to patent discoveries and in return they would give us on the order of $ 30 million base per year and in addition would fund research that might help refine some of the discoveries that they would be patenting. The Congressman took exception to this as giving away our discoveries so that this company could make millions off of the drugs that they would develop. Well the point is that none of the discoveries that we would make at Scripps are going to be pills. What we are going to identify are principles of how cells interact and where diseased cells may interact differently. Starting from that and making a medication that people could take safely requires maybe 10 to 20 times the amount of money and thousands if not hundreds of thousands of man hours of investment and time and a lot of luck.

In the same way Leslie Iversen has done some splendid research and although they may not have anything that is on the market today they've got things that are going to be on the market and they've built a system which is likely to generate things that will be on the market. Merck

didn't have that kind of a presence in CNS research, before. They had some lucky hits but mainly they had l-dopa and some other things that they had licensed in. The process of going from discovery to getting a drug that works is a very arduous one and only companies with enormous resources can afford to stay in there long enough to wait for a new one to come up. Hoffman La Roche hasn't had a new drug in the Benzodiazepine series and its not from lack of trying.

The Private Research Institute is something that is very very different that you find in the US that we don't find anywhere in Europe. Certainly not in the UK. The only person who has got anything comparable in Europe is probably Silvio Garattini. What is it about the US that produces these kind of Institutes?

I guess the Mayo Clinic was the first to do have its own Research Institute because of the feeling of those physicians that having research done on site would give them an edge over people who had to read about it some place else. And because medical research has always grown up with the feeling that good clinicians can be good researchers - you know from Banting and Best who recognised diabetes and went into the laboratory to try to understand what principle of the body was at risk here. There has been a strong relationship between medical researchers and medical practitioners and so it was very natural for the Mayo Clinic and the Cleveland Clinic to have such an arrangement.

The Scripps Clinic was born in an era after the discovery of insulin when it seemed appropriate to have a scientific institute backing it up. The Salk Institute is slightly different in that the Salk Institute has no clinical facility. It was just a private research facility that sprang from Jonas' participation in the field trials for polio vaccine. The March of Dimes said well if he can do that lets give him a place where he could do that for other diseases. That was the origins of it. I think private generosity charitable giving in our country is perhaps more organised to do this kind of thing than it is in other places.

Certainly you do produce very strong Institutes that can produce independent science. One of the arguments that Silvio Garattini would have is that if you work in the University, you can't really be independent. You have to fit in with governement priorities and other such constraints.

Well see we don't do that particular kind of research as much. In fact in this country a lot of clinical pharmacological trial research is done by people at Universities because it is easier for them to get those grants or contracts to do the research than to get the Federal ones at the moment. What I like about the private place is simply its independence. We can work on whatever we choose to work on provided we can raise the money for doing it. I mean that's the other risk is we don't have an endowment so being able to succour us through times of crisis requires a kind of relationship such as the one that we've had with the Johnson and Johnson Company and now that we have worked out the details the one we'll have starting in 1997 with the Sandoz Corporation.

When did you move to Scripps

I moved to Scripps in 1983 so a little over 10 years ago. I moved because I had some growing pains. I had some feeling that the kind of work that I wanted to do was becoming too behavioural and perhaps too much involved with kinds of questions we have discussed - addictions and alcoholism - and if any of our work was really going to be valuable I thought it

needed to be in a clinical environment. So being dissatisfied and looking at other jobs at the time, the people at the Scripps whom I had known for quite a while, and actually I was doing a collaboration with Richard Lerner, who has now become the Director, we were doing some the the first molecular biology asking how many genes are used in the business of the brain. So when he heard I was looking at other jobs, he said "well why don't you come over here, I can get Johnson and Johnson money to help start you off" and I did. And it was terrific; its been terrific ever since. We have now grown from 8,000 sq feet to more than 60,000 sq feet. We have a department of close to 250 people with a faculty of about 30.

There can't be too many larger shows anywhere outside of industry.

I think in terms of kinds of skills we bring together which have the gamut in classic neuropharmacology plus purposefully a very strong emphasis on neurovirology and neuroimmunology.

What role does the industry play here. There's a range of views across Europe from Germany where its a very respectable career to have been a scientist within the industry to the UK well you're not a real scientist if you work within the industry - you really have to be in the University system to be a proper scientist. The attitude in the States here seems to be more open than in the UK.

I think its just based on realism. On the one part industry is a pretty creative place to work particularly in start up industry, where you can be dedicated to a very small frame of activity and you have the promise of good money and the opportunity perhaps for even an enormous amount of personal wealth should you succeed. And so that makes it quite honourable especially when jobs are not available any place else and you want to work and you want to have state of the art equipment to work with and you want to have contacts with good consultants who can keep you on the straight and narrow.

Its not a bad life. Between Scripps and UCSD there must be a hundred start up companies that are based on ideas that have come from our research laboratories and where lots of post-docs are working very effectively in an environment that is very nurturing for them and they move up the ranks. As other companies spin-off there are opportunities for them to take what they have learned and move on. So its becoming a quite reputable area. And there are people in this college both in CINP and the ACNP, Paul Greengard is one, who spent a long time in industry and came out. Larry Stein who is Chairman of Pharmacology at UC Urvine spent a long time at Wyeth and came out. And I think people are moving back and forth; Sam Enna who is now Chairman of Pharmacology at Kansas went to Nova when it was growing and came back out of Nova to the academic area. I would think the transition is becoming more flexible more dynamic. It used to be that people would stay in industry for long periods of time. But not everybody's cup of tea so it is quite natural for people to move on from time to time. Leslie Iversen will be another chapter in that history when he takes whatever his next job will be.

In the UK when people look at the US they say you guys get ahead because you're able to throw vast amounts of money. Are there vast amounts of money here - has the for Decade of the Brain made any difference?

Well there really hasn't been any more money for brain research as a result of the Decade of the Brain. Its a nice banner to carry at the head of our crusade but I don't know where it is

going. I don't want to hop out of the army but personally I don't think its the right way to do it. The people who are leading it don't want to come up with a plan. I think we can't convince Congress that we know where we are going unless we have a plan to get there. And just saying we need more money for brain research because its going to answer questions in the abstract is not convincing anybody. It certainly doesn't convince me. I couldn't get a grant to do it that way.

So we have to do more than just appeal in this way we have to get invovled with the lay organisations the NAMIs and the NARSADs - they're the ones who have the relatives with mental illnesses that need solving. If addiction were less of a dishonourable disease, there are a lot of people out there who could spring to the defence of why this kind of research needs to be advanced rapidly. Take AIDS, which is propagated mainly by dirty needles among addicts at the moment, I mean clearly if we're going to spend all that money on AIDS and we don't deal with the real problem that's..

Why people use needles

Exactly this is a behavioural disease. So anyway I think the Decade of the Brain has not culminated anything and even though it does sound really nice practically it hasn't changed the situation. There is a lot of demoralisation in the young troops at the moment because the criteria for getting a grant funded are so high that you may as well play the California lottery to get a grant. The funding levels are less than 10%. So your chances of getting funded are poor. It just has to be of such infinitely superb quality and what that does it channels you and it eliminates a lot of risk taking, a lot of creativity, at least on paper. You might do that work once you got the money but you can't express yourself in the way that you once could do so and in which creativity even by itself was a redeeming virtue on a grant application.

So in that sense the Europeans may over rate what we can do. And there is a lot of splintering among our groups. There's a strong resistance to the kind of research that I enjoy which is sort of team research. Tinkering in the back room by yourself is unlikely to discover the kinds of answers needed for a problem like AIDS. What is it that causes the neuropsychological impairment of AIDS. That's why we have put together the neurovirology, the neuroimmunology and the classic pharmacology. Because nobody is looking at the degenerative disorders of the brain in a way that would model on the classic techniques that we have used in the past. We know nerve cells are dying. We don't know why. What's in there that is making toxins that are killing nerve cells? The answer to that may be reflective of why people lose nerve cells in schizophrenia which we don't really understand.

The European school of thought is strongly integrative - you produced the worlds' best tissue pharmacologists - all these receptors being cloned need tissue pharmacologists and system physiologists to put them back into living organisms. Physicians are about the last link we have as integrative biologists. Most programmes in pharmacology and physiology are totally molecular at the moment. Opioid peptides wouldn't have been discovered if Hans Kosterlitz didn't know how to do the Guinea Pig Ileum and the Mouse Vas Deferens. The classic skills of screening compounds - they are going to be more important and the premium will be high because there is nobody left teaching anybody how to do that except you guys. So forming an alliance with the classic schools of British pharmacology I think is a very critical thing to do.

To more or less finish up with where in some respects we should have started can I ask you why you went into medicine

It went like this. I went to a rather small high school and when I was approaching the end, we didn't have career counsellors. Everybody in the city of Dallas went through this generic system of aptitude testing after which you were mailed the results and that was to indicate your career path. So my results came back that I should be in public relations, advertising and journalism and that I should stay away from hard science.

That fits what has happened perfectly to some extent in terms of communication doesn't it - maybe not the journalism?

Unquestionably. So I went home and I told that to my father and I said they gave me this list of schools and the one that looked really neat to me is the University of Missouri School of Journalism. He said Floyd you're going to go to medical school. After you get through medical school you can do anything you want to. But the only way that a Jewish boy growing up in Texas is going to be able to secure a life for himself is to be a physician. My father was a pharmacist, worked with doctors all his life, wanted to go to medical school but because of an illness he had to drop out of school. Then he needed to earn a living because it was depression time, so pharmacy was an easier route. And all of his life working with doctors he thought that the only thing his son could be and many Jewish families wanted their sons to be doctors. My son the doctor is a long running Jewish joke in the United States.

Maybe aptitude tests aren't so useless after all.

It was definitely right. While my father was still alive and I would be interviewed and point that out, he'd always say what are you talking about, I never said that. But I can remember the afternoon very clearly.

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