3 *Arvid Carlsson*

The rise of neuropsychopharmacology: impact on basic and clinical neuroscience

How did you come to go to NIH?

In Sweden, I had been working mainly in the area of calcium metabolism. I went for a position and the expert committee who gave the position to my only competitor let me understand that the area of calcium metabolism is not really a central field in pharmacology – this is something that has changed lately but that was how it was. Since I wanted to remain in pharmacology, I decided to switch into a different area, so I went to a friend of mine, Dr Sune Bergstrom, who was in the same building – he was Professor of Physiological Chemistry, in Lund, and he was often very helpful. He later received a Nobel prize for his work on prostaglandins. I told him I would like to switch fields; I knew he had lots of good contacts in the US, so I asked him to find a lab in the US, where they were doing biochemical pharmacology, which at that time was something I felt very strongly for.

He wrote to his friend, Bernard Witkop, a very clever chemist – he was originally from Austria – who had done lots of synthetic chemistry that others have profited from enormously. He was behind very important successes in organic chemistry and biochemistry. Witkop transferred the letter to Sidney Udenfriend. Udenfriend was not independant at that time so he had to give it to his boss, Bernard Brodie. Brodie wrote to me and said 'we would be more than happy to have you but we have no money'. I managed to get a modest sum of money in Sweden so I could go. When I came there, in late August 1955, the first thing they did was to invite me to the cafeteria for lunch. Brodie and Udenfriend were there and I figured out that that was the time when Brodie finally made up his mind whether he would accept me or whether he would give me to Udenfriend. He accepted me.

Coming from outside the area, there can't have been much that you could have actually impressed them with in terms of the knowledge of the area.

No, I didn't know anything about this actually. My first pieces of work in pharmacology dealt with central nervous system drugs but from there I had switched to calcium metabolism. I had worked a little bit on convulsants and on what was called, at that time, central analeptics, metrazol – a drug that could wake up barbiturate-sedated animals, and humans for that matter. But that was the only research I had done in CNS pharmacology.

What was NIH like at that time?

Brodie's lab belonged to the National Heart Institute, funnily, which really shows that the labels don't mean that much. It was called the Laboratory of Chemical Pharmacology and the building, where I worked, was building 10, which is the biggest one. At that time, it was said to be the building in the world that had the largest number of bricks. I don't know if that's true, but it was a huge building and, of course it has expanded a little bit, but it isn't that much different actually from how it used to be. At that time, it was new and in the lab of chemical pharmacology they were still buying equipment and there were still big boxes of equipment that hadn't been unpacked yet. It was really at the beginning of that period, which was to be so significant a period in the development of neuropsychopharmacology.

There was a stream of visitors. Almost every day people would come from all over the world to interview Brodie and find out the latest news. Why did it attract that much attention? I think there were three things. One was that Brodie was the real pioneer in the area of measuring drug levels. Pharmacokinetics more or less sprang out of the work that Brodie started originally in New York and then at the NIH. So they were doing a lot of work on that and it was a really fashionable thing at that time and of course it was very important.

Another thing was that they were in the process of developing the spectrophotofluorometer, which is not used so much any more, but which was of such a tremendous importance over two or three decades. The only instrument in the world, when I came there, was the model that Bowman had built. It was the prototype but still not really packed into anything. It was composed of loose parts all over the room, more or less. You had to put out the light in order to work it. So that was a very important development. Then finally there was the discovery that they had just made that if you give reserpine to animals serotonin disappears from tissues, including the brain. I think it was mainly this last finding that attracted so much attention.

This was really the first hard-core neurochemical finding wasn't it?

I think so, yes. This really bridged the gap between biochemistry and psychiatry – and neurology as it later on turned out. So I think it was a very important discovery. Of course, before that you had a few pointers.

You had the discovery by Gaddum that LSD can block the effect of serotonin in the uterus, on which he built his statement that serotonin is needed to keep us sane. And, there was at the same time two Americans, Woolley and Shaw, who had said the same thing. Actually, they corresponded a little bit about the issue of who was first to come up with this statement. I think they were independent. Before that, of course, was the discovery of serotonin in the brain and also Marthe Vogt's study of sympathin as she called it, in the brain, which was also important in the early 1950s.

But this was the first change in anything in the brain that had been shown to correlate with a change in behaviour wasn't it?

Absolutely, yes, because LSD was rather a loose connection, but to give a drug with a very powerful psychotropic action and discover a very striking biochemical change in the brain, that was absolutely the first breakthrough.

You were working on platelet 5-HT. How did all of that go? Because harvesting platelets is quite tricky isn't it?

Well, there was something tricky in it and I must tell you that I still don't know what it was. When I arrived there in late August I was put on this immediately. They had the equipment ready for me, very good equipment, so they told me exactly how to do it. And I did it. I isolated these platelets. It's not difficult at all.

But if you use the wrong anticoagulant and the wrong G-force . . .

Yes, it doesn't work. That's true but in this case, with EDTA, there was no problem. For some funny reason, they told me I had to use siliconized glassware, which we found out was not at all necessary. I worked, I think, for more than one month on this – I isolated the platelets, put in the reserpine and measured serotonin in the supernatant and in the platelets – and found no effect. That was frustrating because as you already indicated I was entirely new in the field, so they thought probably I was just a joke. But then what happened was that I ran out of the sample of reserpine and they gave me a new one and, as soon as I got that, it worked beautifully. I think there was something wrong with the first batch of reserpine.

Having cutting your teeth on 5-HT, despite Brodie's great enthusiasm for it, you were quite keen to look at catecholamines and not just 5-HT. This was heresy.

Yes, it was, and the reason why I wanted to do that was that I did a little bit of work on my own on these platelets. For some reason, probably because Hillarp back in Lund had discovered that there is a lot of ATP in the adrenomedullary granules and I wondered if there was any ATP in the platelets. I did some analyses on that. I don't think they were very

good qualitatively but at least they convinced me that there is ATP in the platelets and in fairly large amounts. Since this was the case, I felt it was a reasonable hypothesis that the storage mechanism for serotonin and catecholamines could be basically the same and therefore if you gave reserpine something might happen to the catecholamines as well.

So I told Brodie, shouldn't we do that and he said 'no, that would be a waste of time because it's serotonin that's important'. He insisted on serotonin for an unreasonably long time – why did he do that? Well, partly perhaps because of his particular character but perhaps also he had started out with an hypothesis and this experiment with reserpine and serotonin confirmed the hypothesis in his mind. The hypothesis was based on Gaddum's ideas. They had done sleeping time, which at that time was very fashionable – you give either ethanol or a barbiturate to a mouse and you measure the time the mouse is in anaesthesia. Then you put in LSD and you could shorten the time or put in serotonin and you could lengthen the time. Reserpine lengthened the time. So LSD and reserpine were antagonists and serotonin acted like reserpine.

So then they said well suppose that reserpine releases serotonin. That's why they did the experiment and it came out exactly the way they thought. Now that's what they felt on the basis of these rather simple experiments but, of course, they were not really interpreted correctly because serotonin doesn't get into the brain. The interpretation was basically wrong. Nevertheless, they thought that, when you give reserpine, there will be more free serotonin and it is this free serotonin that sedates the animals. That was the story and they were firm on that.

But on the other hand, I must say that Brodie was very generous to me. When I was considered for a position, a Chair in Lund, and the Faculty demanded references, Brodie wrote very generously that I had astounded the world by showing that catecholamines are also depleted by reserpine. On the other hand, of course, we also had some debates, which got a little bit harsh every once in a while. Not so much with Brodie himself, as with some of his younger colleagues.

Such as?

The most memorable debate was with Mimo Costa. There was a meeting in Stockholm, in 1961. It was actually the first international congress of pharmacology. Costa reported on continuing studies that proved that reserpine acted on serotonin and that catecholamines were not important. I discussed his paper and demonstrated that they had misinterpreted their data. While we were debating, it became very lively I must say. Brodie came into the room – he hadn't been there in the beginning – and he said later 'lucky Carlsson that Costa didn't have a knife', because he really was so furious. Actually, it was in the Swedish newspapers the following day. Twenty-five years later, there was an International Symposium on Clinical Pharmacology, that Sjoqvist chaired in Stockholm, and he had

been at this debate and thought it was so memorable, that it must be repeated–25 years later. So he invited me and Costa . . . but it was rather friendly at that time.

How do you rate Brodie?

Brodie I think was really the top. You cannot measure him by conventional academic standards because he might not do very well. Part of his science was very solid but he went out speculating into areas where he was ignorant. He was not a traditional scholar – I think one can say that for sure – but as I indicated before, in a way, that was his strength. It may be that the most important people, the most creative people, do not fulfil conventional standards. But that is also the reason why some people think he was nuts, because if you look at him from a certain point of view, he was. It's enough for one individual if he's got one or two great ideas, that they can elaborate on and bring to a certain level of truth. Then they have contributed haven't they – even if they are crazy in every other respect.

Should he have got the Nobel prize with Axelrod?

In my opinion he would deserve a Nobel prize. But it depends on how you read what Alfred Nobel put in his testament. Certainly, in terms of contributing to neuroscience or pharmacology for that matter, Brodie is far above anyone else. The problem was that he was an organic chemist and his knowledge of physiology and medicine was really not a heavy burden on him. He didn't know much about it and I think that was one of his strengths – his ignorance, yes. He didn't have any idea how complex the brain is for one thing, so he could come up with some very simple concepts. There are several things to be said about Brodie but one of them was his ignorance in physiology in combination with this ability to formulate simple concepts that were testable, which was very surprising. Many times he could sit at the meeting and listen to very complex presentations and then come up with some very simple question at the end that made a lot of sense even though people probably wouldn't accept it. But he would go home and do something about it. So that was the strength, together with his ability to develop methods and to collect people around him who were clever, such as Udenfriend and Bowman and Axelrod.

So he was a terrific guy but when it came to interpret his data – when it came to a stage where knowledge was needed in order to bring it further, that was where he failed. It was his strength and his weakness. By means of this way, he could make a breakthrough but he couldn't develop the concept any further because he didn't know that much. He was an organic chemist and you couldn't demand from him that he should have an understanding of the function of the brain.

So you went back to Sweden and did the catecholamine work with Hillarp. Tell me about him.

He was a very interesting personality. He was a genius, I think one can say. He started out in histology but he was very much focused on function, so that he became just as much a physiologist as histologist. He was very clever and had very fine experimental skills. He had acquired a range of techniques at that time, that were so important, such as homogenization, differential centrifugation to isolate the different organelles in the cells, and so forth. He had set up methods for analysing catecholamines and ATP – he was also a very good biochemist, as a matter of fact. So, when I thought of this in Bethesda I thought I must ask Hillarp if he would like to work on this with me and, luckily, he said yes. So we did some work actually on the binding between catecholamines and ATP but then also we gave reserpine and we analysed the adrenal medulla for catecholamines.

Now I had been very much impressed by the spectrophotofluorometer, which I had started to work on in Brodie's lab. At that time, they had just started to manufacture and sell this Aminco-Bowman spectrophotofluorometer. The first thing I did after coming back home to Lund was to order an instrument. It was very expensive. I didn't have the money. So I applied for money to the Swedish Medical Research Council and got it, but when we were doing these first experiments I didn't have the instrument. However, Hillarp had set up a colorimetric method and it worked beautifully – you add an oxidant, which converts adrenaline into a red-coloured compound, adrenochrome, which you can measure colorimetrically. Of course, when we did this experiment, we found we didn't need any colorimeter because, after we had given reserpine, there was no colour at all. You could see it with a naked eye. It was very dramatic.

At the time, was there any feeling that changing the world from Lund was unusual and people weren't going to pay any heed to you? You weren't operating out of the NIH or Oxford or Cambridge.

Sure, and that came out fairly strongly a couple of years later when Hillarp and I went to a meeting in London on adrenergic mechanisms and there was this . . .

Yes, I was going to ask you about . . . I've read the volume from that meeting. Tell me about that because there are two or three of your articles where, you still to this day, express surprise that the people in the UK at least didn't realize the implications.

Yes, disappointment in a way. But at the same time it aroused opposition and perhaps even aggression to some extent that these people couldn't understand that this was very important.

The really surprising thing is that the participants at the meeting were the very people, who had campaigned for so long on the importance of chemical neurotransmission.

They were the pioneers, they were all there. Dale, Gaddum, Marthe Vogt, Feldberg, Blaschko, everybody was there. Burns, Zaimis, Bulbring, everybody in the field was there. An interesting thing is that the discussion was actually printed, so you can really see what was said. There were very few things that were omitted but one thing that was omitted was that at one point, when they expressed their scepticism against the idea that these amines could be so important in the brain, Blaschko, who had actually replicated some of our most salient experiments, became annoyed and said I think you should recognise that Carlsson has made a great discovery here. What he alluded to then was the effect of the L-dopa on the reserpine treated animal . . .

I'll pick that up in a moment but can I ask you what were Dale and the others like?

I may have seen him a couple of times in other situations but in this symposium we saw each other every day. He was a magnificent personality and it was funny to see how he behaved with the younger guys. The younger guys, of course, were in their 50s or 60s but they behaved as school children more or less to this man. Sir Henry! He was terrific but, also, it was clear that you should be careful not to come up with any statement that was not well taken by Sir Henry Dale. So, for example, coming back to when Blaschko said that they should really recognize that Carlsson has made an important discovery here – he came to me later privately and said that he was sorry that he was so irritated that he said this. In fact, his remark was omitted in the proceedings. That, I think, is a sign of how the people around Dale felt they should be careful. If a statement was not approved by him it should be deleted and he was obviously very doubtful about the whole idea of this L-dopa story, dopamine and so forth. One of his comments at the meeting was, isn't it strange that here we have an amino acid, dopa, that is toxic?

Toxic, why toxic?

Well, the reason why he said toxic was that Weil-Malherbe had done some experiments with L-dopa. He gave large doses of dopa in combination with MAO inhibitors and the animals looked terrible and died. Because he was one of the guys in Britain, what he had seen was more important than what we had seen and for that matter Blaschko or the Polish fellow Crusciel, who was working with Blaschko and had done the experiments, had seen. Weil-Malherbe belonged to the 'real people' and somebody coming from Lund or Poland or whatever, coming to

Britain and telling you stories, that would not be immediately accepted, that's for sure.

From there yourself and Hillarp went on to develop the histofluorescent methods and the mapping of the brain pathways, which was so important.

Actually this was related to this meeting in London because we were both very disappointed. We travelled back together. One of the things that was said at that Adrenergic Mechanisms meeting was that maybe these amines after all were only in the glial cells – it was mentioned in the proceedings there. So we said it would be terribly important if one could demonstrate the presence of these amines in neurones. So Hillarp and I decided we should try it. I had just been appointed to the Chair in Pharmacology in Gothenburg, he had an Associate Professorship in Lund, and we decided we should apply to the Swedish Medical Research Council to enable him to be set free from his teaching position, to come with me to the new department and work on this. We got the money and started on the work.

In the first stage we tried to apply the same fluorimetic procedure we had used for catecholamines before, adapted for a histological preparation, and it worked but it worked only for the adrenal medulla. Nevertheless, Hillarp was very excited by this and he said we must do this in some different way. What he started out from then was another analytical method developed by Udenfriend, where he had added formaldehyde to serotonin and converted serotonin into a fluorescent compound that could be measured. So, Hillarp started then on formaldehyde gas added onto films. Thieme was his technician and Thieme came with him to Gothenburg and what they did was to have a solution with serotonin, for example, and a protein and they put it on the slide, allowed it to dry, so they had a film, and they put the slide into formaldehyde gas and looked at it in the florescent microscope. They had to change the various conditions but finally it worked beautifully.

One day in August 1961, when Hillarp went down to Lund, he and Bengt Falck, who was his former pupil, decided they should try a preparation that Hillarp had used in his thesis – stretched preparations of omentum or iris. You just take omentum from a rat, put it on the slide, allow it to dry in the air, or you take the iris and do the same thing, stretch it on the glass and then you put it into formaldehyde gas. That was when Hillarp was just down for a weekend in Lund. And it worked. They put it into the fluorescent microscope and all of a sudden they could see the same reticulum that Hillarp had described in his thesis, using methylene blue. So the adrenergic nerves were there. It took another two or three months for them to repeat it. They couldn't repeat it, so they had to work on all these various conditions – to change the humidity or whatever and so forth – and they got it working again and then they could apply it to histological preparations. So that was how it was done but

the model experiments were done by Thieme and Hillarp in Gothenburg actually.

When did they get to the stage of mapping the various pathways?

Well, that was rather soon. Hillarp liked to do a lot of work and then to publish the work in very extensive publications that were not accepted usually by the journals themselves. They had to be a supplement. So there was a couple of important supplements in *Acta Physiologica Scandinavica* from 1962 and 1963 that nobody knows about.

He wasn't too concerned to get his name in lights.

No. I don't think he really understood that. He was a fairly shy man. In his whole life, he had been only to one international meeting. That was the meeting in London. So he didn't know much about the world. He had also been to one meeting in Helsinki. So this idea of how to distribute information, he didn't understand so well. Also he had the idea, adopted by *Acta Physiologica Scandinavica* that authors should always be in alphabetical order. You can see that in all his publications. I didn't mind, because my name C is before H. So the first publication demonstrating the neurocellular localization of monoamines in the brain was by Carlsson, Falck and Hillarp.

What was the impact of the maps when they came out?

Oh, it was enormous. I think that probably there were two things that led to a general acceptance of the monoamines as neurotransmitters. One of them was the histochemistry and all the work that we did on pharmacological manipulations, with reserpine and precursors and seeing how monoamine levels changed. The other thing, I think, was the discovery by Hornykiewicz that you have a depletion of dopamine in Parkinson's disease. We had, of course, proposed that on the basis of animal data but it was Hornykiewicz, who really demonstrated the low levels of dopamine in post mortem analyses.

The other big debate in this area at the time was whether vesicles were of functional importance, with Axelrod on one side saying 'no, it's not, it's the neurotransmitters in the cytoplasm that count'.

I connect different issues with different meetings. This was at the 1965 meeting in Stockholm where von Euler, Rosell and Uvnäs were editors of the book called *Mechanisms of Release of Biogenic Amines*. At that, von Euler and Axelrod and Udenfriend said it's the cytoplasmic pool that is the important thing and they quoted especially Udenfriend, who said that the vesicles are garbage cans. We fought this very strongly. At the time, we had just collected pharmacological data by means of the histochemical fluorescense technique and we could actually demonstrate a condition, where you had an excess of amine in the cytoplasm and yet when you

stimulated the nerves, they did not respond, because there was none taken up by the granules. The 1965 proceedings are nice because there was a discussion where people really stated what they thought. We reported on our monoaminergic synapse model that we had proposed a couple of years earlier.

The effects of L-dopa in reversing reserpine-induced behaviour was the point that proved it was the catecholamines rather than 5-HT. 5-HTP didn't make any difference, how did Brodie take that?

Well, he had his own interpretation. In 1957, he actually visited Lund and we did the experiment there so he could see it, so he didn't doubt the finding but he came back then to an idea that goes back to the Swiss physiologist, Hess, who talked about the trophotrophic and ergotrophic systems. The trophotrophic system was serotonin, according to Brodie, and the ergotrophic system was the catecholamines. So he said, okay, what you see here is exactly what I'm saying – if you elevate the function of the ergotrophic system it will counteract the effect of the trophotrophic system that is now over-stimulated by the continuous release of serotonin. So he could easily handle that.

Did that idea come back 10 years later, when you put forward the proposal which led to the 5-HT reuptake inhibitors, that maybe the catecholamines were involved in motor activation and 5-HT was more involved in mood.

Well, no, not really. The reason I proposed this, which may not be true after all, was based on the data by Kielholz, who had this beautiful picture with all the tricyclics and on one side he had a spectrum of mood elevating effects and on the other side he has a spectrum of restoration of drive. And you could see from Kielholz's scheme, which was based on his clinical impression, that it was the secondary amines that were on the activating side and the tertiary amines that were mood elevating. Then we found that serotonin uptake was also inhibited by antidepressants and that it was more so by the tertiary than by the secondary amines and we just put that together and said look it's noradrenaline that is activating and it's serotonin that is mood elevating. That was in 1969, I think.

And this was the idea that led to the 5-HT reuptake inhibitors . . .

Oh, yes, and especially after our data on the effects of clomipramine on 5-HT reuptake. Actually I went down to Basel, to Geigy, it hadn't fused yet with Ciba, and talked to Theobald and the pharmacologists there. I showed them the data that clomipramine was acting preferentially on serotonin reuptake but they were not terribly interested. They had another alternative to develop as a follow-up to imipramine, but apparently the other drug had some problem in the toxicity studies, so they picked up clomipramine finally. And then, of course, clomipramine turned out in the clinic to have a profile that was not the same as imipramine.

It was clomipramine that made us so excited and also we felt that, on the basis of Kielholz's scheme, imipramine and amitriptyline, the tertiary amines, were perhaps more mood elevating than the secondary amines. We were also impressed by the fact that the tertiary amines were the ones that were used more; the secondary amines never came into any broad use, except perhaps for nortriptyline.

Except in the States. Desipramine sold extremely well in the States.

That's right and the reason for that was Brodie. He did a nice experiment. He simply gave desipramine followed by reserpine and he could see then that reserpine, under those conditions, had a stimulant action. Therefore, he said that imipramine acts via its metabolite, desipramine, and it's desipramine that's the antidepressant. It makes a lot of sense and, of course, Brodie was at that time a major figure. So that's true but in Europe desipramine never sold very much. Nortriptyline did a little better but actually it acts relatively more strongly on serotonin. Nevertheless all the careful, well controlled, clinical studies always show the same thing – if you compare any two of these tricyclics in depression you see no difference. Therefore, it was concluded they are the same. Kielholz had a different view he based it on his clinical impression, while all the so-called solid data showed no difference. I think it's partly because the instrument that is used is so crude – so you cannot pick out any subtle differences.

Anyway, we felt that since the tertiary amines are so much more popular it may be due to their serotonergic activity. Then we found that certain anti-histamines also had serotonin uptake inhibitory properties, even though they were not terribly selective. They acted on noradrenaline as well. But, on that basis, we picked up brompheniramine and chlorpheniramine. These were the most potent serotonin uptake inhibitors, among the antihistamines. On that basis, Hans Corrodi, a very clever Swiss organic chemist employed by the Astra subsidiary Hê3ssle, with whom I had close collaboration for several years, came to zimelidine, which is actually very close to brompheniramine in terms of chemical structures.

Now, I know zimelidine was the first 5-HT reuptake inhibitor on the market but was it the first 5-HT reuptake inhibitor? There's some controversy about this. Ciba had one from fairly early on and Lundbeck with citalopram.

I know because I came down to Lundbeck and gave them a seminar and I told them the whole story as we had it and also I told them that if you add a halogen or similar things on the molecule of a noradrenaline reuptake inhibitor, you will switch it and it will become more serotonin uptake inhibiting. So the chemist there, Bögesö, had lots of noradrenaline uptake inhibitors, and he went back to the lab and modified his molecules, so as to make them serotonergic and that is how they got citalopram, which I'm sure was not before zimelidine.

What about fluoxetine?

Clearly, fluoxetine came after zimelidine. The first preclinical lab test of fluoxetine for 5-HT uptake inhibition at Lilly was performed in May 1972, two months after publication of the first patent demonstrating the selectivity of zimelidine as a 5-HT reuptake inhibitor.

Alec Coppen mentions that even after fluoxetine was developed the company weren't particularly thinking of it in terms of depression.

Yes, well . . . zimelidine came first both preclinically and clinically. I suppose that the demonstration of the antidepressant efficacy of zimelidine had an impact on the other drug companies. I'm not sure they would have even developed fluoxetine if it weren't zimelidine hadn't been shown to be clinically active.

We've gone down the road of producing drugs which are more selective to the 5-HT reuptake site. And this has been a major step forward but there's a hint from the literature, it's hard to put it stronger than a hint, that while these are good antidepressants, if anything they aren't as potent as some of the older tertiary amines were. Should we be going back from the route of trying to produce purer drugs to producing dirty drugs?

Well, if we do that, they will not be dirty in the same sense as in the beginning. because then they just happened to be dirty. This is a kind of rational dirtiness, isn't it?

Is there really such a thing as rational dirtiness? . . .

I think so. I think that is how ideal drug development should be. Number one usually is serendipity. You come across something. You have rather a dirty drug that's doing something. The next step is you try to find out how it works and in some cases you find one major site of action and in other cases you find a couple of candidate sites, so to speak. What you do then is you develop clean compounds and they had to be taken to the clinic to see whether they work. Then, for example, we can say serotonin uptake inhibition is an antidepressant principle but I think we can also say that noradrenaline reuptake inhibition is an antidepressant principle. So you've got two at least. The next step then would be to make molecules that are doing exactly these things but built into one and the same molecule. That would not be the same thing as just going back to the tricyclics because they have lots of other problems.

It's going to be very hard to actually persuade people that it isn't the same thing.

Not really. Because if you can develop a drug that is a serotonin uptake inhibitor and a noradrenaline uptake inhibitor and it does not have the cardiac problems, it will be a winner. However, I'm not sure about the anticholinergic action, whether that could also contribute. This is, of

course, generally asumed to be just a side effect. I'm not so sure. The main argument is that an anticholinergic agent does not have antidepressant activity and I think that is true. But that is not the same thing as saying that if you add an anticholinergic component, to a serotonergic or noradrenergic component, that then it won't do something. We have lots of experimental data showing that a drug, that in itself does nothing, can do a lot if it is combined with another drug that has a different site of action. So I don't think we can disregard this possibility . . .

Can you give me an example?

We have lots. This is an area we're working very much in now. Take clonidine, which is a rather striking example. If you have a monoamine-depleted animal and you give clonidine, you see practically nothing in terms of psychomotor activation. Now it was discovered by Anden, in our lab, many years ago that if you give apomorphine in a moderate dose to reserpine-treated animals, you get a stimulant effect and then if you add clonidine you get a lot more. So clonidine, which in itself does nothing, in the presence of a dopamine receptor agonist becomes a very powerful psychomotor stimulant.

You've just reminded me of Hannah Steinberg's work showing that if you co-prescribe amphetamines and barbiturates you get a much greater degree of excitation than you would expect to get from the amphetamines on their own, which seems remarkable. The whole area of the use of two different groups of drugs together is completely unexplored really.

Yes, it is. Actually my daughter, Maria, is very much involved in this field now. There are tremendous interactions at the post-synaptic side. Anden's experiments showed this but now we have so many examples. Another one is with atropine. If you give atropine to a monoamine-depleted animal you see very little. But if you give atropine combined with clonidine or with a sub-threshold dose of a NMDA receptor antagonist, which does nothing in this dosage, you will have a lot of psychomotor excitation. There are so many examples of these interactions. I think this is a very important area actually. The whole field of schizophrenia, I think, is now moving in the direction of trying to look for interactions and trying to look for patterns of aberrations that involve more than one neurotransmitter.

It's very hard to see how treatments which will involve two or more drugs being co-prescribed will get through the FDA because the FDA is geared to handling one compound at a time.

That's true. I think they will have to re-educate and maybe we will have to wait for another generation of FDA people. But I think this concept of powerful interactions between neurotransmitters will have its day. I'm sure of that but not perhaps for the next few years.

One of the curious things to come out of the 5-HT reuptake inhibitors was the idea that the purer the compounds you get, the more specifically you can actually influence very discrete behaviours very quickly. The obvious example is that you can give a low dose of one of the 5-HT reuptake inhibitors and influence sexual performance within hours of having had it. This runs counter to the old idea that it takes a while for the drugs to get in the brain and they work terribly slowly on the receptors, etc., etc. and this explains why antidepressants take so long to work. But the effects of 5-HT drugs on sex prove that this can't be the case. How can we now explain the two or three or four week delay in response of depression to antidepressants?

Some of the therapeutic actions are also rapid. One example is premenstrual tension. That actually was pioneered by a fellow in our department, Elias Eriksson. What he did was to treat PMS patients with 5-HT reuptake inhibitors and the effect was dramatic. There is a very high percentage response and it's a dramatic response. Not only are the patients very grateful but their husbands are too. Now the point is this – they started treating people for the whole of their cycle but then they found out you can actually do it for a very short period of time. Just start a few days before the symptoms usually show up and it will work. So here we have another case of almost immediate response and, therefore, we are left with the problem how come that the antidepressant response shows such a sluggish onset. Maybe there is no true latency but certainly there is a slow development, of response over several weeks.

I have no explanation for it. But the way I try to envisage what happens is that presumably when a patient goes into depression, it takes a long time. Whatever is the first mechanism that becomes deficient, a series of secondary events happen and bring the patient into the final stage of depression. If this is so, it makes a lot of sense that if you manage to rectify some of the aberrations, that were at an early stage of the chain of events, you will have to wait for all these things to normalize and that takes time because it may involve protein synthesis, trophic effects in complex chains and complex circuitries to start to operate again. You get more or less the same lag, if you give serotonin inhibitors, MAO inhibitors or ECT. So it rather suggests that it is the disease that is the cause of this slow onset and now that we see that other symptoms that are not depression can show improvement very quickly, that also brings the focus onto the disorder as such. If this is true, it could have some important implications, namely that maybe there will never be a drug that will act immediately on the depression because it's impossible. Even though, one cannot be sure – one day maybe somebody will find something.

Coming back to dopamine and Hornykiewicz. The story goes back before Hornykiewicz to the idea that dopamine might be a neurotransmitter. Can you tell me how that came about?

Well, that goes back to the original experiment where we gave reserpine and found that catecholamines are also depleted. At that time dopamine was not in focus at all. Actually it had not yet been demonstrated to occur in the brain. After seeing this depletion, we stimulated the adrenergic nerves and found that they didn't respond any more so that argued against Brodie's idea of an excess release and in favour of a depletion. Therefore, we wanted to see if we could refill the stores in the brain. We couldn't give the amines themselves because we knew they didn't get into the brain but the precursors were known to get in. Actually, Udenfriend had given 5-hydroxytryptophan to reserpine-treated animals and I think he had also given L-dopa but probably in insufficient doses, I don't know. He hadn't seen much and he never published on it. But we did it and we were luckier. We could see a very dramatic effect of L-dopa on reserpine-treated animals–10 minutes after L-dopa they were up and running. We published it in *Nature* in 1957 but at the time when we submitted the paper, we hadn't yet analysed the brains. When we did we were really very disappointed because there was no noradrenaline in the brains of these animals.

It must have been very puzzling.

It was indeed. We were forced to look for dopamine because we had evidence that it was an amine that we had to look for. When we gave an MAO inhibitor it strongly potentiated L-dopa actions. So we had to develop a method for dopamine and we found dopamine tied up beautifully; it can be correlated in time and so forth with the arousal. Then we looked for dopamine normally in the brain and found it is there in amounts that are more than noradrenaline, so it couldn't be just the precursor.

Then, of course, there have been some statements that we were not first in the discovery of dopamine in the brain. This is partly true because there was a paper by Montague, where she showed on a paper chromatogram a compound she called X. She said X has the same migration rate on paper as dopamine but she didn't say it was dopamine and she didn't say anything about the amounts it was present in or anything else for that matter. There was nothing in her publication that suggested that she thought this had any particular significance. You see everybody, of course, believed dopamine is in the brain from the work of Blaschko and others on the synthetic chain of catecholamines – dopamine had to be in the brain because there is noradrenaline in the brain. What we did was to demonstrate specifically that dopamine is in the brain, that it is depleted by reserpine, and that it comes back when we give L-dopa and we proposed that dopamine is an agonist in its own right in a paper to *Science* in 1958.

Shortly after that two of my students, Bertler and Rosengren, came to me asking if they could pursue this a little bit. I said, 'okay, you can look

at the distribution' and they did and they found that the distribution is so different from noradrenaline. You have most of it in the basal ganglia and on the basis of that, we proposed that dopamine was involved in extrapyramidal functions because the basal ganglia had been recognized for a long time as being somehow involved in the control of motor functions. And, of course, it was known that reserpine can produce the picture of Parkinson's disease, so we proposed that the depletion of dopamine leads to Parkinson's syndrome.

All too often the only findings that get quoted are those of Hornykiewicz.

That's true but it was very clearly stated both in the volume from the First International Catecholamines Symposium in Bethesda in 1959, and also in the original paper by Bertler and Rosengren (Bertler and Rosengren, 1959), but it was elaborated on in a paper in *Pharmacological Reviews.*

So did Hornykiewicz come to this idea totally separately?

No, he knew about our work. There was a time lag in between. He knew about it even though he doesn't emphasize this a lot, I think one can say. What he rather emphasizes is that after spending a year with Blaschko, apparently the last thing Blaschko told him when he was departing was 'please remember dopamine'. So that was his story.

And when did that lead to people treating Parkinson's disease?

Well, you have two stories – Birkmayer's story and Hornykiewicz's story. Birkmayer said 'I came back to Hornykiewicz and told him that we must get started with giving L-dopa to Parkinson's patients' and if you ask Hornykiewicz he says 'I came to Birkmayer and told him when are you going to start to do this L-dopa in Parkinson's patients'. I don't know. Apparently they remember this in different ways but any way these were the two guys who did it. Birkmayer was a clinician in a neurogeriatric setting and he had lots of Parkinson patients and they gave it by injection.

Of course, they had problems. They saw something but not everybody who tried to replicate these injections could see it but there were some that saw it. I am convinced that they saw something and actually Birkmayer went on with it for a long time. In 1966 Hornykiewicz expressed doubts about the therapeutic usefulness of L-dopa. But Birkmayer insisted and one thing that really shows that Birkmayer was on the right track was his story about the decarboxylase inhibitor that Roche had, benserazide. Actually Roche supplied the drug to Birkmayer, rather reluctantly. They didn't seem to believe much in Birkmayer's L-dopa trials. I don't know who was the initiator of this, again I hear different stories, but in any event, he started to use it. The Roche people said that what you are going to see now is that you will block the effect of L-dopa because this is a decarboxylase inhibitor but he gave the two together and found it was the opposite. It potentiated the action of L-dopa.

Then, of course, Roche had to do what Birkmayer called retrograde pharmacology and they found that this drug didn't get into the brain and the Roche people had missed that. So that's how the first peripheral decarboxylase inhibitor came about and I think that really proves that Birkmayer saw something very significant and I am sure that if Cotzias had not come at about the same time as Birkmayer had made this discovery of the interaction with benserazide, then it would have developed further in Vienna, I'm sure.

But then Cotzias came in and what he saw was so dramatic. He was a Greek fellow, who as a rather young person had come to the US and got an MD degree there. He had access to Parkinson patients. He had some ideas about neuromelanin, that I never understood really, but of course neuromelanin disappears in Parkinson's – there's no doubt about that – and he thought that was important. So, he reasoned that one should give dopa orally in escalating doses and he did that, using the racemate, and discovered a much more dramatic effect on the symptomatology than Birkmayer had seen, at least before he was using the decarboxylase inhibitor. Then, he switched to L-dopa. The doses were rather shockingly high – up to 6, 7 or 8 per day of L-dopa and Birkmayer says that what Cotzias discovered was the side effects. And of course that's true – he discovered the side effects. But that's not the whole thing of course. Birkmayer hadn't seen the dyskinesias.

I heard about this for the first time at a meeting in Canada in 1967. Cotzias had a movie to show that his Parkinson patients responded very dramatically. I remember Duvoisin was there. He is a neurologist who specialized in Parkinson's disease. So I asked him 'what do you think, do you think this is a real thing?'. He said 'yes, I think so because of the dyskinesias. That could not be faked in any way'. I went home and I told the neurologists in Gothenburg and they got started. Of course it spread out world-wide very quickly – in a few years there were lots of observations of this effect.

So you think it was the combination of that and the Falck/Hillarp mapping that led to the change in attitude.

Yes, at the Adrenergic Mechanisms meeting it was argued that the issue as to whether these amines are doing anything in the brain was a matter of how you manipulate brain amines, what kind of doses of drugs you use – it was put down as a kind of manipulation of the system that had no physiological meaning. In addition there was the argument that the amine might be located in the glia.

This is so remarkable seeing that that very same group had been at war with Eccles and others saying that chemical neurotransmission was important.

Yes, and it may be that Eccles had an impact on it in a negative sense – although, of course, you know that Eccles is the one who later claimed

that he was the one who first argued that you had chemical transmission in the brain. After fighting with Dale for so many years, all of a sudden he did an experiment that I don't think was terribly conclusive but he said, now look what I have found, there is chemical transmission in the brain. But I think his attack on Dale had made Dale very cautious. He didn't want to spoil the solid story he and his colleagues had as regards the peripheral system by any claim about the CNS. Of course there were also some good arguments – the synaptic delay in the brain was really very short in contrast to what you had in the periphery. The electron microscope pictures came at about the same time, showing how densely packed everything is in the brain, suggesting there was a lot more possibility for an electric impulse just to cross directly without any chemical intervention. As late as 1963, there was a nice book on synaptic transmission by a Canadian fellow – McLennan – in which he stated there was really no evidence even for acetylcholine as a neurotransmitter.

Talking about dopamine and Parkinson's disease leads on to dopamine and schizophrenia and the neuroleptics. Can you tell me how you got into working on the mechanism of action of chlorpromazine.

We were puzzled by the fact that the pharmacological profile of reserpine and chlorpromazine are very similar in animals and also in the clinic and yet one of them is a depletor of monoamines and the other one is not. We felt that maybe chlorpromazine was doing something to the metabolism of catecholamines. Axelrod had discovered catechol-O-methyl-transferase and we were interested in that. We were looking for the metabolite of dopamine, which is 3-methoxytyramine, and we found it normally in the brain. In order to measure the formation of 3-methoxytyramine we felt we should block monoamine oxidase because then we would have a closed system as it were. We thought that would be a nice way of looking at release because we had some data, which suggested to us, that 3-methoxy-tyramine formation is related to release. Actually this was one of the things that I brought up at the meeting on Adrenergic Mechanisms but Gaddum didn't believe in it at all. We had found that in order to be O-methylated, the amine has to be released first and therefore formation of 3-methoxytyramine would be an indicator of release. This is now generally accepted, but at that time, it was not at all accepted.

Anyway, what we did was to give an MAO inhibitor, chlorpromazine, haloperidol and a number of other compounds and looked at the rate of accumulation of 3-methoxytyramine and we looked at normetanephrine at the same time, the corresponding noradrenaline metabolite, and showed that there is an acceleration of the formation of these metabolites, while there is no change in the level of either dopamine or noradrenaline. So, if you have no change in the neurotransmitters but you have an elevation of metabolite, on that basis we said what is happening here is a stimulation of synthesis and release. In order to make this fit with what was

known otherwise, especially the background knowledge that chlorpromazine and reserpine have the same profile and also some other data showing that the behavioural effects of L-dopa can be antagonized by chlorpromazine, it wasn't really far-fetched at all to say that here we must have a blockade of a receptor.

Receptors at this stage though were still theoretical entities. No one had actually labelled them and we didn't really know, for sure, that they existed.

That's true, but receptor theory in pharmacology goes back decades. It was well accepted in pharmacology long before any biochemist ever started to think of it. So it was not a problem to postulate the existence of a receptor that was blocked here, even though, of course, we couldn't say what kind of receptor it was. But we did experiments with phenoxybenzamine and it didn't do anything to 3-methoxytyramine, so there was some slight hint that maybe there are different receptors but we didn't postulate that – we left it at catecholamine receptors. Actually, in that paper we didn't even exclude an effect on serotonin receptors. So, as perhaps one does often with patent claims, you try to widen the claim as much as possible so we included serotonin – and serotonin receptors are, of course, now very much being discussed in connection with antipsychotic activity.

The way it was interpreted by others was that we claimed dopamine. I do not argue against it; certainly dopamine was in it. Shortly afterwards Anden and his colleagues in my lab and Nybäck and Sedvall in Stockholm studied a fairly large number of antipsychotic agents and found that the effect on dopamine is the common denominator, so that narrowed the whole thing on to dopamine.

Every so often when people write articles on the dopamine hypothesis, you see the name van Rossum mentioned. Where did he come in?

Actually in our 1963 paper, we didn't say anything about the pathogenesis of schizophrenia. This paper deals with the mode of action of antipsychotic agents and van Rossum said 'look, schizophrenia involves dopamine'. That's what he said and of course he may be right, he may be wrong, we still don't know. But what we do know is that neuroleptic drugs have an impact on dopamine and that is important for the effect.

Van Rossum was one of the pupils of Ariens, who has contributed a lot, I think. Ariens was the one who introduced the concept of intrinsic activity, which was very important. This is an example of how far pharmacology had gone before any receptor had even been isolated. There was a whole doctrine about receptors, affinity versus intrinsic activity and so forth. So he was his teacher and van Rossum did a lot of work together with Ariens but this is what is especially known about him.

The next thing was that Randrup and Munkvad found, together with a number of others, that amphetamine depends on the synthesis of cat-

echolamines for its stimulant action. That led to the suggestion that amphetamine acts by releasing catecholamines and especially perhaps dopamine. They became very interested in the stereotyped behaviour that all dopamine receptor agonists induce, and they proposed that this stereotyped, disorganized behaviour was a model of schizophrenia. This is probably not true, in the strict sense, because we now know that in Parkinson patients, L-dopa can induce severe dyskinesia without inducing any psychotic symptoms – even though L-dopa can of course induce psychotic symptoms. Still, it could be true in a somewhat different sense – if the same type of disorganized output that you have in the motor system that leads to dyskinesia were to happen in those parts of the system that are involved in the mental functions, that could lead to psychosis. It's a perfectly sound idea.

Merton Sandler, however, would say that one problem with that is that during the 1950s and 1960s, in the UK at least, probably the US as well, thousands of housewives were having amphetamine to treat mood disorders and they weren't becoming psychotic from it, so much so that when the idea that these drugs can induce a psychosis came out, it wasn't widely believed.

I don't think that argues against the whole thing. It's trivial that we have different vulnerabilities among people. I think that one of the things that really had an impact in this area was the observations in Japan after the War when apparently the American troops had left stores of metamphetamine that came out on the black market. There was a widespread abuse of metamphetamine in Japan and a large number of cases of paranoid schizophrenia. The picture mimicked it so faithfully, that it took a while to find out about it.

That's the first I've heard about that.

Is that right? Oh, there must be a literature on it, I'm sure, it was so striking. It was a thing that happened during such a short period of time and there was so clear a relationship between these stores and the disorder – maybe the Americans don't like to write about it. But, of course, there were also lots of publications from other parts of the world, with a lower number of cases showing that the picture of paranoid schizophrenia was mimicked very faithfully by the amphetamines and of course later on with L-dopa and the directly acting dopamine agonists you can see similar things. Moreover, experiments on healthy and psychotic volunteers confirm this action.

Let me push you on this. Do you think it's the picture of paranoid schizophrenia or paranoid psychosis? Because now these days, of course, a different picture comes out from using drugs like ketamine which act on the glutamate system. Giles Harborne who works with me has been looking at this and it is very different to the effects of amphetamine.

Yes, I think you are right. Observations with PCP, phecyclidine, are also compelling. Adrienne Lahti and Carol Tamminga gave ketamine to schizophrenics and found that the patients say when they inject it 'now I feel exactly what I felt when I became ill'. So perhaps it's more like the natural symptomatology of schizophrenia than what you can produce by means of metamphetamine. However, some people claim that neuroleptics are not at all efficacious against this symptomatology, whereas in schizophrenia, the neuroleptics are efficacious in a fairly large number of cases. So that would argue a little bit against glutamate deficiency as being important.

Well, the interesting thing about these reactions when ketamine is used for surgery is that the minor tranquillizers are used to control the post-op reactions.

Yes, the benzodiazepines are the drugs of choice. So that's another thing that is hard to reconcile – there is no ideal model.

It's fairly complex. Do you think we made a mistake when people moved from saying that the neuroleptics work on the dopamine system to the idea of a dopamine hypothesis of schizophrenia?

Yes, maybe we should have called it the dopamine hypothesis of psychosis. That might have been closer to reality, but even that may not be quite adequate in view of the fact that neuroleptics act on a number of conditions, all of which probably involve hyperarousal. Maybe it's hyperarousal that these various conditions have in common – maybe we should have a dopamine hypothesis of arousal perhaps.

You seem to have moved from thinking in terms of neurotransmitters to thinking in terms of complex circuits lately?

Actually we started out with a very simplistic concept, aiming to explain why neuroleptic drugs can have such an impact on the cerebral cortex even though their main target is probably dopamine D-2 receptors, which are very scarce in the cerebral cortex. Now, the few D-2 receptors that you have, could still be the ones that explain everything but, to me, it seems more likely that the main action of the antipsychotic drugs is in those areas where the D-2 receptors are abundant. If this is so, we must explain how a change in the basal ganglia have such an impact on the cerebral cortex.

In the striatum, in the broadest sense, including the ventral striatum, there are two major inputs – glutamate from the cortex and dopamine from the brainstem. The striatum then has as its main target the thalamus. We postulated that if you had an inhibitory effect of the striatum on the thalamus, it should have an impact on the amount of sensory information being relayed further on to the cortex and if you open this 'filter' too much you may overload the cortex with sensory information and that would lead to delirium, confusion, hyperarousal and psychosis maybe.

If dopamine is assumed to have an inhibitory effect on the striatum it will be inhibiting an inhibitory mechanism and, therefore, dopamine will open the filter and that will lead to hyperarousal. On the other hand, if glutamate is an opponent to dopamine, a deficiency of the glutamatergic cortical input to the striatum would lead to the same thing. PCP would induce psychosis by weakening the glutamatergic input on the striatum.

Looking at psychomotor activity taken broadly, if you remove dopamine from the brain, you get virtually complete immobility. This immobility, according to this simple model, is due to an active predominance of the glutamatergic input to the striatum. Therefore, the simple experiment one can do is to deplete the brain of dopamine, with reserpine and an inhibitor of the synthesis of catecholamines, and you have a virtual complete immobility and then you give an antagonist to glutamate and they should move. And we found that they do. So that was how we started. Of course, it was a simplistic model and sure enough we are not simply dealing with one negative feedback loop, there is also a positive feedback. So going into it, the thing becomes very complicated but still I think the most powerful mechanism in this complex system is actually this negative feedback loop, where dopamine and glutamate control each other in the striatum.

So that is what I have been working on together with Maria Carlsson and collaborators and this is different from what was done before in this area in one important respect, which is that people, who had earlier been working on NMDA receptor antagonists such as MK801, and had found that it is a psychomotor stimulant, had postulated that it is so by means of elevating the release of dopamine. Everything has been assumed to be mediated via dopamine. But this model says that you can control psychomotor activity independently of dopamine by controlling the glutamatergic tone from the cortex to the basal ganglia. Now, we have evidence that this is true not only for glutamate but you can bring in acetylcholine, noradrenaline and serotonin – especially by 5-HT-2 receptors. They can also operate independently of dopamine. So you have a lot of different pathways that go into the striatum and they can operate in opposite directions. Some of them will, in this way, elevate arousal and others will have the opposite effect.

There is, therefore, a very complex interaction between a large number of neurotransmitters and one shouldn't have any predjuice about which neurotransmitter is most important. There may not be just one. It may be a complex imbalance that we are dealing with.

This prompts me to ask you, how frustrated do you get by clinicians. Clinically, there's a range of psychoses. You really need to get one or two of them to match up against the model you've got, rather than say this is a model for all of schizophrenia.

That's exactly the way of thinking that we are pursuing now and we have

actually a little bit of evidence that we find quite encouraging. Let me tell you a little bit about this. This is a rather strange story and I would like to see the thing confirmed before I really believe in it. We have done postmortem studies on schizophrenics and controls and measured monoamine levels, precursors and metabolites in different brain regions. In each individual, we use 60 variables. In order to handle this you must use multivariate analysis and we have a very clever guy in our group who can do this, Dr Lars Hansson. Before he came we couldn't get anything out of this material. We tried the usual statistics and couldn't see anything really striking. And then he came and showed that these schizophrenics form two different clusters that are actually located on either side of the controls. The most amazing part of it was that when we looked at the cases that were on one side, they were the paranoid schizophrenics and the other ones were the non-paranoid schizophrenics.

This makes sense. If you look at the genetic inheritance of schizotypy versus paranoia, they don't go together.

We also found something with family history there, and that was that the non-paranoids had a much greater family history than the paranoids. Another very interesting part of it was that there were 10 out of the original 30 schizophrenic patients, who were discarded by the psychiatrist who made the diagnosis, Dr C.G.Gottfries. He said applying strict Bleulerian criteria. So we put those 10 back to see where they ended up and some of them ended up among the controls, some of them among the non-paranoids and some of them among the paranoids. Then when we looked at the family history of those that ended up among the controls, none of them had family history. Those that ended up among the non-paranoids had the heaviest family history and in between you have the paranoids.

Now, coming back to your question, could we come up with a model that will deal with only one of these groups and not with all of it? After having done all this, we went back and did the conventional statistics on the paranoids versus controls and non-paranoids versus controls, and there were statistical differences. We hadn't discovered that because, actually, I hadn't paid much attention to the distinction between paranoids and hebephrenics and catatonics. I stupidly thought this is rubbish; this is psychiatry – I don't want that. But now we found that the paranoids, for example, have higher levels of serotonergic metabolites, such as 5-HIAA, whereas these are reduced in the non-paranoids. So there is a pattern of changes involving dopamine, noradrenaline and serotonin that distinguishes these groups.

What we then did was we gave rats, MK801, and we analysed the brains in the same way as we had analysed the brains of schizophrenics and we did multivariate analysis and we found that the pattern of deviations involving dopamine, serotonin and noradrenaline, was similar to

the paranoid schizophrenics. We think that this may be a strategy that can be used – you could try to replicate a pattern of deviations by means of a drug with a known site of action. If you can do that, you could formulate a hypothesis that this is a site that is out of order in the disorder in question. I think it's a fascinating approach.

Now, we were a bit surprised by some of our findings. We would have predicted, if anything, that the paranoids would have been the ones where dopamine would be primarily involved because neuroleptics are much better for the paranoids but it was not the case. Actually, there is a trend for dopamine to be low in the paranoid schizophrenics and we think this could be a compensatory phenomenon. Suppose that the primary deficiency is in the glutamatergic system, if the brain is smart it will reduce dopamine in order to try to restore the balance and if it cannot do it sufficiently, adding neuroleptics may help.

That's exactly the opposite to the conventional dopamine hypothesis. How does this fit in with the pure D-2 story? Under the influence of the dopamine hypothesis of schizophrenia, the companies went down the route of producing purer and purer compounds and we possibly got to the purest with Astra's compound, remoxipride, which may not have been the most potent but it seems to have been a good agent that was reasonably free of side effects. Now with all the fuss about clozapine, we've gone back to the old idea that we want dirty drugs, acting on D-1, D-2, D-3 D-5, plus 5-HT-2, etc., etc.

Well, you can use two arguments. Take remoxipride – you could say that look here we have a very clean compound and it seems to be very useful; it has a profile that's very acceptable and that would argue in favour of getting drugs that are very clean. On the other hand if you compare it with haloperidol, which is reasonably clean too, it has a different profile and we don't understand why the pharmacological profile and the clinical profile of haloperidol is so very different from remoxipride. There are a number of possible explanations but we don't know – and, as for clozapine, I don't think we have the answer to your question.

The dopamine hypothesis seemed to fit in with an older idea, which may date back to Jean Delay and Paul Janssen, that you've got to produce extrapyramidal symptoms in order to have a neuroleptic. Hanns Hippius and clozapine seemed to be arguing the opposite case but no one paid any heed to it, until of course clozapine came on the market again, then all of a sudden we hear people now saying 'well you don't have to produce extrapyramidal symptoms to have an anti-psychotic drug'.

That is true and that's a most important contribution from the clozapine story. You can be sure of this now. Of course, earlier one could have said that, I think, because in many cases you could find a dose of other neuroleptics, where you had an antipsychotic action that was satisfactory without extrapyramidal side effects. So that would also argue in favour of

what is now accepted. But the most puzzling thing for me is remoxipride versus haloperidol. I think the pharmacology of remoxipride should be studied more carefully. We have some data that indicates that it has some preference for autoreceptors.

The remoxipride story also contains the twist about how one company can be struck by lightning twice. Astra, if anything, seem to have been the company that has been most guided by rational principles in drug development, but after having the misfortune they had with zimelidine, it seemed a cruel twist of fate that remoxipride should also have had problems. God doesn't want us to be rational!

That's right. That is the moral of the story and I was involved in both to some extent. So maybe it's me. I was closely involved in the zimelidine story and I was consulted by them for remoxipride. The idea was to distinguish between locomotion and stereotypy. They were using apomorphine and were looking for drugs that would antagonize its effect on locomotion rather than stereotypies and, therefore, would not have extrapyramidal side effects. It was a very simple concept.

So they haven't consulted you since!

That is only partly true. Actually, shortly after zimelidine, serotonin was a word that you shouldn't mention at Astra. It was a bad word. Even after zimelidine, they were in an extremely fortunate situation. They had all the know-how. They knew exactly how to make another SSRI in a short time and they could still have been the leaders in the SSRI field but they dropped it altogether. Actually the boss of the company was inclined to stop doing research and to switch Astra into a generic company.

That would have been terrible.

Yes, a disaster of course but he died from cancer shortly afterwards. And remoxipride, yes, that was really very sad. Anyway, it may be that remoxipride has relatively low EPS problems because it is a preferential autoreceptor antagonist. We have such compounds and they don't cause EPS. They have a very interesting pharmacology because they are what we call stabilizers. This means that if you have a high baseline activity they will inhibit behaviour and if you have a low baseline activity they are stimulants. So, they are very interesting drugs.

Why has Scandinavia has produced so many neuroscientists and psychiatrists? On the psychiatric side you've got Langfeldt, Stromgren, Gottfries and then Hillarp, yourself, Hokfelt and others – there is an endless list of people who've made major contributions, I'm sure out of all proportion to the number of people who are actually in Scandinavia. And you had one of the first psychopharmacological associations.

Yes, it came early. I was among the founders of this Scandinavian Society for Psychopharmacology – that was in 1959. I think it's a chance phenom-

enon because one cannot link it to any particular school or individual. For example, von Euler, who was early in this field, was not linked to any of the rest. He had some very successful pupils. Then you have Hillarp and actually his school was very strong because he was really very good in gathering skilful people around him. And it was in a way fortunate that he started out in Lund, then he moved to Gothenburg and then from Gothenburg he went to the Chair of Histology in Stockholm. Since he started out in Lund and Falck was still there, on the basis of the histochemical fluorescent technique, a group could be formed there and then in Stockholm so there was another one.

In the case of the Society, the originator of this Society was the Danish Lundbeck Company to some extent. Because Lundbeck had been very successful with both antipsychotic and antidepressant drugs thanks to a clever medicinal chemist, P.V. Petersen. There was also a clinician – Jörgen Ravn, who came to Lund to visit David Ingvar. It was the three of us who started the Society in 1959. Lundbeck served as generous sponsors from the outset.

But the neuroscience interest isn't just in Denmark and Sweden. There are people in Norway and Finland, like Linggaerde and Toumisto – and Scandinavian work always seems methodical and systematic.

Thank you. Maybe we have more crazy people up there so we have a greater need for this kind of research I don't know. I have no statistics to support that, but there are some very interesting families in the North of Sweden with genetic disturbances, porphyria and various schizophrenic disorders. That has attracted a lot of attention.

As regards the methodicalness, to be philosophical about that, perhaps one could say the further out you get in terms of climate you have to be careful. In warm weather down around the equator, you can almost sell your bed in the morning, can't you? But in the far North, you have to plan in order to survive, because the winter is quite severe. So it's possible that there has been some kind of selection of people who are planners, I don't know if there is anything to it.

Some years ago, in Human Psychopharmacology, *you wrote an article saying that we're really on the brink of an era where we won't just be treating mental illness, we will be engineering personalities and human abilities. This was before all the fuss about cosmetic psychopharmacology. Do you still think that, or . . .*

Yes, I think this is something that will come. I am sure there will be a lot of debate and a lot of emotions will be stirred up because of this trend but it will come. I am sure that when we have a drug that will improve the memory of old people without causing that much side effects – it's going to be used. Even if the doctor says 'never mind getting a little bit forgetful when you're old, that's normal'. People will take it regardless of that. They are not so impressed by clinical diagnostics. If they feel better

when they take a drug and even if they are aware of the possibility of long-term use causing severe problems, they may consider, nevertheless, that they are taking a good chance by using it because they gain so much.

I think that is true now with fluoxetine and all these drugs. There are people who feel so much better, who didn't have any diagnosis really. For example, if you are shy among people, so-called social phobia, which is more or less normal isn't it, and if you get rid of that it must be a tremendous, a dramatic change for a person, mustn't it? Someone who has been shy and deprived of so much and all of a sudden you can do it, of course you will take it. I remember from the zimelidine period, that there were people whose income went up when they started to take the drug. If there are such very striking results as this, people will say all right, I will take the risk. I feel reasonably okay and the side effects are not that much.

As this field develops we will have more and more drugs that will do this and people will be taking more and more drugs. It will become a natural part of life – well it is already – we tend to forget that we use caffeine as coffee and tea all the time and we do it as a drug of course. We need to get a little bit more stimulation in order to work a couple of more hours – this is pharmacology isn't it? We have done this for a long time – take alcohol. Alcohol has done more good than bad to mankind. I am convinced of that. There is so much that has come out of the increased interaction between individuals because of alcohol. Some individuals have had to pay very much for this but mankind has done very well I think. And this will go on I am sure. Prozac is perhaps the most striking example but before that we had things such as the beta-blockers for stage fright. Those violinists, who started to perform a lot better while on the beta-blockers, you cannot say that they were sick. They just performed better.

The companies have begun to move away from trying to give drugs which act on the classical neurotransmitters to look at the neurodegenerative disorders, which seems to me to offer scope for some more radical engineering.

Oh, yes. I think molecular biology will come in very strongly. It has done a lot already even though it has not had too much of an impact on the clinic yet. But you also mentioned neurodegeneration and it could be that things that we don't think about so much in terms of neurodegeneration will turn out, I would guess, to have a component of neurodegenerative mechanism. For example, take the kindling phenomenon that comes up in many different contexts. If you have changes like that, isn't it very likely that it involves neurodegeneration? What I think here, of course, it's again very simplistic, is that in many cases, you have two glutamatergic inputs, one directly onto the neurone and the other indirectly via an interneurone that's GABAergic – now if these operate at a moderate level, you will have a kind of a balance and your output

will be at a modest level. Suppose the GABAergic neurone is especially sensitive to cytotoxicity: if it goes, all of a sudden you would only have the gas; the brake has gone and you will have a tremendous elevation of the output that will remain forever because the GABAergic neurone has gone. And I wouldn't be surprised if this kind of mechanism is involved in kindling and it could also be in some aspects of memory and learning. When we learn, do we kill neurones, in order to get a more efficacious message through, what do you think? When we talk about addiction, which lasts forever – once an alcoholic, you will never be the same. And also if you think about tardive dyskinesia and kindling.

Does any of this link in with the issue of redundancy in nature?

This is extremely interesting. I think it has a lot of support from molecular biology. Various random phenomena such as gene duplication and subsequent mutations can sometimes lead to the production of proteins without any function.

Another thing that was brought up by C.W. Bowers in a recent article in TINS (1994) entitled 'Superfluous Neurotransmitters?' deals with gene regulation. There are mechanisms that determine whether or not a gene is going to be expressed in a given cell and these mechanisms are not always very precise. That means that you could very well have expressions of proteins in cells, where they are not functioning. The genome is the same in all cells so, in principle, all cells can produce all the different proteins that other cells can but the expression is restricted in different cells. The regulation of this expression is not precise – this means that you can have protein in places where they have no function. You should be particularly careful if you see the occurrence of a certain protein, maybe an enzyme or a receptor, in a site where you don't have it in the same region or organ in a related species. For example, if you have it in a rat and you don't have it in a mouse or in a guinea pig, you must start to wonder. Is it really likely that this protein is going to be an essential thing in the rat, while it's not needed in the mouse or the guinea pig. So that brought in the idea of superfluous neurotransmitters, and a number of neuropeptides were given as examples in Bowers' article.

In 1988 I published some rather similar speculations. I called my paper 'Peptide Neurotransmitters – Redundant Vestiges?' (Carlsson, 1988b) I came to a similar conclusion from a pharmacological point of view, starting out, for example, with naltrexone or naloxone, where you have so little functional loss even if you have blocked the receptor as indicated by a blockade of the action of morphine. There are other examples where antagonists of peptide neurotransmitters aren't doing anything.

My reasoning was based on evolutionary considerations. The peptides are enormously powerful as signalling molecules because they have an identity that is terrific. By means of changing just one amino acid you have a different identity. And they are tremendously powerful because

you can have very high affinities. And they are easily made by the cell because after all the cell is a peptide manufacturing machine. So all this makes the peptides so convenient as hormones or neurohormones. But, once upon a time, one of these endocrine cells started to make a process to become a neurone. At that point, there is a drawback, because the production has to be around the nucleus and you had to transport the transmitter to the nerve ending. If the thing has to operate very quickly, it may become awkward to have a peptide as a neurotransmitter.

In evolution these things can be solved. What nature does is to produce enzymes and a machinery and so on that is transported down the nerve and they will manufacture the neurotransmitter – a small molecule – at the nerve ending. That is how the small molecule neurotransmitters evolved. So how about the neuropeptides? They are made in very small amounts. The negative selection pressure on such small amounts is virtually nil, so they can go on forever being there because they don't make any harm and that's why we have such a tremendous assortment of them. Now, if that is how they evolved, it's not surprising to find that there are enormous species differences because if a mutation happens and this peptide is no longer functional in a certain species it doesn't make any difference. That was my way of looking at it.

This idea would open up a whole new way of looking at chemical neurotransmission because, at the moment, the fashion is for people like Sol Snyder to write articles talking about the neurotransmitter orchestra – that there are hundreds of them. This is quite a different idea.

Yes. One thing that has to be added to it, which I think is important, is that we have now reached a sensitivity of analytical methods down to the levels of the background noise. We can pick up practically everything. So it means that while in the 1950s, when I started in this field, we could detect a compound by means of the techniques that were available at that time, it had a much higher likelihood of being functionally relevant than today.

Another fascinating possibility is this. Suppose it's not true when we say that different genes are expressed in different cells. Suppose all genes are expressed in all cells. What would happen then is that the expression is suppressed but nature doesn't take the trouble to suppress it all the way down to zero. Why should it – I mean it's down to a level where it doesn't matter. If so, when our methods become sensitive enough we will find that all cells produce all the proteins that the genome can produce. What made me think of that was when I went to see a colleague in Gothenburg, who demonstrated this enormously sensitive capillary electrophoresis. What they could do was to take one white cell, put it in a little funnel at the end of this tube and then extract this single cell and do electrophoresis. They found dopamine, tyrosine-hydroxylase and monoamine oxidase in this white cell.

One might feel that dopamine is an important compound in immunology but suppose what they see is just background values. It's just that nature doesn't take the effort to suppress the genome 100%. There is a little bit left. If that is true, people should be aware of it because otherwise we will waste a lot of resources on things that we should perhaps use on something else.

Select bibliography

Bertler, Å. and Rosengren, E. (1959) Occurrence of distribution of dopamine in brain and other tissues. *Experientia*, **15**, 10.

Carlsson, A. (1959) The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol. Rev.*, **11**, 490–93.

Carlsson, A. (1966) Physiological and pharmacological release of monoamines in the central nervous system, in *Mechanisms of Release of Biogenic Amines* (eds U.S. von Euler, S. Rosell and B. Uvnäs), Pergamon Press, Oxford, pp. 331 – 46.

Carlsson, A. (1982) Recent observations on new potential and established antidepressant drugs. *Pharmakopsychiat.* **15**, 116–20.

Carlsson, A. (1987) Perspectives on the discovery of central monoaminergic neurotransmission. *Ann. Rev. Neurosci.*, **10**, 19–40. Also published in: *The Excitement and Fascination of Science: Reflexions by Eminent Scientists*, Volume 3, Part 2 (ed. J. Lederbeg). Annual Reviews Inc, Palo Alto, California, pp. 1335–58.

Carlsson, A. (1998a) The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology*, **1**, 179–80.

Carlsson, A. (1988b) Peptide neurotransmitters – redundant vestiges? *Pharmacology and Toxicology*, **62**, 241–42.

Carlsson, A. and Lindqvist, M. (1963) Effect of chlorpromazine or haloperidol on the formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol* (Kbh), **20**, 140–44.

Carlsson, A., Lindqvist, M. and Magnusson, T. (1957) 3,4-Dihydroxyphenylalanine and 5-hydroxytyramine in brain. *Science*, **127**, 471.

Carlsson, M. and Carlsson, A. (1990) Interactions between glutamatergic and monoaminergic systems within the basal ganglia – implications for schizophrenia and Parkinson's disease. Trends in Neurosci., **13**, 272–76.

Dahlström, A. and Carlsson, A. (1986) Making visible the invisible. (Recollections of the first experiences with the histochemical fluorescence method for visualization of tissue monoamines), in *Discoveries in Pharmacology*. Volume 3. Pharmacological Methods, Receptors and Chemotherapy (eds M.J. Parnham and J. Bruinvels). Elsevier, Amsterdam, New York and Oxford, pp. 97–128.

Hansson, L.O., Waters, N., Winblad, B. *et al.* (1994) Evidence for biochemical heterogeneity and schizophrenia: a multivariate study of monoaminergic indicies in human post-mortem brain tissue. *J. Neural Transm.* (GenSect) **98**, 217–35.

von Euler, U.S., Rosell, S. Uvnäs, B. (eds) (1966) *Mechanisms of Release of Biogenic Amines*, Pergamon Press, Oxford.