

GEORGE ASHCROFT

I came up to Edinburgh in 1956 having just come out of the army. I came up to do the membership course in medicine. Whilst I was up here, there was a job advertised in psychiatry and I'd always intended going into psychiatry eventually, so I went in slightly earlier than I'd intended. I came at an exciting time because reserpine was already in use, chlorpromazine just came into use more or less when I hit psychiatry and the monoamine-oxidase inhibitors and Tofranil followed in the next year or so. So it was an exciting time. I became interested in why reserpine did produce depression and why did the antidepressant drugs work.

You were saying to me before that reserpine produced fairly dramatic responses in some cases.

Yes. I think it produced recovery in some cases, which makes me doubt the whole of Crow's theories of schizophrenia because on this theory you couldn't produce recovery in a person with schizophrenia. So I've always doubted this - I've always thought that it was potentially recoverable.

So you saw cases respond in a way they didn't to chlorpromazine for instance. Was this response anything like the response people talk about these days to Clozapine.

Yes. Probably better. I saw people get well in a way that I've never seen anybody get better on any other drug, with that sort of severe schizophrenia. They'd been ill for 8 years or more. I saw a number of these get better and go home to their families. It didn't do it for many people but when it did it was very striking. I wonder what happened to them. It should be possible to get the notes out of the records department.

Why did Chlorpromazine take so long to come through. It was licenced in 54. But....

That's right. I started in Edinburgh on the 1st of January 1957. It was just reaching Edinburgh then but we were still using Reserpine because they knew it. It was about 9 months later that it really began to take over. Reserpine was an interesting drug but it also produced depression in some patients.

Was this real depression.

I think so. I know that Jenner's group eventually suggested that it didn't produce depression and there was just an association between hypertension and depression, well I think that's probably wrong. You saw patients with schizophrenia treated with reserpine develop very severe depressive symptoms and become suicidal.

It also produced akathisia didn't it which could potentially make you suicidal

It gives very severe parkinsonism. I don't know that it produces akathisia as much as Haloperidol, for instance. It was very toxic. We had two deaths which were due to a myocardial fibrosis which probably was because it depleted the heart of noradrenaline and affected its metabolism. But we were giving up to 15mgs a day. Because of its toxicity when chlorpromazine came in we largely switched to chlorpromazine for schizophrenia.

Did the idea that it depleted 5HT lead into your early work on 5HT and depression

Yes and I'd read Brodie's hypotheses about this. I was lucky because in Edinburgh there were a group of people who were working on cerebral monoamines. Martha Vogt had discovered noradrenaline in Edinburgh. Tom Crawford and Gaddum had discovered 5HT in brain in Edinburgh and I..

At the time they found 5HT in brain what you read is that they weren't sure if it just leached in from the blood you know.

Crawford was sure. I mean he did it so carefully that he would have allowed for the amount of blood in the brain. I mean he was probably the most careful biochemist working in the field that I've ever come across. He wouldn't let you claim anything that he hadn't checked about a dozen times. A very obsessional man but a very good scientist and ...

What was his background.

He was a chemist initially then he became a biochemist. He worked during the war on British Anti-Lewisite, the chelating agent and then Gaddum persuaded him to start to work on amines and he was really the person who did all the work on noradrenaline for Martha Vogt. And he discovered substance P as well in the brain. I was doing psychiatry and my boss, Elizabeth Robinson, knew Martha Vogt. Now Kennedy was the professor of psychiatry then and my boss and Kennedy didn't speak to each other so I wasn't allowed time to do the DPM course even though I worked in the hospital where it was held but I was allowed time instead to go and work in the neurology unit and in the pharmacology department. These days I would have never known anything whatsoever about 5HT because I wouldn't have been allowed to do this. I'd have been made to do the course. So in fact I got my membership in neurology, in medicine that is with neurology as the main subject, before I sat any DPM subjects. I didn't sit those for about 3 or 4 years and then I sat them all in a week. So it was a very idiosyncratic sort of development.

I initially tried to measure 5HT in the CSF. I had the idea that you might actually get a direct measure of what was going on in the brain by looking at the CSF. So initially, I spent about 6 months measuring 5HT in the CSF using bioassay. This was good for your soul because you had to wait 4 minutes between each drop that you put on the rat uterus, so being a very impatient person this was good for my soul. It taught me to be patient doing work. Then there was a chap there, Dennis Sharman, who developed a technique for measuring 5HIAA and from then the work took off. We measured 5HIAA in CSF, we did experiments to show that 5HIAA was a better measure of turnover than 5HT in brain and we then later on actually looked at 5HIAA in depression and showed that it was low in the CSF in depression.

How common at the time would it have been to take CSF from patients

Well remember that there had already been studies on brain using air encephalography and quite a few psychiatric patients went for that and you could get CSF while that was being done. We did CSF as a routine. My boss was interested in pre-senile dementia and you did quite a lot of CSF studies in those cases. Remember also that I was attached to a neurology unit where it was a common thing to do. So it was this sort of linkage that made me not afraid of not taking CSF. So it may have not been common as a routine but we explained to patients why we wanted to do it and they were happy. I got quite good at doing lumbar punctures. I even used a technique of using double needle to try and avoid post lumbar puncture

headache. We also looked at CSF that we obtained from neurology and neurosurgery units which I developed a link with. We found that there was a gradient of levels in the amine metabolites with the highest levels in the ventricles and lower in the basal cisterna and lower still in lumbar space. I spent about 2 years trying to find out why that was and discovered the probenecid blocking effect on CSF in animals and the fact that there was a transport mechanism for 5HIAA. In man it appeared to be in the choroid plexus of the fourth ventricle. We looked at the physiology of that in the same way that you would at kidney. We did clearance studies and tidied it all up. In the end we came to the conclusion eventually that lumbar CSF was like looking right down the wrong end of a telescope you know. That you were very far from the main event but that it may still give you some sort of indication. At that point I had a fairly mechanistic view of what depression was all about. I thought there was probably some genetic abnormality in the production of 5HT.

At that point in time, when you would talk to people say in the evening at a party or whatever, and they asked what were you doing and you'd say I look at things like 5HT in the brain, would they have thought that this was ungodly in a sense? Such a mechanistic view of how the mind works.

Not in Edinburgh. Because Kennedy, the professor, for example had a very organic view of psychiatry. And my boss had a very organic view of psychiatry. There was a if you like there was an organic or biological group in Edinburgh. Sir David Henderson was only just leaving the place when I came and he'd got a very open, very eclectic view of psychiatry. I mean you could argue in Edinburgh. It was good to be here. In the big ward rounds, the weekly meetings, you could say what you felt and you wouldn't get shot down or if you did get shot down, you were allowed to retaliate. So it was very healthy. I found it different elsewhere where you were regarded as aggressive if you dared to speak out. Here you were regarded as stupid if you didn't. So it was a good place to be and also it was a very active pharmacology department. Gaddum had only just left and gone down to Cambridge.

What was his impact and what was the effect of his leaving.

His impact was to look for all these active substances in the body. In other words it was a sort of endo-pharmacology. He encouraged people to look at the brain and at the gut. He was also a bloke who encouraged people to think of ideas. It didn't have an enormous impact when he left because interestingly he hadn't done the work. The people who were left behind were the people who had done the work and you still had Crawford, Adam, Vogt, Barlow. There was an interesting chap called Stevenson who was a receptor expert. Every 4 or 5 years he would write a paper on receptors that destroyed everything that was known at that time and then he played tennis for another 4 years basically and think. Then he would do another paper. All the background work on producing analogues and testing relative efficacy was done by Vic Barlow, who was a chemist, who subsequently went to Oxford. So there was a lot of debate. I was the only medic wandering about the place at that time and they were actually quite keen to apply what they were doing to something to do more directly with medicine. So it was a good place to be. I was just lucky.

When the ideas of the 5HT in the brain were first mooted, there must have surely been some question about whether it was a neurotransmitter in the

brain. Yes it is a neurotransmitter in the periphery but that doesn't mean it is one in the brain. Where these ideas still there.

Yes they were. And eventually people like Ginsberg, a neurophysiologist, came into the department probably as a result of these questions. John Kelly, the current professor of pharmacology here, did his PhD with a neuro-physiologist in the next lab to me. Neurophysiology came in and brought with it the functional side of things. So we worked on CSF we looked at the mechanisms for transport, how it got into the CSF and so on. We found HVA in CSF, one evening in our lab over the infirmary. We discovered this in the CSF and to my horror when I arrived home at about 11.30 at night, there were a set of cars outside my house - 20. I'd forgotten we were having a party. My wife had been trying to get me but I was in the wrong lab. So that was the night we found HVA in CSF. We got so excited. It was a very exciting time. It wasn't unusual to work until 2 and 3 o'clock in the morning.

Then in animals we did loading with the 5HT precursor, Tryptophan, to see if we could get a measure of the maximal synthetic ability - to see if you could push the system, overload it and show there was a maximum. We showed it in dogs and then we thought right we could do that in man. So we tried it in neurological patients and found you could give a load of Tryptophan that would load the system and CSF would mirror the rise of 5HT. Then we did it in a range of psychiatric patients and showed to our horror that there was no failure of production in depression. People with depression or recovered had exactly the same maximal synthetic capacity to people without depression and that together with another few facts led us to think that if 5HT is involved - or if any of these transmitters are involved because the same thing probably applies to other transmitters - then there must be more than one variable at the receptor. There must be more than just the release of the transmitter.

Before we move on to that which is late 60s, how was your early 59 paper saying that there is low CSF 5HIA in people who were depressed received. This is really one of the earliest claims that there were.....

There was another one just about the same time by a chap called Roos in Sweden and we met and discussed it. I think the paper was well received - people were interested. I am not a great meeting attender and I didn't go and push it. Once I've found something I'm not really worried whether anybody else knows. I'll publish it but it there's anything I get any satisfaction out of its finding the answers. The eureka experience. It's happened about three times.

It was interesting. It meant I got scholarships. I got an MRC fellowship so instead of doing the work part-time I could do it full-time. I subsequently got a Mental Health Foundation Scholarship. They enabled me to break off and do lab work pretty well full time for about three years and then I went back and did both clinical work and lab. There was a lot of lab work. We used to have to wash all our equipment 40 times there were no dishwashers or anything like that. We didn't throw out test-tubes. We had to steep them in chromic acid, wash them 20 times in tap water and then 10 times in distilled water. This was because the only way you can measure the small amounts of substance spectrofluorimetrically was by having low blank measures; if your blank measurements were high, you couldn't measure them and so you had to do all the things you could to keep those down - using desperately clean glass wear was the main way you did it.

Did the spectrophotofluorimeter make a big difference when it came around.

Yes. Because you couldn't measure metabolites by biological methods. See all the methods that were used to measure these amines in the first place were biological methods. Later on you had HPLC, which gave you a lot better resolution.

This is the age old question then - how much does the progress in the field depend on the technology as opposed to the great ideas.

A lot. I mean Dennis Sharman had one of the first fluorimeters of this type -the one that you could scan input wavelengths and output wavelengths with and by doing that you could get very specific measurements of substances. He had one of the first ones imported from the States. It was not as sensitive as subsequent HPLC but you could measure metabolites and a range of substances in nanogram amounts. We would use paper chromatography to identify compounds. We had a paper chromatographic technique which took about six hours and the only way you could live a reasonable life was to go in and set it going in the middle of the night. So we had an alarm clock with a lever on it that turned a tap on a separating funnel, which let a solvent into this tank in the middle of the night. Occasionally this would fail and you'd go in in the morning to a mess. To try and avoid oxidation of these small amounts we ran the chromatograms in a nitrogen atmosphere. It was quite an elaborate procedure. We actually showed that the American work on Tryptamine, which we were looking at was all wrong, because they their technique hadn't separated it from ???

Tom Crawford was hovering over this the whole time. He was the one who provided the carefully validated techniques that I would then apply to ideas that I thought up. It was a good combination and we worked very closely together. I can remember the first paper we ever wrote together. We got to 20 odd drafts - eventually I sent it. I went in one morning and said I'm sorry I can't bring it back for any more drafts I've sent it off. I can't face it. He didn't annoy me though in the way obsessional people usually do - I'm not very tolerant but there was something about him that you knew he was doing it for the best and it was good for me. So we got on very very well but he would make you work until 1 or 2 o'clock in the morning to complete an experiment.

When did Don Eccleston join in

I can't remember the year but he came from Aberdeen. He was looking for somewhere to do a PhD. He had looked at one or two places and the came down to see our laboratory. Professor Miller arranged for him to come down and he decided that that's where he wanted to be. He was mainly looking for tryptamine but he also worked on the 5HT work that we'd already started and he also did clinical work. Eventually we developed the clinical side of the Brain Metabolism Unit.

Okay now you're in the mid 1960s, beginning to say that the 5HIAA story is more complex that when you gave the Tryptophan loading to people you weren't able to show that people were depressed were any different.

What we believed was that 5HIAA levels was probably a measure of functional activity of the systems and wasn't a cause. It could just as well have been that people with depression had low activity in their system and that 5HIAA was mirroring that and then when they got better it didn't necessarily go up. Now that was slightly worrying. We had to say well it doesn't go up and yet we are saying that the overall

activity beyond that - the system is going up or is changing. There must then be another variable. That was my approach to it. If you're going to try and maintain this theory, we have to introduce another variable and the other variable which we found would explain most of the facts we had at that time was a change in receptor sensitivity.

When did you begin to think that way. The revised receptor version of the Monoamine Theories came out in 1972. But how long before the article were you thinking this way?

I think about two years. Remember we were in a department of pharmacology. My university post at that time was Honorary Senior Lecturer in Pharmacology not in Psychiatry. And we were teaching there - we had to teach for our supper. We were aware of denervation super-sensitivity in cholinergic systems and so the idea that we could get a change in receptor sensitivity was already there in pharmacology. I don't think anybody at that time had applied it to brain but why not. So being in a pharmacology department was good and you could sign your ideas off with scientists. That's the way we started to think about it and then I wrote that paper and stuck everybody's name on it. The way I tended to write papers was to sit down and write them in one day. I can't do it in little bits and join them together. I'll edit it and refine it but I'll write it all in one go. So I wrote the whole of that paper in one go.

What did the receptor look like at the time in the sense of what did you think you were dealing with. Was it a lump of protein that was going to take a while to change and this might explain the slow response of the anti-depressants etc?

That's what people said. I never believed that. I still don't. I wasn't sure how long it took for a receptor to change. I thought that what was happening was that a system was trying to return its activity back within the normal range variation. I actually wrote a paper about 1960 putting forward this idea - that there was a norm in these systems. So I thought that changes in output and changes in receptor sensitivity were designed to try and return the system to the norm and what happened in depression and mania was it didn't bounce back. We did put forward the idea which has never been taken up that there was a low output depression and there was a low sensitivity depression. We put forward the idea that the sensitivity depression was the bipolar one, with mania being the high sensitivity pole. Nobody has ever taken this up. There may even be a high output mania as well and that may be what you get with amphetamines. I still think there might be something in this.

Just to come back to historical context, receptors hadn't been isolated at this point - you were still talking about a somewhat mythical beast, even though you were in a pharmacology department.

Yes you were. Although we were talking to people like Stevenson and Barlow who believed in their existence and believed that by testing them out with partial agonists and antagonists, with a range of compounds, you could identify the characteristics of the receptor.

All of that goes back to A J Clark, who originated receptor theory and who of course was also from Edinburgh. Was he around then still - a ghost hovering in the background.

No but in 1960 I went down to Cambridge following Martha Vogt to finish work that we were doing with Dennis Sharman. And were did I finish living - in Fulbourn Hospital with David Clark, A J Clark's son. When I went down there, he'd done the clinical job that I was doing in the past. So my boss who knew him very well wrote to him and said look any chance of him staying in your hospital? So I sang for my supper. I lived in Fulbourn and worked at Babraham in animal physiology.

Father and son were very different then - one was the archetypal pharmacologists and the other was not so much an anti-pharmacologist but very much the social psychiatrist.

Yes but I presume the two had one thing in common - enormous drive. Not in the same direction but they both had tremendous drive. David Clark carried through what he did with virtually no psychiatrists. Possibly because he didn't have any doctors. He wouldn't have done it if he'd had doctors.

Fascinating. Okay so we're back now to receptors. You produced your article and within months receptors were radio-labelled making your article highly topical.

At that time I wanted to radio-label them and I wanted to work with the people at the Western General who had a cyclotron. I produced for the MRC a programme that would have involved us developing what was virtually PET but the MRC procrastinated and messed about as was their wont and by that time I was getting disillusioned with the MRC and having major arguments with them and a meeting with some crookery from them. On one of their visits a neuropathologist came to see what we were doing. We at the time were also working on Alzheimer's and appeared to have found a cholinergic deficit. He came and told us to stop this work and to stop work on the Aluminium model in animals. I said we weren't stopping it. A fortnight later, he was on the radio saying how they were developing the Aluminium model in his unit. We also found out that they were working on the cholinergic system.

That's serious trickery.

Very serious yes. We then wrote a paper and sent it in. My name was on it and it got rejected by Nature. Now this was ridiculous because this was a very original finding and it was the first time anybody had said there was a cholinergic deficit in Alzheimer's, so I rang the Editor of the Lancet and said I think we're being done here. He said send it to me and if it's what you say I'll referee it and I'll give you a year's jump in publication. I felt a bit disgusted so I took my name off the paper because I didn't think I should benefit from this sharp practice personally. So we got our paper on the cholinergic deficit in 1976 and the others didn't get it until 1977.

The whole thing disillusioned me. It was one of the reasons why I left the MRC. The other reason was that I felt a lot of the studies now had to be done in a different way. Move away from animal work almost completely and work on man. And they were virtually saying you are the animal people you keep doing that and so to get freedom to work on man I moved up to Aberdeen.

Your approach towards all these things seems very honourable but over in the US it would have been par of the course to play the game more vigorously.

Yes. The Swedes were like the Americans too. I never had trouble thinking of another idea. So it never worried me. I didn't see the point of getting all tied up in whether this was my idea or their idea I still don't see the point in it.

The ethos has changed. Science was a very gentlemanly thing to some extent - yes there was competition between people but it's become a much more self serving business now.

Yes and I think it loses people who would otherwise make a contribution. How many major contributions have been made in the last 10 years in biological field - I can't think of one. Not really fundamental. I think also that you need people coming in from the clinical field. We need people to meet. There is another problem now and that's that the scientific field is so complex that it's very difficult for a clinician to grasp the issues ...

Psychiatry is actually very complex as well

You still need people to do both things. Just before I came up to Aberdeen, I was toying, myself and a fellow called Roger Makendula, who became a Professor of Psychiatry in Iba in Northern Nigeria, with the idea that really the parallel to mood in man was exploratory behaviour in animals. We did a lot of animal work showing which systems were involved in exploratory behaviour in animals. And based on that we launched a hypothesis on the way in which depression, mania and certain types of anxiety were related to changes in exploratory behaviour. And I still believe this - that the most fundamental change in mood disorder is involved with exploratory activity and thinking and that mood is just a label for this.

Quite a few people hold this idea - that there is no such thing as mood in one sense, that activity is actually the core variable.

And the type of activity - you've got exploratory thinking and you've got stereotyped thinking and we looked at which systems were involved in each of these. You could argue for instance that the depression you get with panic is really because panic anxiety inhibits exploration. People who are experiencing a panic attack don't explore and then they become depressed. I wanted to go along these lines and look at this in both animals and man and the MRC wouldn't let me. They said no you're a CSF man, so I said fine I'll go and do it somewhere else then.

Also when I got to Aberdeen the Prof of Physics then, Mallard, came along across to me and said "look I'll show you how to image a rabbits brain". He took me to his lab and he showed me NMR in rabbits. He developed NMR. He developed it in parallel with the people in Nottingham and he asked me what would you do with it if you could do it in man. I said oh we'd start by imaging people with dementia. And all the work that John Besson did on dementia stemmed from this "what would you do with it". So we got into that and then we got into PET, which was the work that Adel Mousawi did.

Can I pick up another angle on the receptor story. This links back to the Reserpine story which is that Reserpine and the 5HIAA work is all pre-synaptic. Does the receptor open up the area of post-synaptic changes - were you thinking much about those issues at all?

Yes, if you look at some of the work that Donald Eccleston did. He actually imported a neurophysiologist from Aberdeen, Gordon Arbuthnot, who had worked on lesioning

and sensitivity changes with Ungerstedt in Sweden. We imported him with the idea of introducing neurophysiology and looking at pre and post-synaptic changes.

Was there any thinking that pre and post-synaptic changes might link up to different kinds of behaviour. Learning theorists might have linked pre-synaptic changes with behaviour that can be conditioned...

No. I became more interested in the systems and this is where all the exploratory thing came in - it was what was happening in the system. I thought we got obsessed with the synapse and lost the idea of what different systems did. Looking at the system and arguing that you could get obsessed with the synapse and that clinicians can tell you more about what's happening at the systems level and that the basic scientists should be listening to them.

So paradoxically, you were at the forefront of what was happening actually in the synapse but conceptually you were almost moving in the opposite direction. Were you aware of people like Tom Ban in the US who were quite excited by the receptor hypothesis because up till then the focus had been pre-synaptic and this fit in with learning theory and conditioned and unconditioned stimuli but the post-synaptic receptor opened up the notion of a lesion.

Yes well I was in a way giving up the idea of a lesion. I was going the opposite way. I was saying most depression is nothing to do with a lesion.

I can see that but the oddity is that you were changing just at the time when the Holy Grail of a lesion comes into view.

Yes. I was aware later that some of the things that we'd talked about -changing receptor sensitivity - could have been due to autoreceptors turning off, so the system left room for a lot of other control mechanisms to come in you know. But no I thought very few cases of depression were due to a lesion.

The work you'd done laid the path open however for the idea of a lesion and it appeared with Fridolin Sulser's Beta adrenoceptor downregulation hypothesis - this is where all the antidepressants worked regardless of what else they worked on. Did you ever meet the man and what was your reaction to all this?

No. Never. But I obviously knew what they were saying. By then I'd lost the idea that anybody was going to find the Holy Grail - find one cause of mood disorders. I still believe that perhaps bipolar illness has some sort of lesion in terms of post-synaptic receptor sensitivity and we said that was probably a failure to be able to readjust sensitivity. But I didn't believe there would be any specific lesion for most cases of depression. And to prove that, I can tell you we actually took on Ivy Blackburn at that time and sent her off to Beck to learn cognitive therapy to try and broaden our view of depression. To bring back new ideas on how you can go into depression from a psychological point of view. I believed a lot of the biochemical changes had been precipitated psychologically or at least you could get stuck in depression. I thought it was interesting to try and find out why you got stuck and why you couldn't come out. I actually still believe that many antidepressant drugs from a functional point of view restore the ability to explore and I think the delay in recovering from the depression is the time it takes to develop exploratory behaviour when you've been deprived of it. I think you're locked in to not exploring and you've got to start again and if that doesn't take three weeks what will. I didn't believe it was

a biochemical reason why it took 3 weeks. I believe there's a behavioural reason for that - exploring outside your little burrow takes a bit longer than 5 minutes. Initially you'll be defeated and go back in and it probably takes 3 weeks to be able to re-explore. So its an interaction between biology and psychology.

But then there's a group of people that you worked on here in Edinburgh which is the treatment resistant group, where you add in a little dose of Tryptophan and you seemed to have flipped a switch almost - this looks very biological .

Once you've stopped exploration it's very difficult to re-establish it. Now if these drugs re-establish the ability to explore, then you may need to give the systems a real kick to restore their ability to deliver this sort of behaviour.

You say you didn't go to meetings much. Did you go to any?

No. I went to some small meetings. I went to a lot of pharmacology society meetings. I went to some meetings on depression run by the College. I remember going to one in London and I gave papers at meetings.

What would people in the Royal College of Psychiatrists have made of this stuff in the 60s. How many people would have thought the same way as you. Alec Jenner, Alec Coppen, Herman van Praag and a few other people but...

Yes and a few foreign people. We were going a long time before Alec Coppen in this area. He made some contributions but it was as much in terms of raising the profile of the area. I read van Praag's work but we actually had already done the probenecid work but couldn't make sense of it so never published it. I've still got it somewhere. I was the first person to take probenecid. I did this with tryptophan as well. When we were going to give tryptophan, I took 2G of it every hour for 24 hours to see what would happen. It gave me an attack of migraine but I think that was just because I never got any sleep. I did the same thing with probenecid, I took large doses of it to see what a patient would tolerate. That made me just feel very sick. I've taken various things to test them out on myself first. I took bromocriptine once. I felt very strange after taking it - derealised. We were going to give that because we had this idea that a dopamine agonist might stop mania.

Stop mania. Now that's creative.

We actually tried it and there's a little paper somewhere with amphetamine. And it does, you can stop mania. Not reliably, in some patients you appear to switch them off.

Is there any way of knowing who it would work for.

No. At that point, I thought a steady stimulation of the receptors if they were hypersensitive might switch off the sensitivity. I now believe it acts by switching off the neurone via autoreceptors. So that was another idea. I don't have a problem with ideas. At home I've got a file with all sorts of other projects.

On the map Aberdeen looks remote from everywhere else but it has quite a pedigree in terms of people like Hughes and Kosterlitz being there, the development of NMR etc. You didn't regret moving?

Oh no, I spent 20 years in Aberdeen after leaving the MRC Brain Metabolism Unit and was able to continue what I've always considered to be the most important part

of our activities which was clinical work with research and teaching being carried out in parallel. During this last 20 years I was pleased to see the development of young "biological" psychiatrists in Aberdeen who have gone on to senior positions - John Besson in London, Klaus Ebmeier who is professor in Edinburgh, Ian Reed and Keith Matthews who are both professors in Dundee and Adel Mousawi who is now in London.

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