THE RECEPTOR ENTERS PSYCHIATRY (2)
DONALD ECCLESTON

So how did you end up in psychiatry?
Well I wanted to be a farmer. I was in the sixth form doing science so that I could go to agricultural college and I remember my mother was ill. I was swotting at the table when the GP came, a man called Gill, and he asked me what I was doing so I said I was going to do agriculture. He said you'll always be working for other people. He then began a harangue not only about medicine but about medicine in Aberdeen. As a result I decided to do medicine and I applied to Aberdeen and took it instead of Manchester, which is where the other friends I had went. So it was a sort of religious conversion.

Why did you move then from medicine to psychiatry and pharmacology.
I hadn't actually seen myself as being a conventional psychiatrist. When I graduated in medicine I wanted to do biochemistry. When I had done my house jobs, I started a BSc in Biochemistry but I was married and it was going to be another three years minimum and I just couldn't face it. At that stage a dilemma came did I go into the army or did I go into psychiatry - at the time, you either had a job in the hospital or you went into the army to do National Service. I felt that any job would be better than National Service and I had a friend John Norris who had been doing psychiatry with the Prof in Aberdeen, Miller. He said if you want a job I'll fix it for you. And sure enough he did, so I became the next SHO in the Department of Psychiatry. I had to stay in Aberdeen until the threat of National Service was over and by that time I had got what was then the DPM in psychiatry. I left because I was desperate to do research. I didn't feel that orthodox psychiatry, particularly the psycho-analytic version, as it was practised in Aberdeen, suited me.

Was there any feel that the new drugs had become to come on stream and they were going to change things?
No I don't think so. I think Imipramine was first mentioned just as I was about to leave the department. I remember we had a Dutchman who was a Senior Lecturer, a fairly interesting chap, who had a rather hypochondriacal patient. He treated her with imipramine and she got better. He marvelled at what had happened. That was about the first antidepressant drug that I'd heard about.

When did you go to Edinburgh?
About 1961. I met Carstairs who was the Prof then who sent me around a variety of laboratories the last one being pharmacology. It was on the top floor, the atmosphere was heavy with the fumes of chromic acid. There were two people working there - one was George Ashcroft. As soon as he spoke I said you're from Lancashire too. Yes, he said, Bolton. We got together and applied for Mental Health Foundation Fellowships and got them and that's how it started. George had been there for a few years and he'd established contact with the MRC neuroendocrine unit. He was working with Tom Crawford who was a methodologist who had been working initially with Gaddum and Martha Vogt, the original pioneers of biogenic amines in brain. Crawford set up the assays and supervised amongst other people me doing a PhD looking at metabolites in the brain.

When did your first 5HIAA work come out?
Well my thesis was in 1965. What we were trying to do was to measure 5HIAA in rat brain. There was a method going but it was very insensitive and what we had to do was to develop methods for looking at normal levels of 5HIAA following on George's work looking at 5HIAA in CSF. So it was method development. We evolved a system which looked at 5HT and 5HIAA and if it was there 5HTP. It was very slow, if you did six samples a week you were doing well.

And at this stage why the interest to look at 5HT at all?
Well in that laboratory Gaddum had speculated that 5HT had something to do with mental illness. He was thinking about schizophrenia but with George finding low levels of 5HIAA in a depressed group, we were interested in mood. His original paper with Dennis Sharman and Tom Crawford in Nature is often missed by people charting the developments.

How much of this thinking had George been doing before you came?
Oh a lot. George knew where he was going. I see George as the first biological psychiatrist. In the general introduction in my thesis here, I list the first paper as Amin, Crawford and Gaddum in 1954 - the isolation of 5HT from brain. They said it was possible that disturbances of the metabolism of biogenic amines may be aetiologically significant in psychiatric disorder. Woolley and Shaw said something similar in 1954. Undenfried, Sourkes, Vogt and others came then. So the ideas were current as early as 54 but they were not specific.

Okay when you joined George, how did the field look, how rosy or otherwise did the prospects for this kind of work look?
It looked absolutely marvellous. It was the first exploration into something you could actually measure in a psychiatric disorder. With the optimism of the young we just pressed on. I was almost deflected because it was such hard work. The methodology was so boring. For five days you did chromatography - you eluted the strips of paper and you measured each one - hundreds of measurements and if you were lucky you saw a little rise in 5HIAA at the appropriate place. That kept you going!

Was there any feel that this was a very crude thing we are measuring how could it possibly account for anything?
Well no because we knew that there was a 5HT system, probably of neurones, and while at that time all the criteria for neurotransmission hadn't been met, we did feel that 5HT in some way was responsible for the control of mood. At that stage maybe it was crude but at least it was something you could measure. We began to look at psychotropic drugs in rats, once we could measure things, using a tryptophan loading technique. You gave rats a large dose of tryptophan; that pushed the 5HT pathway. If you then gave things like monoamine-oxidase inhibitors, the 5HT went up and the 5HIAA down. If you gave decarboxylase inhibitors, for the first time you could actually measure 5HTP in brain. So the drugs being used in psychiatry could actually produce changes in the system. They may not have been aetiological but the drugs were working on these systems.

How much hostility would you have encountered at the time from the neuro-physiologists on the one side for whom still the idea that neurotransmission was mediated by neurotransmitters rather than electrically still hadn't been fully conceded perhaps and on the other hand the lay public for whom the whole idea at the time I'm sure of messing around with brain constituents had to seem leary?
Well I think for the professional pharmacologist there was a big literature on the motor end plate and transmission with acetylcholine. We knew a lot about the 5HT system in the gut, which was clearly a neuronal system. So the concept that it was a neurotransmitter in brain wasn't all that awry. Few people still conceived of it as a soup floating around in brain. In fact when I went to the States to work with Julie Axelrod and he asked what do you do Donald? I said, well I look at 5HT in brain. "Remnant of our marine past" he said "of no significance". That was 1967.

Catecholamines had really caught hold in the USA then. But until brain 5HT pathways were actually mapped in the mid 1960s by Fuxe there was the idea that perhaps 5HT in the brain is just filtered there from blood.
I never heard that. We had worked quite a lot on blood as well because we wondered whether patients who were depressed would have 5HT synthesis reflected in platelet 5HT synthesis. It wasn't. We did a lot of measurements of 5HT in blood. I think we were fortunate in that we were in a department that was very much into neurotransmission. The Prof, Perry, had worked with the leading lights in the field of receptor technology. So we were in an atmosphere where it wasn't unreasonable to think of 5HT like this.

How did you find things at the NIMH?
It was a highly paranoid set up. It was like a beehive - they were all in separate little cells and you didn't talk to anybody else about what you were doing because the pressure to get results was such that what you said might be seized on and the next day would be published by someone else. I think from a technical point of view the methodology was inferior to what we were doing in Edinburgh. They had a reliance on using large groups of animals so that the variance you had because of the techniques was reduced. Technically, it was a mostly waste of time, although there were techniques that they had for injecting small amounts of radio-active substances into rat ventricle which were new, which I picked up and brought back. By and large I was unimpressed. In the 5HT area, of course, the motivation wasn't there. Julie wasn't into 5HT. They were doing a lot of work on melatonin at the time. I saw Sol Snyder and Richard Wurtman, who had huge numbers of papers on melatonin amongst other things. Snyder and Wurtman were vying as to who would get to 200 papers first.

Then there was the huge amount of travelling the scientists did. They were always commuting to Boston from Washington, it was quite unbelievable. NIH of course got the absolute cream of graduates from schools in the States and they were being directed by Julie so he got a lot out of them. I remember that Julie used to have to give these talks and there was one at the Albert Einstein in New York and he said he couldn't. "These guys" he said "they're so bright,

they're going to ask me questions and I won't know the answer". I suppose I did my first cognitive therapy then. I said "Julie how many talks have you given" "Oh hundreds". How many times have you not been able to answer the question? Really poor old Julie was so anxious yet he got a Nobel Prize. I had gone out with the sneaking idea that I might go to the States permanently but I came back feeling how much freedom we had here - freedom in the very general sense.

How do you explain the lack of interest in 5HT over in the States.
It was almost a continental divide. America was noradrenaline and England anyway was 5HT. But at the time when you look at the literature Swedish scientists quoted Swedish scientists, American scientists quoted Americans and I suppose we did the same. Any global feeling of research was rather lost in this nationalistic approach. There were times when looking at lists of authors I felt that George certainly should have been amongst them.

Had the 5HT story begun to play at that point as a European interest.
It's very hard for me to say retrospectively. We had always believed that 5HT was important. We conceded that noradrenaline had something to do with it as well. Later on we were talking about the interaction of the various monoamine systems like dopamine and 5HT which interestingly is now being talked about. We did some work which was never published on the interaction of dopamine with 5HT. We weren't unimodal - we didn't just believe that there was one system and that was the complete answer. But our work has stood the test of time. Its quite extraordinary that one could be working on 5HT 30 years ago and there are still circulars coming through my door saying you know this antidepressant works on 5HT.

Did you meet Joe Schildkraut?
Yes, I remember being at a conference with him in Mexico. We agreed to disagree as to what was more important noradrenaline or 5HT. Alec Coppen was also pushing 5HT. I suppose there was competition between groups but it was never acrimonious.

Did the amine theories have an impact on the ground? Did they switch people into thinking that perhaps it is reasonable to go into a research career in psychiatry because now you can actually measure etc.
Yes I think it did. This also tied in with the linking of the new drugs like imipramine to reuptake of noradrenaline by Leslie Iversen. That really made one feel fairly confident that there was a link between these illnesses, the drugs that you used and the functioning of the systems. Leslie Iversen's work was astonishing. His PhD was published as a book in 1967 and I used it to teach pharmacology students psychopharmacology. It was absolutely wonderful to show students. He was a true pharmacologist - his dose responses, Vmaxs and Kms were all there. Iversen's contribution was enormous. Re-uptake mechanisms, that's Iversen.

Iversen also worked with Axelrod for a while. I think he was the one who told me that Julie would always agree an experiment for the Monday on the Friday afternoon, then wander around Rock Creek Park over the weekend and come

in on Monday morning and say you know the experiment we were going to do, well I've changed it. So what Iversen and Sol Snyder used to do was go into NIH about 4 in the morning to start the experiment so Julie wouldn't change it.

You went and talked at the Prague 1970 CINP Meeting and gave a very straight amine talk really - there was no hint of anything to do with brain receptors in it. Yet a year or two later you and George and a few others in the group came out with what was the first receptor theory. Where did all this come from?
It came from the Department. In the common room having coffee, they were chatting away about spare receptors and sensitivity of receptors and so on, admittedly in the cholinergic system, but the ideas rubbed off on us. And it did seem sensible that there were two things - that if there was a transmitter there was also the possibility of receptors and even that their numbers varied. So it was the atmosphere in the department. We had somebody there called R P Stephenson who was an International Guru on receptors. I remember I was somewhere in the States and someone said where do you work and I said Edinburgh and there was a sort of gasp "that's where R P Stephenson works". What they seemed to do, as far as I could see, was drink coffee and think and get the PhD students to look at various preparations. It was a heady atmosphere. Stephenson, at the time, was probably in his mid 30s. And there was a chap called Dick Barlow, who was an organic chemist, and he used to synthesise all these compounds that could stimulate or block cholinergic receptors.

What did the receptor feel like to you at the time? It hadn't been radio-labelled then. What kind of a beast was it - a lump of protein that would change slowly in line with treatment?
I cannot remember the ins and outs of what was thought about receptors generally at that time. I'm sure they were into conformational changes but I was not particularly familiar with receptor techniques and what was going on. It was a concept. There was nothing known about 5HT receptors at the time. One assumed that they would have similar properties to the receptors that they did know about. The concept of 5HT receptors in gut preparations was obviously there.

Where you surprised when the idea was picked up so quickly and all of a sudden there were these fairly specific receptor hypothesis - Sulser's Beta adrenoceptor hypothesis and Snyder's D2 receptor hypothesis.
I don't think we were unduly surprised no. Whether they were important or not was the question one was asking. How do you prove it?

In retrospect are you at all surprised that you caught the wave as it were so neatly. The idea was there and then within two or three years people were actually trying to tie the idea down from its more general form.
I don't think we were surprised. Science was heady stuff at that time and it was fascinating to read these articles. Somehow you have a certain confidence in your ideas and the fact that somebody comes along and shows that there are receptors and so on is very gratifying but its not that you doubted it if you see what I mean. You have to have that sort of confidence in

science. But we never got into receptorology with 5HT. Why not - I don't know. It's hard to explain what tracks you take. We continued work on metabolism looking at 5-hydroxytryptophol and things like that instead. You couldn't measure receptors clinically and I suppose we were really trying to look at the clinical end and see if we could pick up changes in the CSF. That was a pretty thankless task because you didn't have very high levels of prediction as to whether a 5HIAA was going to be low or not. It looked as though it was associated with endogenous depression but it became a bit of a routine and we seemed to be amassing more data but not more knowledge. Also the unit got very much bigger and expanded into all sorts of other spheres - Alzheimer's Disease and things like that.

How were links with the MRC?
I think the thing about the MRC is that you have a sort of honeymoon period, then you have a plateau period and then watch your back. It becomes clear that other units are coming on. We worked out that at the time the average life of an MRC unit was 13 years. We didn't of course start as an MRC unit we started as a group and we became a unit in late 60s. Like anyone else I began looking around for Chairs. My feeling is you do your best research when you are quite young and you've got the drive and the ideas. Some people have ideas continuously but often interestingly they're ideas that they had when they were younger and they're reviving them. You can see this with Axelrod. My feeling was that I was beginning to get stuck in research and I would have been less productive and so it seemed to me sensible to go for a Chair. Then George decided he ought to as well. I left in 77 and George went to Aberdeen in 78.

He's a very quiet man George. Did that hold back the area because as you say you guys were doing all this really for anyone else but to some extent didn't get quite the recognition you might have done?
George wasn't a great publicist. He didn't like travel or big meetings. So there was a lot of light hidden under a bushel, which in some ways is a pity but I think in all honesty some people over do it. We could have published things earlier but it had to be good, with Tom Crawford there it had to be almost perfect. Crawford actually revised my PhD six times. In the end when he was correcting his own corrections.

Tell me more about Crawford?
He was very much a methodologist and his forte was biological preparations - guinea pig ileum and things like that. He had a series of PhD students and they initially were looking for a substance P but they found this extract from brain, which didn't have the characteristics of substance P - it had some of them. They decided it was Erpsamer's enteramine and they showed it was 5HT. His work then became developing the methodology of trying to isolate this and 5HIAA from brain. Dennis Sharman did his PhD at a time when they were trying to isolate 5HIAA in brain. Reading Dennis' thesis you can see the trouble they went to - they produced extracts from mushrooms to break down particular substances and leave others. I think Dennis had about six months to go to the end of his PhD and he had no results at all. Then with Crawford they finally cracked it and he could measure 5HIAA in CSF which he did with

George. So Crawford was about methodology almost completely. But he was a highly obsessional man - all the 'i's and all the 't's had to be dotted and crossed. So it was good to have him in the laboratory because he would advise you on methods.

When you moved down here to Newcastle, had Martin Roth left?
He'd left about a year previously. He'd gone down to Cambridge and there was a bit of a vacuum here. The department was being run by an administrator, who left as soon as I arrived. A lot work had to be done.

Newcastle psychiatry had had a heyday in the 60s with the Newcastle Scale and Newcastle endogenous-reactive formulation of things. How much of that legacy was here still when you arrived?
Quite a bit. There were people like Bernard Tomlinson, a neuropathologist, Garry Blessed who'd worked with him and worked in old age psychiatry. The background biology of Old Age Psychiatry was still fairly strong.

Where did the Newcastle Cocktail come from?
In Edinburgh, George and I became more and more interested in clinical problems and people were beginning to send us patients who had resisted treatment. Very frequently the answer was simple - you started Lithium and they got better. But George had read an article, I think by Coppen and Shaw, that said a combination of phenelzine and tryptophan was as good as ECT, so we began trying that combination but found that while patients might have a marvellous six weeks, it faded. We got the idea that if we added lithium the response might be perpetuated. And that was how the Newcastle Cocktail really the Edinburgh Cocktail evolved.

That was before you came to Newcastle then?
Oh long before yes. It had been going for a while before. There are papers that the British Journal of Psychiatry refused to publish. For instance 22 cases treated with the cocktail, many described in detail, but they said they only took double-blind trials. They said you've no control for this. But if somebody has been ill for - the average was 7 years - then in some ways they act as their own control. Anyway it wasn't published. This was the early 70s.

You didn't ever get it published.
No we never got it published. They were so scathing about the fact we hadn't done it double blind. How do you do it double blind on patients who are as severely ill and as ill for as long as this? So no we never got it published.

That's extraordinary because that's a good 10 or 12 years before Claude de Montigny had his 4 or was it 8 cases, which the British Journal of Psychiatry took without any controls.
Certainly I talked about it in the States if ever I was doing talks. I remember doing a talk in Toronto at the Clarke Institute and talking about the Newcastle Cocktail there and the feedback later was they'd been using it and it worked. I was beginning to be asked to speak at meetings and I think that it got propagated through meetings.

The data is still there in some recesses of my cabinets - 22 patients documented in detail, followed up by nurses rating scales and doctors rating scales and so on. I think the thing was you saw such dramatic improvements. It really was extraordinary. It was easy then but now when you get patients who are treatment resistant they've had the works and it's not easy any more.

Why then did it get called the Newcastle Cocktail.
It should actually have been the Edinburgh Cocktail but because I was from Newcastle it somehow got called the Newcastle Cocktail. I don't know who was responsible for that. I think somebody else called it that. I used to see patients throughout the region who were treatment resistant and I think one of the consultants there might have called it the Newcastle Cocktail. I think I felt much more confident about what I was doing when De Montigny came along.

Did you feel cheated at all though in that he had credit for doing what you had been doing 5-10 years earlier.
I don't think I function like that but we've been so poor at publishing particularly on things like the Newcastle Cocktail that if other people publish and get acknowledgement well good luck. I suppose, if I were 25, I'd feel quite differently. I'd have the NIH mentality. I'm saying all this but I'm not sure its true. You're asked questions like that and the right thing to say is yes I wasn't bothered but I suppose the thought is there that we should have done that but we didn't and it's now water under the bridge.

Can you fill me in on what happened when the authorities withdrew tryptophan?
Yes. I mentioned the use in rats first of all. The next step was to try to show that the 5HIAA in CSF reflected what was going on in the brain and to do that we did tryptophan loading in dogs and we produced a curve showing an increase in 5HIAA in CSF, which reflected what was happening in brain. So then the question was would tryptophan loading be therapeutic. Coppen had started that in man and we began using it.

Pretty soon then it was very much in use across the country for treatment resistant patients and I had a lot of patients on it. Then cases of eosinophilia-myalgia syndrome swept the States. It was found to be associated with across the counter l-tryptophan, and a particular brand made by Shawadenka, a Japanese firm, who had changed two things. They'd changed the purification of the l-tryptophan and they'd changed the bacterium that produced it. As a consequence, toxic metabolites were getting into the drug and it was these that were giving the eosinophilia-myalgia syndrome. The result was that it was stopped world-wide but once the research began to show that it was a toxic product and not the tryptophan itself, efforts were made to get it back on the market. Nicol Ferrier and I went down to the CSM to put the case forward for bringing it back. This was agreed but they wanted to be cautious and so eosinophils had to be measured if you were going to prescribe it, which is reasonable. A monitoring system was set up. It can now only be used in chronic depressive illness by a consultant psychiatrist's recommendation. I suspect it will fade. I think we're now have so many potent drugs that l-tryptophan will not be used.

I understand that you had a few people on the cocktail, who had been otherwise treatment resistant and when it was withdrawn they relapsed.
Yes. I think this is a feature of l-tryptophan - if you stop it suddenly you can get a relapse. If you're going to stop it you have to do it slowly. I assume its because you've increased the turnover of 5HT, the receptor sensitivities have changed as a result of that, and when you withdraw it you're not in the status quo. Some patients actually can't get off it. On sudden withdrawal there's a relapse of the illness with all the symptoms they had initially.

Did the people who relapsed pick up on anything else?
I can't remember exactly. I think with most of them we soldiered along changing various things and doing what we could. Some of them did go back on the cocktail once it was available again. But as I say I think we're getting into another era of antidepressant prescribing now. I think you've also got to be pretty careful with l-tryptophan because of the 5HT syndrome.

The 5HT syndrome only got written up about 88 by a guy called Sternberger. You must have seen it before that.
Well I'm not certain we recognised it as such. Certainly I remember an elderly lady getting some confusion, confusion was part of it and muscle jactitation was another thing we recognised. I think we were always very careful in elderly people. I don't recall any case of hyperpyrexia.

So it took the SSRIs to produce the syndrome good and proper?
I suspect so. If you really want to develop it you give l-tryptophan and an SSRI.

You've said you think we're at a new era with antidepressant prescribing. I'm not sure I can see it. If one goes back in the history of the whole thing, you can get the impression that desipramine, trimipramine, imipramine and clomipramine are it - there's nothing really new and we're just going round in circles now.
You may well be right. Certainly clomipramine was the drug I used a lot but it does have its drawbacks. Okay it's a noradrenaline and 5HT reuptake inhibitor, so it does all the things that one or two of the new ones are supposed to do, and given with lithium its pretty good - or phenelzine given with lithium. But you may be right. Although when I say a new era, I've recently seen a patient who went into the ward under Nicol Ferrier, a man with very severe psychotic depressive illness, highly suicidal, really on line for neurosurgery for mental disorder and he got absolutely well on olanzapine. Now that's a turn up for the book. So I think we are beginning to look at not just our conventional drugs and their offspring but perhaps some of the new antipsychotics may have something to offer in affective disorder.

I suppose basically I'm an optimist. I'm pretty optimistic about pharmacology. What it can do and so on. But on the other hand lets not over state it. My best friend is an analytic psychotherapist and I believe that treatments of psychiatric disorders have to be eclectic. Cognitive therapy, which we developed here with Jan Scott, is extremely important. I think we see better

results with the treatment of affective disorder now than we did 20 years ago. The broader approach looking at patients in teams and so on, I think that has influenced the outcome enormously. But I'm an optimist and it may not be true.

Why do you suppose you are an optimist? Having been there since the early 60s and having seen the wheel go round a few times?
I was just born one. I suppose overall I must have seen thousands of patients and in spite of the fact that I see the very difficult ones I still have a certain therapeutic optimism. I think you need that. Once you lose it, forget it because the patients pick that up. Lots of patients come and say "look I know it didn't work but you give us hope". I think if you lost that hope you would be a very poor therapist.

On that score though, the kinds of things you do in the area of people who are treatment resistant is very much off the beaten track, off label, off-licence, never supported by RCT evidence and probably unsupportable by RCT evidence because the patients are so complex. So you're prepared to take risks.
Yes. I'm prepared to take risks but litigation is now becoming such an important area that if I'm taking a risk I talk to the patient about it and I write it in the notes. If I use a new drug like olanzapine and haven't been using this before I would talk to the patient about it and so on. I think you have to take risks. Apart from suicide, I can't recall having a death that I could actually attribute to medication. We now have anticonvulsants which work extremely well - and that's certainly an area that has advanced, they weren't available 20 years ago - but the potential for toxic combinations is higher if you get into that field. So you've got to be very careful.

Can I ask you about the anticonvulsant story? How did you become aware of them coming on stream?
Well I think I went to a talk by Post on carbamazapine in the early 80s. It was Post's influence and I was quite taken by the fact that carbamazapine could be almost as good as Lithium. The fact that you're teaching also means you have to keep up with the current literature. And if you're in clinical practice and you have difficult patients you have to try these things and yes they were very helpful. They didn't always work and now we've gone on to another generation of anticonvulsants - lamotrigine, gabapentin and so on. This unit has always been enterprising in this area.

The drugs now may be more receptor specific and clinically people have been taught to recognise mood disorders in a way they perhaps missed during the 60s.. but have we really done people favours? Do you think the health of the nation has improved?
I think so yes. I think our therapeutic armamentarium is much larger.

Clinically though have we not ended up in the pocket of the drug companies. People are increasingly scared to prescribed off-licence, even though the licence is there to constrain the claim of the drug company rather than the clinician

I suppose you're right yes. We do have our difficulties but looking at the scene overall I think it has been for the better.

I can see you're an incurable optimist. I've been trying to shake you.
Well you see having worked in pharmacology and being able to at least appraise these treatments, there's nothing coming out now that hasn't a rationale to it - theoretically there are things that they do that should work. It's not an entirely hit or miss approach. So I think that's heartening and there's so much going on. I was at a meeting in Spain last week on receptors and medication, which was an eye opener. There is so much going on in receptorology.