Interview with Dr. Arvid Carlsson
Interviewers: Edward Shorter and David Healy
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ES: Arvid, we have a lot of questions that we're going to be asking you, but why don't we start out at the beginning of one of the stories that interests us, and that of course is a story that you have been interviewed on many times, the SSRIstory. So, would you just tell us how you came to zimeldine?

AC: Yes. In the late '50s and early '60s we did a lot of general work onneurotransmission in the brain, especially monoamines.

ES: You were at Lund then?

AC: I was in Lund until '59 or '60. The lab moved in 1960 to Gothenburg from Lund, and we developed a lot of methods for studying neurotransmission, monoaminergic neurotransmission,in the brain. First, we had biochemical techniques, and then we added histochemistry. We could visualize the monoamines in the neurons. So, we had both these histochemical techniques and biochemical techniques to studyneurotransmission.

ES: Now, Arvid, let me just ask you, in these techniques, was there anything that was particularly Swedish that you and your colleagues had developed? Tell us about that.

AC: Yes,pretty much Swedish. Well, if we start with the techniques, I got into this field by a visit to the National Institutes of Health Laboratory of Chemical Pharmacology, headed by Dr. Bernard B. Brodie. He had developed techniques for measurement of lots of compounds – not only drugs, which he was very much involved in, but they also got into endogenous compounds. So for example, they could measure for the first time serotonin in the brain by means of a chemical

technique, which was efflorescence methodology, and they developed an instrument.

ES: Yes, the spectrophotofluorimeter

AC: Yes, the spectrophotofluorometer. So, when I came there in August 1955, they had a first prototype of such an instrument. That instrument occupied more or less a whole room, so you had to darken the room, and there was in one place a cuvette where you had your sample, and then you had a lamp across it, I think it was an argon lamp, and then you collected in 60 or 90 degrees the light, and you could vary the wavelength of both the activating and the fluorescent beam. That was the trick. It was very sensitive – of course, in those days it was a revolution. For serotonin the only thing they had done before was bioassay, soit was the first time that compounds such as serotonin could be measured in the brain by means of chemical methods. Very accurate.

ES: Ok, that was in Bethesda in 1955. What then were the Swedish contributions to these measuring techniques?

AC: When I got home after half a year, I had proposed to them that we should not just do serotonin, but also catecholamines. We developed the methods for catecholamines. The first thing we did was really very primitive. I got in touch with Nils-Åke Hillarp, who was the histologist. He had a method for measuring adrenalin in the adrenal medulla, and that was certainly not original at all. It was a colorimetric method, you oxidized the adrenaline and you got a red color. That was how we started. But after the work we did at that time with reserpine, we found that adrenaline disappears from the adrenal medulla. Before that, the Brodie group had found that serotonin disappears from the brain and other tissues after you treat with reserpine. Brodie didn't think much of catecholamines, so we did that.

ES: Now the technique that you and Hillarp developed was this oxidation technique?

AC: No, that was an old technique.

ES: So, tell us about the technique that you developed.

AC: As soon as I got back to Lund I ordered – because at that time the Aminco-Bowman spectrophotofluorimeterwas commercially available – I ordered it right away. I got it and we developed a technique, not very sophisticated technique, but it was sophisticated in the sense that we used this instrument. We oxidized the catecholamines to form fluorescent compounds. That had been done before, but we measured by means of this instrument, so it was much more specific. In addition to that actually we did a separation technique by means of an ion exchange column, so we could separate the different catecholamines on this column.

ES: This Swedish contribution to technique, what was it called?

AC: Well, that was not really called anything. We have a publication dealing with adrenaline and noradrenaline measurements in tissues. Then after that,that was a more original thing, dopamine. That was the first time, the first technique for dopamine,that was our technique – butin essence, it was, let's say, a modification of the oxidation technique that was used for adrenaline and noradrenaline. Dopamine needed some special tricks in order to become measurable. We had to do some ultraviolet irradiation of the samples in order to get full fluorescence development. That was an original technique. That of course started out the whole work on dopamine. Nothinghad been done really, measuring dopamine before, that was worth mentioning. But then, in collaboration – I collaborated with Hillarp more or less all the time – we thought that it would be an enormous advance if we could visualize the amines in the tissues. Actually, the inspiration came from Brodie, in the sensethat we thought of fluorescence. If you go from

absorbance to fluorescence, you add one order of magnitude at least, in sensitivity. So that is what we were working on at the time, to develop a histofluorescence methodology. We did that first with the oxidation type of technique that was used in our biochemical measurements, and that worked, but was not good enough. It was good enough for the adrenal medulla, but we could not visualize the nerves.But then Hillarp came across another technique that had been developed by Udenfriend. Actually, Udenfriend was also in Bernard Brodie's lab.

ES: There's a photograph of you and Udenfriend together, that is quite famous.

AC: That was with using formaldehyde gas. Actually, that was at the time when I moved to Gothenburg, andHillarp joined me. We could set him free from his professorship in Lund, by theSwedish Medical Research Council, and he joined me. That was one of the goals we had, the two immediate goals, was to develop this technique. They had an object glass and a protein solution, they just spread it out on the object glass and in the solution, they had for example serotonin or they had dopamine or noradrenalin, and let it dry, and then they put this glass into an exicator where they had formaldehyde vapor.There was a combination between these two, between the amine and the formaldehyde, to form a strongly fluorescentcompound. That was developed in Gothenburg by Hillarp and his technician Thieme. So, these basic conditions to try to optimize the development of fluorescence in these dried protein solutions, it was Hillarp and Thieme who did that work

But Hillarp was still touch with his old lab in Lund, and his student Falck was there. Hillarp had earlier been using this kind of technique in his thesis work, where he took the iris of a rat, and spread it out on an object glass, and then stained it with methylene blue and could visualize the nerves. They did the same thing, they took the iris, andthey also took the omentum and spread it out and allowed it to dry. It was very similar to the protein solution they had done in

Gothenburg – and exposedit to formaldehyde – and: it was there. They could see the nerves, it was very dramatic, actually. He was down there in August, we can easily find which year. I think it was in 1961, or possibly ’60. He was there for a weekend, talked to his student, Falck, and they said, “why don’t we try the iris and the omentum,” and it worked immediately. He came back to Gothenburg and said “Hey, we have it,”but then it took several months to repeat the thing, because it wasn’t that simple. There are lots of things – you have the humidity and you have temperature, there are lots of things you have to really control. Then after a few months it worked on these preparations. Then of course the next step was then to have the histological blocks, where you have to do the cutting from organs, the brain, and other tissues. Falck came in then, and did a lot of that work, down in Lund. So that was how the thing developed, to a certain level. But then, after a while, Hillarp had an offer to come to Stockholm, to take over the chair of histology there. That was maybe in ’63 or something, this of course we can easily find out. When he came there, he collected very rapidly, with this fantastic technique, a big group of young people. In my Nobel lecture I have a picture of these people in Stockholm. They started then tooptimize this methodology, a lot. There were lotsof things, still, that could be improved upon.And they were doing some similar workdown in Lund. We were collaborating, then, Gothenburg, Stockholm and Lund. That was a very fruitful period.

ES: Yes, it must have been very exciting. Do you recall now your excitement then?

AC: Oh, of course, ohyes.

ES: Tell us a bit about how you perceived this personally.

AC: Well, the whole thing – the first time when we saw the fluorescence, on the screen we saw the curve for dopamine, the biochemical part. To see there is dopamine in the brain, there was of course tremendous excitement about that. Then all these

other things. Well, first of all, Hillarp and Thieme with their model experimentswithsolutions was exciting all the time. They reported every day about the improvements of that technique. So, there were several steps of excitement.

ES: You must have lived in a state of continual excitement from the time that you were with Brodie, through all of these dramatic events.

AC: Oh, that's true. Of course, the atmosphere in Brodie's lab was absolutely exciting. I was very much excited by this because this was really at the cutting edge of modern pharmacology.

ES: You were the only young Swede who'd been with Brodie

AC: No, later there came more Swedes

ES: But you were the first one.

AC: I was the first one.

ES: Did you bring any of that atmosphere back with you?

AC: Oh, yes, I think so. I was enormously excited by the whole serotonin story. And of course, then,I came back in January, in late January of '56, and then after maybe only two or three months, we had the first results with adrenalin, in the adrenal medulla disappearing. You didn't need any colorimeter, you could just, when you did your oxidation, there was no color after giving reserpine – so that was another thing,and very dramatic. So,one very dramatic thing after the other.

ES: Just in terms of the approach to research, or the whole outlook. Of course, Brodie and all these people were Americans, and, I don't know – maybe they had a

particularly American orientation to their work. Brodie was known to work late every night, and so forth.

AC: Absolutely.

ES: Did you bring any of that back?

AC: No, not at all. (Laughter) Actually, I was never – Brodie and I never became very close to each other. I was not the guy that he brought with him at night to write a paper and that kind of thingand then go to a movie, mostly a western kind of movie.

ES: But Pletscher was.

AC: Pletscher was. He was there when I came, and we were there together in the same lab room for maybe two or three months, and then he went back.

ES: Did you see that Pletscher was closer to Brodie than you were?

AC: A little bit, I think. But there were others later on that were much closer, a fellow such as Gessa.

ES: How do you spell that?

AC: G-E-S-S-A, from Sardinia. Luigi Gessa. Brodie liked him a lot, so he had to be there.When I was there, I had family at home, but I didn't bring my family, with the three kids, they were still in Gothenburg. But Gessa, he had his wife, and there was one story about the wife at night calling Brodie at home. The phone was picked up by her husband, which she didn't know, she thought she was talking to Brodie. And she yelled at him, "How can you do this kind of thing, night after night – I cannot accept it!" but it was Luigi, Gigi Gessa who caughtit,

fortunately. I don't think I really mind that I was not invited to spend these nights with Brodie.For some reason, we were –I think it's kind of chemistry.

ES: Did you feel a rivalry with Pletscher at all?

AC: Not at all, no. Certainly not at that time, later on, perhaps. But he took another path. One of the things that Pletscher later focused upon was the platelets. I was not so intrerested, even though the work I did in Brodie's lab was on platelets,actually, to see reserpine act in vitro on platelets, on serotonin.

ES: Pletscher even then worked for Roche, didn't he?

AC: Oh, yes, he came with Marsilid, more or less every day he said "we must try Marsilid" – that was iproniazid. He brought iproniazid. That added something very interesting to the story, because if you pre-treat with iproniazid and then give reserpine, rather than animals calming down, they got excited. That was of course a very important finding, and actually I think that inspired Nathan Kline. Nathan Kline came a number of times during my time.

DH: Is that how you met him? How did he come over to you, when you met him first?

AC: I was a small guy at that time, he didn't notice me. He went to talk to Brodie, and he learned about this Marsilid story, so that's why he started to treat his depressed patients with Marsilid, and discovered that, and he got the Lasker after that.

ES: Oh, is that how he found out about iproniazid?

AC: Yes.

ES: Ahh. And Pletscher didn't know that iproniazid had potential as an antidepressant?

DH: He wouldn't have.

AC: I don't know. I guess he must have had the idea that it could be, but I didn't talk to him about that at that time at all. We were so much involved with the reserpine psychosis aspect, so I don't think we ever did discuss depression.

ES: Now, Parkhurst Shore was also a presence in those days. He's very much a kind of cipher on the radar, a blank, in that he's never written anything that I know of, and nobody has ever written about him. Tell me about Parkhurst Shore.

AC: He was my mentor. He would be sort of in between Steve Brodie and myself. He was the one who taught me the tricks.

ES: Tell us about him. What was he like personally?

AC: He was a lovely person, and his wife too. They were lovely people.Brodie once said about Park Shore, "his knowledge isn't that much, but he has some good ideas." And he really had. The first thing he did dealt with the stomach, and he was the one who pointed out that the acidity in the stomach has an impact on the distrbution of a drug – because the drugs were of course amines, many of them. I don't remember the details, but certainly his concept of the acidity of the stomach as an important factor for the distribution and the absorption and so forth of a drug was influential.

ES: How did Shore get this prestigious post at the National Heart Institute?

AC: Well, this first thing was his original contribution, and it was published – but actually, he was the one who got the idea of giving reserpine and looking for serotonin. His reasoning was very simple. The reason why he got into this was, of course, because the main theme of Brodie's lab was this kind of thing,

distribution and metabolism.He pioneered the chemical pharmacology. He was the one who started to measure drugs and their metabolitesand develop methodology for that. His spectrophotofluorometer was part of this. So,they were doing interactions between different drugs, and LSD was one of them. Of course,LSD was very much talked about in those days because it was only in the late ’40s that the effects of LSD had been discovered. Then LSD and serotonin came together, and that was by two different labs: one of them was Gaddum in England, and the other one was Woolley at the Rockefeller Institute, as it was called at that time. They found that if you give LSD – for example, if you treat the uterus in vitro, serotonin causes contractions of the uterus; if you pre-treat with LSD you block it. Gaddum formulated that Wooley did a similar thing, the idea that “serotonin is needed to keep us sane,” as it was said. So,Brodie became very muchinterested in this, and he wanted to see what the interaction was in terms of drug distribution, how that could come into thisSo that was the topic that Park Shore was working on.

ES: How did Park Shore come into the picture? How did Brodie know about Shore?

AC: Well, he came there as a post-doc. Brodie was his mentor, he was young, it was probably just a couple of years after he got his PhD, I would guess.

ES: Was this an alternative to going into the army for Shore?

AC: It’s possible. I know about Leathers (?), but in the case of Park Shore I don’t know. Park Shore was the one who said, “Look, here we have three compounds, we have serotonin, we have LSD, and we have reserpine, and all these are indoles. That must mean something.” So, he said, “Why don’t we give reserpine and measure serotonin?” That was a tremendous leap, of course. Nothing was thought of that kind of thing in that lab. It was alwaysdistribution, dealing with lipid solubility, that kind of thing. So, there wasthis fellow Herb Weissbach, he could measure – at that time I don’t think that the method for serotonin was ready

yet – but they measured 5-hydroxyindolacetic acid in the urine. That was the first experiment. He told Herb Weissbach, "Here, look, I have given reseprine to this rabbit" – I think it was – "so please collect the urine and see." And then there was a huge increase in 5-hydroxyindolacetic acid, of course. So, the next step was then to measure serotonin, and see serotonin disappear from the brain and other tissues.

ES: Was it the work of these younger investigators such as Shore that really dragged Brodie into the neurotransmitters?

AC: Yes, I think so. I don't think his thinking was in terms of neurotransmission before, this is what brought him in.

ES: I didn't realize that. Did you know that, David?

DH: That makes sense – but just to actually add this, Ned, at this point they wouldn't have had a concept of chemicalneurotransmission, would they? Did they know?

AC: No, but …

DH: They did have the findings, but….

AC: They had the findings, but I think to Brodie – I have one picture on PowerPoint I'm going to show the day after tomorrow, saying "the ignorant pioneer." Brodie was in this context the ignorant pioneer. He was the one who saw this – actually he was in Florida on vacation when this experiment was done, and as soon as he heard about it, he rushed back, and all of a sudden he said –this was something that he had said to others several times before, for example, also with the previous work that Park Shore had done with the stomach acidity – all of a sudden he said "our project." It was "our project."Park Shore was a nice guy, he said, "well, that's part of the system, it's ok." Others were not – Axelrod certainly did not

agree when he did the same thing to Axelrod, because they became enemies. But Park Shore was like this. He accepted that the story was that Brodie discovered this. He accepted that. Actually, when he was interviewed, which he was in the book Apprentice to Genius, when he was directly asked about it, he said "well, it so happened, I did it."I don't know if it was in the book, but that's what people were joking about in the lab, that Brodie discovered the effect of reserpine on serotonin on a beach in Florida. (Laughter) That was the joke.One funny thing about it is that most of the people were rather like Park Shore. For example, Udenfriend was very loyal all the time to Brodie, and many of the others were, they looked upon him as the father, more or less. Axelrod, he was a bit different. He got furious – well that is very interesting, to talk about Axelrod also. (Laughing) So that was how it happened. Nobody talks about Park Shore, really, much. When I was giving a historical symposium at an ACNP meeting maybe two or three years ago, I wanted to have a picture of Shore, and finally I managed to get one. I have one, but I had to ask him for it. I have a portrait of Park Shore.

ES: Would we be able to get a copy of it?

AC: Of course, I can e-mail it to you.

ES: Oh, great. That would be terrific. Let's just talk about Axelrod for a second since you bring him up. Did you get to know him well?

AC: No, the funny thing is – yes, I did later, but when I was there, he was not there. He had left just before I came

ES: He was getting his PhD.

AC: That's exactly the thing, and the reason why he left, was that – you know the story how Brodie discovered this guy?

ES: Axelrod tells this in his ACNP interview, and he also talks about being really pissed off with Brodie. But is there a story behind the story here that has never come out in public?

AC: Well, as I have heard it, Brodie was a consultant for some vitamin factory – I don't know which one – and at this factory, or lab, Julie was there. He was standing there, more or less as a technician.

ES: This is Goldwater Labs, I think

AC: Could be, yes. And Brodie started to talk to this guy. He was a very smart fellow, Brodie, even if he was ignorant insofar as the brain was concerned, and that was of course why he had no problem thinking about serotonin in terms of a neurotransmitter. He didn't know which criteria had to be fulfilledin order to talk about neurotransmission – he couldn't care less. (Laughter) That was how he got into neurotransmission without any problems. But they talked to each other and he said"you must come and work with me." So, Axelrod came there, and he helped to develop lots of methods for drugs. He learned the Brodie technique, to inject the drug, develop a technique for measuring drugs, metabolites, all that, Brodie taught him. But then, what happened, I guess a number of times Axelrod had started to feel a bit uneasy about Brodie taking all that was done as his. But the dramatic thing that happened was that Axelrod went to a neighboring lab, it must have been at NIH – at that lab they had developed a technique for fractional centrification of the liver, so they had microsomes. He got a microsome preparation, and he then discovered the role of the microsomes as a detoxifying system in the liver. That was a great discovery, and Axelrod himself said that was his biggest discovery. So,he came to Brodie, and he said, "our project." (Laughter) Axelrod said "no." That's why he left.

(Brief phone interruption) Where were we?

ES: You were talking about how pissed off Axelrod was – how irritated he was.

AC: He was furious, I'm sure. So, he went to get his PhD, and then afterwards he came over to Seymour Kety.

ES: Right, at NIMH.

AC: And Seymour was the one who gave him the radioactive epinephrine. That was because in Canada they had this oxidation product that was supposed to cause schizophrenia.

ES: Oh yes, the pixbaw (?)

AC: Pixbaw, yes, and some chrome, not adrenocrhrome?

ES: It was adrenochrome, wasn't it?

AC: Yes, I think so – he injected this radioactive stuff, and he did exactly what Brodie had told him. He measured the levels in plasma and tissues, and that was how he discovered the uptake mechanism.

ES: Right. Axelrod must have been a very smart guy.

AC: He was absolutely smart, oh yes, he was smart, and the step between the thinking and doing the experiment was very short, and he was right many times. But to some extent he was also an ignorant pioneer becauseboth Brodieand Axelrod were chemists. They didn't know much about tissues. Brodie looked upon the body as a containerwhere you had a lipid phase and a water phase, and then some enzymes to convert the thing such as to get it out through the kidney – that was the body, in Brodie's world. And of course, Axelrod was also a chemist, so when he did this, he did what Brodie had told him, and so he had his curves for

adrenaline in the blood, he had the curve for the tissues, and the concentration in the tissues. Then there was a fellow there, a German, named Hertting…

ES: H-E-R-T-I-N-G?

AC: I think it's a double T.

ES: Double T, right. Ok.

AC: He was a physiologist, and he said, "look – this looks funny, the distribution of adrenaline here is just like the distribution of the sympathetic nervous system." "Aha," said Axelrod, "what can we do in order to do something about that?""Well," Hirtting said, "you just take out the ganglion here, and then it disappears from the salivary glands around the heart, and we can see." I think it was salivary glands that they focused upon …

ES: It was the parotid gland, I think, was it not?

AC: Yes, I think it was the parotid gland. So, they did that, and then they had it, so there was an uptake. It was taken up by the nerves. So that was how that discovery came about. It's funny.

ES: Have you kept in contact with Axelrod over the years?

AC: Oh, yes, when I visited several times there. One was a funny time. That was actually the time when we had discovered the transport mechanism for serotonin and the role of this transport mechanism for the mode of action for antidepressants. I gave a seminar there, and after that seminar, I had lunch with three people: Brodie, Udenfriend, and Axelrod, and that was something remarkable. I guess that was perhaps the first time after they became enemies that they had lunch together.

DH: This was when?

AC: I guess around 1970.

ES: Was there tension at the lunch?

AC: Not that I – oh, maybe, maybe yes.

DH: So was this just before they gave the Nobel prize to Axelrod and not to Brodie?

AC: No, that was before, that was a number of years before.

ES: Was Brodie dead when they gave the Nobel prize to Axelrod?

AC: Oh, no, oh, no. You can read about that in Apprentice to Genius. Actually, Brodie called Axelrod and congratulated him and said, "You did the right thing, you specialized in one thing."That was true. Brodie – I consider Brodie much more important in the science he opened up, compared to Axelrod, absolutely – but the problem with Brodie, from the point of view of the Nobel prize, was thatin the testament of Alfred Nobel, you had to point to one discovery. Brodieopened up the field, and paved the way for discoveries, but it so happened that it was others that made the discoveries under him. He understood that was his problem: that was why he said, "our project." And he was right. I must say, I rather think that Park Shore was perhaps too generous to Brodie, but I think that Axelrod was not generous enough to Brodie. Because Axelrod after all was a nobody, he was picked up by Brodie, put into this atmosphere, and that was how he could grow and become something.So,Brodie has tremendous merit. In a way I think the testament, Alfred Nobel's testament, should not be interpreted the way it has been. Because what is in the testament is "the one who has made the most important discovery during the past year." Then of course there was an addition,

that it could be that it was not immediately obvious. But it was so very much focused on this one discovery, andof course you can understand that, from a person who discovered dynamite – because if you discovered dynamite, then you know exactly when it happened, and everybody understands what that is.

ES: Now, Arvid, among the among the names we have discussed so far, Axelrod is the only name, I think, that is Jewish.

AC: Brodie was Jewish.

ES: Was Brodie Jewish?

AC: He was at least half Jewish, I think his mother was Jewish. He came from, I think, was it Manchester? He was born in Manchester, the family moved to Canada, so he went to school in Canada and became a rather famous boxer in Canada – and then he switched to organic chemistry, fortunately.

ES: I'm just wondering if Axelrod might have been very, very sensitive to anti-Semitism in any way.

AC: Not from Brodie. Absolutely not from Brodie. Park Shore and I discussed this Jewish aspect, and he considered Brodie Jewish. He said "there are always ties between the Jews." So, if you were Jewish, in that particular environment, that would be a merit – in Brodie's lab. That was his point of view about the Jews, even though he was not anti-Semitic, it was just an observation, which is of course true. One could not blame them for it either.But Axelrod of course had a problem at school. I think he wanted to study medicine …

DH: And he didn't get in.

AC: … because he was Jewish, there was a quota. So, he was certainly aware of being Jewish. And I remember, he was visiting in Gothenburg at one time, and I thought I would like to treat him for lunch, with a typical Swedish dish, it was Swedish meatballs, and that was a mistake!

ES: Why was it a mistake?

AC: Because there is pork in the meatballs. He didn't eat it, and he made it perfectly clear it was bad food (laughing)

ES: Well, Sid Udenfriend I guess must have been Jewish as well?

AC: The funny thing about Udenfriend is, actually the original name was Judenfreund, the German, and as it was described to me, his father was not Jewish, but he was very friendly with the Jewish, so that's why he got his name Judenfreund. Then when the father moved to the U.S., it was easy to change it from Judenfreund to Udenfriend.

ES: Right. So, Sid Udenfriend was not Jewish? I didn't realize that.

AC: Sid's mother was Jewish, so he also obeyed – at least he had the gut feeling that you shouldn't eat pork. His mother told him that.

ES: It must have been interesting for these guys to visit Gothenburg. (Laughter)Well, to get back to the Swedish story, now, we were with Hillarp and techniques. Tell us what happens next.

DH: Actually, I'd like to ask a bit more about the people.

ES: Yes, by all means.

DH: Hillarp came from where, and what kind of a person was he?

AC: Hillarp like myself, grew up in the southernmost part of Sweden.

DH: Where did you grow up, where were you born?

AC: I was born in Uppsala. My father was then an assistant professor of history in Uppsala. Then he got one of the two chairs of history in Lund, so when I was three years old, the family moved to Lund. So, I grew up in Lund. That was the town of my childhood and young age. I lived in Lund until 1960, when the family moved up to Gothenburg.

ES: The nane Hillarp is scarcely known abroad. Do you think his own contributions have been under-recognized?

AC: Absolutely. Actually, his thesis was very interesting, because that dealt with the old question from – oh, the name, I wasdown to celebrate this man in Madrid. It's my age, sometimes the names disappear …

ES: Lopez-Ibor?

AC: No, no, this is a Nobel laureate from ….

DH: Cajal?

AC: Of course. Ramon y Cajal. The point he made, and that was when he was fighting with Golgi – he used Golgi's technique to prove that Golgi was wrong. They got the Nobel prize at the same time, but they didn't talk to each other, and their lectures were against each other. His point was the concept the neuron is a distinct entity and there's no synthesium, that was Golgi's point, it's a network. Hillarp continued along that line, dealing with the autonomic plexus, as it was

called, that is where both the sympathetic and the parasympathetic nerves come together. The question in his thesis was to find out whether this was a synthesium according to Golgi, or a neuron with synapses or synapse-like construction and he came to a very firm conclusion that Cajal was right. He used methylene blue, and he did what I said, he had the iris and the omentum, and he had lovely pictures – they were drawn in his thesis, these pictures – and he came to the very firm conclusion, I cannot give you the details, that Cajal was right. That was a very important contribution., but nobody knows about that anymore. He did other things. He was in endocrinology, on the hypothalamus and those hormones,very good work, but then, of course, the most important work was the histochemistry, this method. That was certainly his most important contribution.

DH: He was a bit older than you, wasn't he?

AC: Yes, he was born in 1918, I think.

ES: And you were born in what year?

AC: 1923. Five years between us.

ES: Did Hillarp die prematurely?

AC: Oh, absolutely. He died in '65, it was a malignant melanoma. Within less than a year after diagnosis, he was dead.

ES: You were close personal friends?

AC: Yes, we were close. He was a very interesting person. He came from a religious family, one of these – not the State church.

ES: Piestistic, or something like that.

AC: Something like that. He was very religious to start with. He married a girl from the same sect. They got a couple of children, and then for some reason, he changed. He became entirely free of religion and started to study Marx.His second wife – he married another wife – said that Hillarp is probablyone of the very few who read every page of Marx's Das Kapital. He was very careful with everything he did, very detailed. That was part of his success, he was very good in methodology, very careful. Another thing:he learned everything from reading. He hardly ever went to another. He once went to von Euler to spend a few months there, otherwise everything that he did learned by reading and he set up the techniques on his own.

ES: Where was von Euler?

AC: He was in Stockholm.

ES: Do you think Hillarp would have been changed, if he had ever studied abroad, like you?

AC: I'm not so sure. I think he did the right thing, for him, for the person he was. He was so clever he could learn things himself. One thing, he was reticent, perhaps one could say, but the strange thing about him – in a small group, for example with young people around him, his students, he was very enthusiastic, and he could really cause a lot of enthusiasm. That became so clear, especially when he moved to Stockholm, and collected this very big group. That was one part of him. Another part was, he only once went outside Scandinavia to give a lecture. Only once, and that was a very interesting meeting in London in 1960, and before that, he was very nervous. He actually was very nervous also when he went to give a talk in Lund: his mouth became dry, so he had very great difficulty in giving a lecture.So before going to London, he wrote letters to Blashko(?) and all these

other guys to explain various things to him –it was just because he was so nervous to come to London and give a lecture at an international symposium.

ES: Was this the same meeting in London that you went to and felt that your own ideas were discarded by the English establishment?

AC: Yes. Exactly, that meeting. He went to one more meeting outside Sweden, that was to Helsinki – once. That the reason why he is notso well known. He never went anywhere! (Laughter) He was in Lund, he went to Gothenburg, and then Stockholm, and then was in Helsinki once, and London.He could go to Paris a couple of times, and have a lot of fun, because that was another part of him: he liked girls a lot. (Laughter)

ES: Are you telling us that fame is just as much a function of how many people you meet as of your scientific accomplishments?

AC: To some extent, but of course we must remember that some of these papers are very, very much well quoted. The technology, the first one, where they described the work that I have told about, Hillarp and Thieme. For some reason Bengt Falckand his brother-in-law are co-authors on this paper, and they didn't do anything.They were down in Lund, they didn't do anything on this paper, and still Falck is the first name: Falck, Hillarp, Thieme and Torp.

ES: Why is Falck the first name?

AC: Well, that has also to do with – there was a little bit left of Hillarp's period in a religious sect, in that he always had easily a bad conscience. Falck told him, "Now you and Carlsson are professors, but I have only a limited period for my research position, andwhat will become of me?" And Hillarp said, "Ok, I'll put you on the paper." Hillarp came back to me and told me he felt a bit uneasy about it: "These will be the authors of the paper, but we will put on the paper that the

work was also done in the department where I was chairman," so I got a little bit of that. From my point of view, I was not involved in that particular experimentation, so, alright, even though I felt as if I werevery much involved in this technology, and I was the one who first came up with the idea of using an established biochemical analytical technique, the von Euler technique, to apply on histochemical preparation. So, I felt very much beingin it, but I was not in it. But I gotcompensation in a sense by the first publication showing that you have these monoamines in the brain, and the nerves being shown in the brain:there, I was the first author. Because Hillarp – and that was not unusual in those days – Hillarp was very particular thatauthors should always be in alphabetical order. So Falck, Hillarp, Theme and Torp – alphabetical order.

ES: No kidding. This is why Hillarp isn't so well known, then.

DH: In around that time in Germany, the boss in the lab wouldn't know the names, particularly, of the people who worked in the lab also. They may know the surname, but they wouldn't know the first name. It was very hierarchical. Were things like that here, or were they more informal?

AC: No – well, it was not as bad as in Basel. What was the name of this guy who was working for many, many years with Pletscher, an Italian name, and he then became head of pharmacology at Synthélabo. They were meeting every day, probably for more thanten years, and it was 'Dr. Pletscher' and 'Dr. Bartolini,' I think it was. That was it. But in Sweden, we were perhaps also a bit hierarchical. Well not with my students, they were first name of course. But my secretary, certainly during the period in Lund, with the secretary it was Miss Such-and-Such and Dr. Such and Such, or Professor, whatever. After maybe a couple of years, when I moved to Gothenburg, I put up an announcement "from now on everybody here usesno titles," we said 'you' to each other, we had 'du,' just like the French, and first names, "and if anybody objects to it, he will come to me." And nobody came to me, of course. I think it was a good reform.

ES: Is this informality something that you brought back from Bethesda?

AC: Not really. In a sense, in the U.S. there is also a kind of hierarchy. Somebody who is a doctor is indeed, "Doctor," and if he or she is not a doctor, I think it's – isn't it still like that?

ES: It's been reduced, I think, especially in the internet age, where it's de rigeur to use people's first names in internet communications, e-mail.

AC: Yes, but certainly at that time, in Brodie's lab, it was 'Dr. Brodie' – I'm not even sure – well, yes, they called him Steve, and I did too, after a while. Yes. But I don't think the secretaries did.

ES: Well, that's a bit different. Even today, the secretaries aren't really part of the community of investigators, but within that community, it's certainly a first name basis now.

DH: I think the joke about Brodie was that hiswife used to referred to him as "the Doctor."

ES: Did she? 'The Doctor'? Is that right?

AC: Oh yes, that's true. (Laughter.) There is another funny story about Brodie during his Goldwater time: when he got his salary, they say when he got these cheques, he never cashed them. He was so involved with his research that he didn't consider that anything important. I'm not sure if that's true, but that's what they said, that's one of the stories about him.

ES: Well, let's take the Swedish story forward now, past Hillarp. What happens next?

AC: The 1960 meeting in London was important, and that was important also for really stimulating us to go ahead with histochemistry, because in London, one of the things they said was – they said many different things, but one of them was "look, there's no evidence that these amines are even in the nerves." They quoted some work that never was published, that actually they are located in the glia. That was one of the things they said. And Sir Henry Dale himself said, "look, dopa is a funny thing, it looks like a kind of poison. Isn't it funny that an amino acid could be a poison?" and they discussed it and said, "yes, it must be a poison." That was the conclusion of the meeting.

ES: This must have been infuriating to you.

AC: Well, in a sense, yes, but at the same time I felt very much stimulated.Because we knew we were right, we had such enormously solid evidence that it was impossible. It was very strange that they couldn't just look upon it straight. That was because they had the opposite of ignorance, you see – they were so much involved with all these criteria that you need in order to be able to mention the word "chemical transmission." There was quite a list of criteria. Sothese data that were not at all the kind of data that could be applied to the criteria: We gave theprecursor, first we took away dopamine by means of one drug, we put it in again, and we could see that it was dopamine that did it, it was so obvious. And for some reason, they were so involved with all these other things. Also, I think they were probably fighting the electrophysiologists, with great success, but they had a great respect for them as well, because it was by and large the electrophysiologists, together with Sir Henry Dale, who had come to a list of criteria for neurotransmission – and the kind of data that we had could not be applied. They were so different.

ES: But this dismissing of your scientific findings strikes me as being very narrow minded. David, what do you think about this? Is there something distinctively English about this?

DH: No, no, I think the problem was that up till then, people couldn't actually conceive of the brain working that way. Yes, you had neurotransmitters, but out in the periphery. The idea that we were made of little bits, as opposed toan indivisible soul, in a sense, was a big problem.

ES: But bible-ism was dead by this time, though

DH: No, sure, but this was a big break in how people had conceived of the human being working. Wejust didn't have any models of how we actually function.

ES: So, there was something too mechanistic about what the Swedes were bringing to this London conference, that repelled the Brits? This just sounds like a colossal breakdown in science here – I'm just trying to figure out why this would have happened.

AC: Well, first of all, I understood when I came there, that they wanted to put me in my place. They thought that I was a young fellow who was a bit arrogant, and they wanted to show me my place. Even before the meeting, I still remember Marthe Vogt, because I had alittle bit of interaction with her before. She was also into reserpine and catecholamines,but she missed it. She found it couldn't be the same as the effect of serotonin because they denervated the adrenal gland, and then the reserpine didn't work. So therefore,she said, "it cannot be, it must be something very different." Well, we went ahead and said, "it's the same, it's like serotonin. It's the same mechanism." And she didn't like that at all. She thought it wasa kind of toxicity – she worked in toxicology, not pharmacology. The doses were too high, and there were all kinds of things that were bad. So that was one thing. And then of course, I think they do have in England a bit of that "what has not been discovered in England needs to be re-discovered" – I think so. But the funny thing is, they had done it. Because there was a Polish guy who was working under Blashko, and they repeated what we did, but less elegantly. They

gave very high doses, and they added monoamine oxidase inhibitors, so a lot of them died and they looked terrible, these subjects. That was probably why Dale said it was a toxic phenomenon. But they did haveit. There was another interesting thing about Blashko. All these people coming from Germany: Marte Vogt, Blashko, Feldberg – there were lots of them coming. They were of course taken care of to some extent in England. They were given opportunities; they added a lot to British pharmacology, but I think they were aware all the time that they were not British, they were not English. They were not really accepted – professionally, ok – but otherwise, perhaps not. So one thing became very clear to me in London: At one point in the discussionswhen the others said, "Carlsson's work was no good," Blashko said "I think" – because he had repeated the experiments with this Polish fellow – he said "I think we should all congratulate Carlsson for making a great discovery,"and all the discussion is printed verbatim in that book,Adrenergic Mechanismbut not this. It's not in there.

ES: Blashko's comment is not in there?

AC: No. It was taken out. He came to me afterwards, and he was very embarrassed, actually. He said, "I'm sorry, I became a bit irritated so I said something I shouldn't havesaid." It was this comment, and this comment was deleted from the text.

ES: So Blashko told you that he said something he shouldn't have said, namely that Carlsson had made a great discovery?

AC: Yes.

ES: Why should he not have said that, if it was true?

AC: Well, I'm sure he was told. He was told "you shouldn't have said that." Because the way they behaved, the British – there you had Sir Henry Dale, the central

figure, and the British people and also lots of other Europeans and Americans where he had been their mentor, so he was an enormously dominating figure. I couldn't say how he exercised this domination. Maybe it was just because of his charisma, but in any event, it was clear that they behaved at this meeting like a football team, and Blashko did something that you shouldn't do on a team – and he was told.

ES: Blashko praised a member of the other team.

AC: Yes. That is the only possible explanation of why that happened. I have never written about this, but I think I will sometime.

ES: Ok, you're back now from London. What happens next?

AC: There was as I said a tremendous increase in activity in Gothenburg, Lund, and Stockholm when Hillarp got there. Tremendous activity. Certainly, in 1965 there was another international meeting, and all the big shots were there, even thoughnot Sir Henry Dale, he was an old personin his 90s at that time – but lots of British people were there.

ES: Where was this meeting in '65?

AC: In Stockholm. In 1965,in I think in January. And at that time it was said already in the introductory remarks, "As we all know, these monoamines serve as neurotransmitters not only in the peripheral nervous system but also in the central nervous system." There was no objection to this,it was agreed upon, so that was a very dramatic change, and I think that was very much the whole story. But certainly, the histochemistry: I mean, if you see something, if you see a picture, it tells much more than if you have some figures of something that has disappeared, even if it goes down to zero, it's not the same as if you can see the thing, so therefore it had a tremendous impact, even though there was a lot of debate at that

time, as to for examplewhat was the role of these synaptic vesicles. They said, it was a bit facetious perhaps,"They are just garbage cans," and we of course said "No, they are essential. If they are not functioning, there will be no release by the nerve impulse." There was somebody from the U.S. who agreed to that, I don't remember his name now, he did some very good work on the adrenal medulla.

ES: So, this is a story that is really dominated by the Swedes.

AC: Yes, but there is one thing I would like to say that is funny. At this meeting in 1965, I had a picture of the chemical transmission mechanism with all the details in it, and then a little later there came up something called 'the NIH synapse,' that was about just the same as my picture, but now it had been invented at the National Institutes of Health. That has disappeared for some reason, but the NIH synapse was there for maybe a couple of years.

ES: Who was it that propagandized the NIH synapse?

AC: Perhaps Irv Kopin, I think he was one of those – but I must say afterwards he has commented on our work in a very generous way.

ES: Well, what else could he do? It was clear that you were right.

AC: And in that picture that I had I also had put in the major drugs: reserpine acting on the vesicles, chlorpromazine on the receptor, imipramine on the transporter, and MAO inhibitors acting on the MAO in the mitochondria. All this is in that picture.

ES: Are all four of these your own contribution?

AC: Well, no, not – that picture with all these in there, that was the first picture.

ES: That's a beautiful picture, with these four. Can you help us sort out the credit for this?

AC: That is again for example coming in with Axelrod. Axelrod never understood the difference between reserpine and cocaine, though he did later.
(Tea arrives.) Well, perhaps you think we are moving forward a little bit too slow?

ES: No, not at all. This is perfect.

DH: As long as you are able to keep going, we can keep going all day.

AC: (Laughing) Yes. As you probably understand, I enjoy very much talking about all these things.

ES: I know that you have been interviewed many times on these subjects.

AC: Yes, but I can go on being interviewed forever on these things, because it's so exciting. The whole thing, the whole story still causes a lot of excitement in me.

ES: Oh, yes. Arvid, what have been the other major interviews with you, that you can think of, or are there just too many to count?

AC: Well, we have this one; you (DH) have interviewed me, and that's in the book of course, in Psychopharmacologists;there was one at the ACNP, which is not published

ES: Who interviewed you there?

AC: Biff Bunney, I think it was Biff Bunney. And onenamed Hargittay, an interesting Hungarian guy. He was written a series of books, interviews.

ES: Has that been published?

AC: Yes.

ES: That name doesn't even ring a bell.

AC: Hargittay. Very interesting person. That was a long interview. He came to Gothenburg and we spent, I think, a whole day.

ES: I hope David will want to publish this in one of his own collections of interviews, even though you published one already, because I think we are breaking some new ground. here.

Arvid, we were just on the threshold of 1965, and I was asking you to help us sort out the credit for linking these four drugs to neurotransmitters. Will you just continue that train of thought, please?

AC: Let's start out with the vesicles and reserpine. We had, Brodie and us, we had an opposite opinion both with regard to reserpine and cocaine, and the tricyclic antidepressants. They wanted to have reserpine on the cell membraneand the tricyclics on the vesicles –exactly the opposite. So that was one area where we disagreed, and that disagreement was still there in '65, we had been debating that several times.

DH: That went through to the '80s, that issue about the vesicles. There were still people that I wasaware of at meetings in the '80s that were asking the question, "Are vesicles involved in neurotransmission or not?"

AC: That was in relation to Axelrod. It's also interesting because that has entirely been disguised or covered. Axelrod reported that reserpine and cocaine – and I

think there was also some tricyclic – they did more or less the same thing. His method was to inject radioactive adrenalin, for example, and look at the uptake in spleen, heart, whatever, salivary gland. Then he found that if you give cocaine, you block the uptake, and if you give reserpine, you block it too. It's only that you don't block it, but that's what he didn't understand.

ES: I didn't understand what you just said.

AC: Well, with reserpine, if you give adrenaline, the membrane transporter, which is in the cell membrane, is still intact, so thereforeadrenaline is still pumped into the nerve, but it cannot be stored. But he did not distinguish between the two transport mechanisms, the one in the cell membrane and the one in the vesicle. He didn't distinguish between these two. And that has been entirely lost. So, he is now the one who discovered the membrane uptake mechanism – in a sense he did, but he couldn't tell the difference between two drugs acting on entirely different mechanisms. He thought reserpine acted in the same way as cocaine.

ES: Now just clarify this for me. Is reserpine or is cocaine stored in vesicle?

AC: Well you have – this (drawing) is the transection of the nerve. This is where reserpine – it blocks the transporter here.

ES: This is a vesicle?

AC: This is a vesicle. And you have cocaine, and imipramine, for example, it blocks this transport mechanism here.

ES: At the membrane

AC: Membrane. So, these are two different mechanisms.

ES: So,cocaine blocks the transportation mechanism in the vesicle and cocaine blocks the transport mechanism at the membrane. Got it.

AC: So, he lumped these two mechanisms together.

DH: Just to take this point a wee bit further, why did people not have problems?I mean, clinically a drug like cocaine is very different to the antidepressants, but it appears to work the same way. Did you have any idea during the 1960swhy the reuptake blocking of cocaine, which appeared to be the same as what the antidepressants were doing, led to a completely different clinical outcome?

AC: Well,I cannot comment on how different people thought, but Axelrod probably didn't think so much about it because he was not a pharmacologist.

DH: Sure, but I wasn't thinking of him. It was more generally, when it became clear thatboth cocaine and the antidepressants block reuptake, but yet they're not clinically the same.

AC: I don't know for how long people really had that idea. I think they changed, but I cannot tell. But we understood it from the beginning. We did work on these and isolated it, and found that reserpine blocks here, so us it was very clear.

DH: No, no, with that. But at the point when you showed that the tricyclics block reuptake….

ES: Just clarify this for me – so tricyclics block reuptake at the membrane?

AC: Yes, and you also have imipramine and cocaine, essentially doing – it's not quite the same, but ….

DH: So, what's the difference between them, then., because clinically they're very different.

AC: Very different, yet. It's probably a complicated thing, but one very clear difference is that imipramine is very weak on dopamine reuptake. It acts on serotonin and noradrenaline, but hardly on dopamine. And we know that selective dopamine reuptake inhibitors are stimulants, like cocaine. So that is probably one, but it may not be the only thing. The other possibility could be that cocaine has a little bit of amphetamine, in other words that it not only blocks reuptake, but actually reverses the pump such as to have it pump out rather than pump in, like amphetamine is doing. But there are some data from the Karolinska, where they did some interesting work on removing calcium – which you can do with micro-dialysis, you can have the fluid transfused, it's free of calcium – then cocaine loses its effect on release, so to speak. That would support the view that it's a reuptake inhibitor, a clean reuptake inhibitor, whereas in the case of amphetamine, when you reverse the thing, that can happen in the absence of calcium. But there is not so much data on this. I'm not quite sure about cocaine, whether it's entirely an uptake inhibitor or not at all a releasing agent.

DH: Can I just chase one more thing, and this brings us 30 years forward, so we'll need to go back to the '60s in a moment. What do you make of the work of Joseph Knoll on the …

AC: Selegeline?

DH: Well, the whole catecholamine release enhancement mechanism? Do you think this is real, do you think it's valid?

AC: I'm not quite sure. How does he formulate his idea?

DH: He says that underneath the classic amphetamine release effect, there's a much more sensitive physiological mechanism in the drugs that he's been working on, which are release enhancers, which don't just release, they enhance….

AC: The physiological release. We have actually some data that go far back in time that support this idea, that low doses of amphetamine perhaps will show up their action only if you have an impulse flow. In other words, the lowest concentrations of amphetamine perhaps will enhance the physiological release, that could be true of amphetamine as well, and if he has drugs that are more to that, that might be reasonable, but I have not looked into the details of his work

ES: So Arvid, you haven't seen Joseph Knoll's new book,about his kind of total field theory of how mind, brain and society work together?

AC: No, I haven't

ES: A grand synthesis. Springer published it about two years ago. It's quite interesting.

AC: That sounds lovely, yes.

ES: I just wondered, but you haven't seen it. David, did you want to ask about anything further?

DH: No, no, no – but given that we have gotten down to the nitty-gritty of this point, it seemed worthwhile to clear these issues up

ES: We're just trying to sort out the credit now for linking these four drugs to their effect on neurotransmitters. You mentioned Axelrod. Are there any other names that you want to mention, in addition to your own, and the Swedes?

AC: As it is now, Axelrod is given the credit for the membrane, which is not the whole truth.

ES: Ok.

DH: Just to ask on that: What, then, is the first article which talks about membrane reuptake only, and leaves out the vesicle reuptake component?

AC: I remember our own work, we called it the membrane pump.I'm not sure who else did that. But there is one thing also that has been entirely forgotten, and that's actually going back to 1960, to that London meeting. Thatwas a man, Burn – he was, in my mind, the one who discovered the uptake.

ES: Tell us now your views on that.

AC: What he found, I believe I remember that. He did not use radioactive material, he used adrenaline, or possibly noradrenaline. He injected that into the animal, and then – I don't remember every detail now, but I think he used reserpine also, and what he could demonstrate was that when you stimulated the nerve, which did not respond, perhaps because of reserpine, he could make the nerve respond again after infusing adrenaline, and this he could block by means of cocaine. The concept that he put forward there, that was based on sound data, was that there is an uptake mechanism of the nerves for adrenaline, that can be blocked by cocaine. That is in that book, Adrenergic Mechanisms, you have it there, the 1960 book. And Axelrod was there.He was at this meeting, actually, so he was present when we had all that fighting, by the way.

DH: Was he present? Gosh. Right.

AC: He was present, yes.

DH: So did he play a role in the conversation?

AC: No. We had somewhat different opinions on one detail at that meeting. I proposed something there, I think I said "I am skating on thin ice," but what I proposed was that, if we have this, this is the nerve terminal (drawing), and this is the subsequent cell with the receptor here. I proposed that monoamine oxidase and COMT are not in the same compartment.Monoamine oxidase is closer to the synthesis than COMT, and the reason for that was we had data with MAO inhibitors, and we could see that you have an increase in the level of stored material, and yet no response to start with. In other words, the behavior of the animal did not change. But we had a poor method for measuring products of COMT, so we could see as soon as…

ES: This is the post-synaptic neuron you're pointing to? Ok.

AC: Right. We could see as soon as – even though we didn't put that in there, COMT and MAO, but that was the distinction between the two

ES: He writes: "MAO in the pre-synaptic neuron and COMT in the post-synaptic neuron"

AC: What we could see was that when the animal started – and we were using aMAO inhibitor that is also a releasing agent, I forget the name of it, but this is what we had. As soon as the animal started to be excited, we found a dramatic increase in the o-methylated metabolites. So therefore, we said that MAO is close to the synthesis and not to so close to the other site, so to speak. COMT is away from it and is more correlated to the effects.And what Axelrod commented upon was his data on differential centrification, where he could show that MAO and COMT are in different compartments. So, we commented on one and the same thing from different angles, so to speak.

ES: You say that this has been forgotten. What has been forgotten, exactly?

AC: Well, this concept, this hypothesis here, is now well accepted, of course. This was the first time that we discussed that.

ES: Oh, it's forgotten that this is the first airing of that concept. Ok.

AC: Yes. So, you had the question again of …

ES: Who else is represented here?

AC: Well, of course that chlorpromazine acts on the receptor, here…

ES: The post-synaptic receptor.

AC: Yes. There of course is a lot of competition for priority here. One thing is that when we first published this, that wasin 1963, two years before the Stockholm meeting, we did not emphasize dopamine receptors. We said – because our data indicated there was probably an effect also on noradrenaline receptors – in that paper we said "It's quite possible that these drugs, chlorpromazine and these antipsychotics, could also have an effect on serotonin receptors." So we were rather open there. And then later, the fieldshifted very much in the direction of dopamine. The first thing was in our lab, Andén and colleagues, and then in Stockholm, Sedvall and colleagues…

DH: What was Andén s first name?

AC: Nils-Erik Andén. They did lots of antipsychotics, and they they found that there are some antipsychotics that act only on dopamine and hardly at all on noradrenaline, so therefore they said, "it's the dopamine receptor that is really the

important thing." That is true. We never said that. So of course, one can say the origin of the dopamine hypothesis of schizophrenia in a sense is our paper.

DH: Your 1963 paper.

AC: 1963. And our data showed the strongest effect on dopamine, but we did not emphasize that.

ES: But the people that talked about the antipsychotic effectof this were Andén and Sedvall?

AC: Sedvall. Nybäck and Sedvall. They were the first ones. And then later on, in the '70s, the binding came in, receptor binding. That wasSol Snyder and Phil Seeman. And they were very much, they were even more positive. They said, "It is dopamine. Forget the rest."

ES: How do you feel about that hypothesis?

AC: Well, now, in retrospect, if we look at how people feel about it today, of course, noradrenaline is not out, and certainly serotonin is not out. It's very much being discussed in relation to the atypicals, especiallythat maybe blockade of serotonin receptors could be important in changing the profile from typical into atypical, in other words, less EPS. I don't believe, I think that is much exaggerated.

ES: What is much exaggerated?

AC: The role of serotonin.

DH: The atypicals also cause EPS, to a slightly greater extent than is often conceded.

AC: That's one thing. Another thing is that you have the benzamides, which are atypical, and they have no effect at all on serotonin receptors. So,you can have an atypical profile without any effect on serotonin receptors.

DH: How much has it all now become a case of marketing, as opposed to the kind of meeting that you had back, say in '65, when people were actually trying to understand the science. They're not trying to understand the science any more, they're trying to use the science for the purpose of marketing. Does that seem right to you?

AC: Oh, yes, I think so. Of course, when you have powerful companies such as Lilly and olanzapine, that plays such an important role for opinion building her. And there was less of that in the beginning. It has become much more commercial, the whole thing.

DH: The meeting that you had back in '65, what role would the pharmaceutical companies have had in that, if any?

AC: That's a good question. I guess that there was some sponsoring, but I cannot point to any of the activities at the meetingthat could be related to any particular drug company. So, I think it was pretty much neutral from that point of view.

DH: And this meeting had all of the major figures in the world at it, didn't it?

AC: Yes – but some of the British were not there. Of course, Sir Henry Dale had an excuse, he was close to his 90s, but why Sir John Gaddum was not there, I'm not sure.

DH: Gaddum had died.

AC: He died rather early, but…

DH: He got ill. He had a tumor as well, he was ill for a few years before he died

AC: Maybe, that could be.

DH: And he'd also moved jobs. He'd moved from Edinburgh down to Babraham

ES: What other Brits were not there?

AC: Well, Burn was not there, but I think his health was not really very good in 1960, so that could be why.There was another guywho was there, and he was a very nice fellow. I have forgotten his name.He had an idea about adrenergic antagonists having an interesting pre-synaptic role, but it was not what came out later, that they acted on pre-synaptic receptors. He had another idea about what they did to the nerve endings, which I have forgotten now, and he had abandoned that at that time. He probably defended that in 1960, but not in '65. He was so funny, because he said "I have confessed." He had defended this idea, but in '65 he said, "I have confessed" – he was out of it. And then of course, the story became that of pre-synaptic receptors.

ES: All the people that we have been talking about between 1960 and 1965 as getting credit for the drug and neurotransmission story, were they all at the '65 meeting?

AC: Well, there were several of the British who were not there.

ES: Right, but they didn't get of the credit that we have been assigning.

AC: That's correct, yes. Well, Udenfriend was there. He was one of the guys who, I think, talked about the vesicles as garbage cans. Well, he also was an organic chemist, you see. It was very clear that those people who came from organic chemistry had enormous strength as organic chemists, but also their weaknesses.

DH: It's an interesting difference, because the Brits were all physiologists, and I guess what you're seeing at this point is a generation of physiologists who are being moved out of the picture and being replaced.

AC: Yes. It's interesting in a way, that the battle in London, as I sometimes call it, that was the battle where the Brits who together with the German refugees– especially Feldberg, who was a very important person in thedevelopment of the chemical transmission concept, starting out, of course, with Otto Löwy, but then together with Dale. Actually, it was said that Dale had more or less stopped going to the lab, but when Feldbergcame there, and he had this bioassay method for acetylcholine, Dale came back to the lab, because now it was really doing something. The Brits, together with the Germans, they were the ones who carried Löwy's concept forward, very efficiently, but they stopped at the blood-brain barrier. So, they missed, because after all practically all of the nervous system is in here, and they stopped at the wall, so to speak, so they lost the final triumph. They lost the final triumph of chemical transmission.

ES: That's a nice formulation.

DH: How muchcould that have been driven by the fact that when they looked at the brain, it just looked too complex. How do you sort this soup out?

AC: It's interesting. There is a correspondence between Dale and Eccles, that is in book form; the whole correspondence, extending over two decades, I think. Very interesting. In one of these letters Dale says, "I doubt that in my remaining years I will be able to learn which are the probably true transmitters that occur in the brain." And at the same time he locked out Eccles, in a sense, because Eccles based on his spinal cord dataand this recurrent fiber, advocated acetylcholine. And for some reason, Dale felt sure that it was not acetylcholine. But there probably were two, and he didn't think that in his remaining years – and that was

about I think in 1953, or something like that, so he lived for more than one decade after that. I just wonder what he thought at the end, andmany of these peoplewho in London, what they really thought. They missed so much at this meeting. I know indirectly a little bit about Gaddum, because at this meeting Gaddum said, in his concluding remarks, "The meeting was in a critical mood, and no one ventured to propose anything about the role of the catecholamines in the central nervous system." And that was what I had insisted upon throughout the meeting.

ES: Completely ignored the Swedish contribution.

AC: So, I was obviously nobody.

AC: And Gaddum, what I know is that Leslie Iverson as a young man came to Gaddum and he said"I want to go to some lab abroad. Can you give me suggestions?" He ended up in the U.S. of course, but one of the things that Gaddum said was, "Well, you have this fellow Carlsson." So maybe he finally understood I was a little bit more than a nobody. That Leslie Iverson has told me. There is one more interesting thing, by the way. We had a catecholamine symposium in 1983 in Gothenburg, and we invited two people to become honorary presidents. One was Marthe Vogt, the other one was Hermann Blashko, and both of them were invited to give introductory remarks. It would be interesting, these two people were at the London meeting, what would they say? Marthe Vogt said a little bit, very vague comments on dopamine that seemed to indicate that dopamine probably was not really importantafter all, and Blashko didn't say anything. Blashko was the one who wanted to congratulate me, but he didn't do it this time. He had learned his lesson.

ES: (Laughing) No kidding! Do you think there is a kind of national rivalry between the Brits and the Swedes?

AC: Well, there is also a rivalry among everybody. I don't think there is anything special between the Swedes and the Brits.

DH: No, I think this is just an older generation of Brits who were physiologists. You've got people who came after them who were Brits, like Martin Sandler, and all who had no absolutely problem with these ideas.

ES: Good point.

AC: And von Euler, I think it was, spent some time with Henry Dale, I'm almost sure of that.

ES: Now here's a question. After 1965, as far as you are concerned, your own particular contributions, is the main storya drug development story or is it a basic neuroscience story?

AC: I think these are parallel.

ES: These are both stories we want to hear about. Tell us about the neuroscience story first.

AC: Well, they are different lines. One is a dopamine story, and the other one is a serotonin story. The dopamine story, if we take it broadly, summary-wise: First of all, I had the opportunity to have in our group, and also collaborating with Uppsala, a medicinal chemist, so that was enormously important for me, because we started to make our own molecules.

ES: This is Hans Corrodi, in particular.

AC: Yes. He was the one, actually, who inspired mewith this idea: We should have medicinal chemistry in the pharmacology lab under the same roof. They should be together, having lunch together, and so forth.

ES: And how was it that he came to be hired in your department of pharmacology?

AC: He was an enormously interesting person. He was Swiss, he had done his thesis in Zurich, Institute of Technology, very famous of course, that dealt with mushrooms, mushroom poisons, and then after that he looked around for a job, and at Hässle – which was at that time very small, it was a subsidiary of Astra in Gothenburg, they had one chemist, a very clever chemist, but they decided that they wanted two chemists. So, they put in an ad in Swedish newspapers, and there were a numnber of responses. And one of them was from Hans Corrodi, in Switzerland, and it was written in Swedish – and it was perfect Swedish. There was only one spelling that was not correct, and that was what we call Pflugsvamp, which is a mushroom, that was one mushroom he was working on, and he put it as Pfygsvamp, that is a y instead of a u. Otherwise it was a perfect letter. So, they became interested in this guy, but they didn't have enough money to invite him for an interview, because they had a very small budget. But the head of research there, Östholm, had some collaboration between Hässle and Geigy, so he had a good excuse for going down to Switzerland, and then he interviewed Corrodi. It was a very funny interview. It started out, "How come you know Swedish?" "Well," he said, "I do like the Alps,but there are too many tourists. I like the Kemp de Kaiser in the far north, there are wonderful mountains and not too many people around."

DH: But there are an awful lot of mosquitos.

AC: Mosquitos, absolutely, yes, that's correct! "So that's why I have learned Swedish." And then he said, "Do you know any other language?" "Well, yes, Finnish." "How come?" "Well, that's because when you are wandering up there

and you come across some other people up there, they are likely to speak Finnish rather than Swedish. And then they become much more friendly, they can invite you for a cup of coffee or so." And of course, as a Swiss, he already had Italian and French, and German – German was his mother tongue. "Any other languages?" "Well, Russian." "How come?""Well, that's because the best chemical textbooks" – he was an organic chemist – "the best chemical textbooksare the American textbooks, but they are so expensive. But they are translated into Russian, and the Russian translations are cheap, so that's why I have learned Russian." So, you see, it was an unusual person. Then when he came – he was employed of courseas chemist at Hässle – and very quickly we were in touch, and he became so fascinated by the whole monoamine story and also the histochemistry, so he also did some work on the histochemistry to identify the fluorescent product.

ES: Did he get a university appointment at Gothenburg?

AC: Yes, he became a docent – that's assistant professor – in medicinal chemistry, in our Institute

ES: When he came up, did he simultaneously get this appointment?

AC: That took a while, maybe a year or two.

ES: So, you knew him when he was at Hässle?

AC: Yes, as soon as he came to Hässle, almost immediately we got in touch. He was so fascinated by all this. Another thing we did, where he played a crucial role, was that when I became a consultant for Hässle, I proposed to them to work on beta adrenergic blocking agents. He was very instrumental in convincing the people at Hässle that this was a good idea. This was just the time when there were a lot of publications on beta blocking agents came out. So that was how

they developed their beta blocker, and of course the first one they never managed to sell so much because they didn't have any marketing power, but the second one, selocaine, became of one of the biggest beta blockers in the world, it's still a blockbuster. So that came out of my interaction with Corrodi.

ES: They must have made a lot of money from that.

AC: Oh, billions, billions. That together with the other aspect of beta adrenergic pharmacology, the beta stimulants. They also came out of my proposal. They exported that down to the other company, Draco, down in Lund, becausethe management up in Södertäljethought Hässle wouldn't be able to handle both beta blockers and beta stimulants, so they brought that down to Draco, and thatbecame brickamil, another blockbuster. That was what really made the Astra group grow. They had almost nothing, the only thing they had before that was xylocaine, which was of course a tremendous thing, but that was far away back. They had nothing really to export.

ES: When did Astra acquire Hässle?

AC: It was during the war, it was in the early '40s. The reason why they bought Hässle, which was in Hässleholm, down in the south of Sweden, was that Hässle had a big store of chemicals that were not easily available during the war. So, it was actually the chemicals that they bought, and at the same time also moved up to Gothenburg, to stimulate academic interaction.

ES: And when did they arrive in Gothenburg, in Mölndal?

AC: It was not in Mölndal they started, it was in central Gothenburg, it was just two former apartments, very primitive at that time.

ES: So, you were a consultant to Astra, in fact?

AC: To Hässle.

ES: Right. But Astra owned Hässle.

AC: That's correct. I later became a consultant for Astra, but in the beginning, it was only Hässle that I consulted for. I would say if it weren't for the beta blockers and beta stimulants, AstraZenecawouldn't exist today, they were so important. And they did one thing more, that also came out ofHässle, and that was the hormones, the turbohalers for asthma treatment, for inhalation of corticoid hormones. That became very important in asthma treatment. They bought this patent from Bufors. All this came from Gothenburg and Mölndal. The rest of Astra group, they haven't done …

DH: Much.

AC: Not much.

DH: Right. Who all else was in Hässle, who was responsible for all of this happening? They had the links with you, they brought in Hans Corrodi, but who in the company was actually responsible for this?

AC: I have mentioned already, Östholm, Östholm was enormously important, and also the CEO was a very important person, a very nice person.

DH: What was his name?

AC: Norlindh, Sven-Arne Norlindh. I can tell you the contrast between what they did and what they had done down at Draco, when I was still in Lund. At Draco they approached me in the conventional way, and said, "Look, we would like to have you work so-and-so many hours a week on our projects, and we will pay you

such-and-such," and I said "I'm not interested." So, when I moved to Gothenburg, they said, "Have no idea to approach Carlsson, he doesn't like drug companies." But Östholm did nevertheless approach me.He approached me the same way he had done other professorsup in Gothenburg, he said, "We are small, but we have a little money. Wecould perhaps find some common ground to do research on that could be useful for both sides."Falkof, the circulation pharmacologist, he said yes, Verker, the cardiologist, said yes, and some others, so he collected some people to become a kind of advisory board. And that was one part. The other part was that he was enormously insistent. They tried to turn down his different projects, they said for example "these beta blockers, what is that? This is an academic playground, this is nothing really serious," that kind of thing – but he insisted. Same thing with elucic, that was also, they wanted to terminate that project, but he insisted. So, he was enormously important, and also the way he treated the people under him. He was an internal entrepreneur, one can say.

DH: What was the background? Why did he get into the pharmaceutical area?

AC: Well, he was a pharmacist, so that was rather natural for him. He started out down in Hässleholm, together with Sven-Arne Norlindh, and they moved up together to Gothenburg

ES: Now, Arvid, we picked up the story back in 1965, on the two tracks, with the drug development track and the science track, and then you started talking about dopamine and Corrodi. Let's just take the science track a little further down the road now.

AC: When we got the medicinal chemistry on board, we found some interesting molecules.The most important one that we found in the early '80s was the one called 3-PPP. It's a molecule that's rather similar to dopamine, but is more stable, and it has two enatiomers, so there is a plus and minus.The plus turned out to be a full D2 receptor agonist, and the other one a partial agonist. And it was the partial

agonist that became so interesting, because that was a new concept. A partial agonist might be something important because it might as a stabilizer. If you give a partial agonist as compared to a full agonist, you would stimulate if they are low, such as in Parkinson's, but only to a certain level, thereby avoiding an excessive stimulation. That, for example, L-dopa does,via excessive dopamine, and that certainly leads to lots of problems in the long term – these on/off and dyskinesia, and all that, that's due to an excessive stimulation of receptors. So, a partial agonist might interest from that point of view. On the other hand, an antagonist such as chlorpromazine and the others, they have EPS and tardive dyskinesia, and all these problems, and a partial agonist would be able to bring down an elevated tone of dopamine, but not all the way down, thereby protecting the system from all these problems of blockade. So that was the concept, and we developed that. First, we collaborated with Astra, and they brought us to a certain level, we did have somethree months toxicity on it, and then they said they didn't want it any more – and that's another story, that's always the story about the 'NIH syndrome.'But then we managed to have a collaboration with Upjohn, they took it on for a while, and we took it all the way to clinical testing. It turned out to be an antipsychotic agent– no EPS of course – but with a problem. The problem wasthat here we have a drug that has a very clear-cut antipsychotic action, but if you go on with the treatment beyond one week – already after two weeks, the thing has gone. There is no antipsychotic action left.That was done by Carol Tamminga, we had some very important collaboration with her.

ES: This is 3-PPP. Was it marketed under a name?

AC: It never got marketed because of this. Also, Upjohn finally said, "We don't want to pursue this."So, we had no money. But we were rather sure that we were on the right track, and the only thing was that this thing as a partial agonist has too high intrinsic activity. It should be at a lower stimulating level. So, we started on that, and what we did – because we didn't have facilities for synthesis and all that, to go on with that is a Big Pharma project, of course – so what we did was to add

a little bit of haloperidol to bring down, so to speak the activity,to titrate it down, and we did some work on it, but finally we couldn't pursue it, we didn't have enough resources. But we predicted that a molecule like 3-PPP minus, with somewhat lower intrinsic activity, would make it. You would have an antipsychotic action without EPS, and with a sustained activity. That was where Otsuke came in, with Kikuchi. He knew our work and took up our methodology. We have worked very much with an emphasis on in vivo methodology in our screening, so he did the same thing, and he had our criteria for a partial agonist.

ES: Who is this fellow?

AC: He is a Japanese pharmacologist

ES: He works for a company?

AC: Yes, for Otsuke.

ES: Got it.

AC: His first molecule also had too much intrinsic activity. Itdid some nice work on negative symptoms, but it couldn't do anything on positive symptoms, sothe management at Otsuke said "Stop it." But then, Otsuke is a family-owned company, so he went to the owner, Mr Otsuke, himself, and said, "I want to go on with this, I believe in it," and Mr.Otsuke said "yes," so he came up with the next molecule and that was Abilify, aripiprazole

DH: What year did he do that? In the '80s somewhere, isn't it?

AC: No, it had been later.

DH: You think?

AC: The second compound, yes. Possibly in the late ’80s, but more likely in the early ’90s.And then Otsuke formed an alliance with Bristol-Myers Squibb, so this is now a compound that has been doing very well on the market. It certainly has no EPS, it doesn’t increase body weight, and it is antipsychotic. The problem, what we still don’t know, is if you have a really severe psychosis, if it’s enough. I am not sure. Some people say no. Another problem is that most of the patients are on conventional – although mostly now atypicals,and when they switch to a partial agonist, you have a period where you can have some …

DH: Withdrawal problems.

AC: Yes, something like that kind of thing, so they get more sedation and that.

DH: Given that the drug’s gentler, is there any scope for saying, “well, these drugs weren’t actually created to be antipsychotic drugs.”Chlorpromazine was a drug that was used to treat people who were anxious, so if you had a milder version of it, there’s a huge number of people out there in the community who have nervous problems. Are there people there that it could help? What’s the profile of the drug outside schizophrenia?

AC: Well, that’s a very interesting question. What I think is that dopamine is involved in so many circuitries, and imbalances in these circuitries cause a variety of psychiatric – and neurological – problems. So, there is a wide scope. And now the reason why we got into psychosis, I think, was mainly the contact with Tamminga. Maybe it’s not entirely true, maybe we had some ideas about psychosis. But of course, in view of the fact that dopamine antagonists were for psychosis, we got into that. But I knowin the next generation of drugs that we had, that were not partial agonists,but the other ones, we thought this is going to be a good drug for the elderly, because it’s a mild stimulant.You know, you have all these elderly people that are just sitting there, they are alone, they don’t have

the energy to make new social contacts and therefore they are going downhill. If you have a mild stimulant, you could perhaps have them overcome this, so they could start a new kind of life, many of them. With the aminotetralines that came after minus triple-P, that was our first goal, actually. But the reason that we ended up with psychosis again was Carol Tamminga because she was available, and her area is psychosis.So that's why we did that, but it could have been something else. That drug, that was UH-232, has a profile remarkably similar to a partial agonist, but it has no agonism. So, then we get into a very complicated receptor pharmacology.

ES: Where does UH-232 come from?

AC: That was from our group. UH is Uli Hacksell. Uli Hacksell was in Uppsala, he was a member of our group. He is now CEO of Acadia in San Diego, and they are doing well. He is a very good chemist, and now a very good CEO. That compound, when we came across that, we actually had in mind to stimulate the elderly, but nevertheless, we ended up with psychosis, because of course, if you have a stabilizer, you could goeither from a case where you believe you have a low dopaminergic tone and that you could elevate it, or you could come when you are up, as in psychosis, to bring it down. You could go either way. But there was a problem with UH-232, it had some – not very marked – but still some stimulating action on 582 receptors, in other words LSD-like. When we did healthy volunteers, there were a couple of them who had some funny perceptions, looking up at the lamp, something creeping out of the lamp, others were closing their eyes, and seeing something.A little bit of LSD in it. And in the patients – it was only single doses – in some of them their psychosis actually got worse. So that was the end of that, but in a way we felt very much encouraged. We were doing something, we were hitting something (laughing), so we thought we should go on. Then we came across the phenylpiperidines, which are closely related to minus triple-P, only you take away the OH, which is responsible for the partial agonism, and you put in an electron-drawingcompound such as SO2-CH3,

metylysulphone, such as in OSU-6162. So, then we had another compound which had a profile very similar to a partial agonist,yet devoid of agonism.

ES: So, when you say, "we," this is the department of pharmacology at Gothenburg that's creating these compounds?

AC: Yes.

ES: And how many of these then went into development?

AC: UH-232 was one. Well, first of all minus triple P, the next one was UH-232.Actually, in our collaboration with Upjohn, we also synthesized a 5-HT-1A agaonist, but that came to nothing because– well that's a different story. But it was already in Phase I when it was stopped. But then OSU-6162 was ….

DH: Sorry, that's OS??

AC: OSU, which means Organic Synthetic Unit. That's because of the chemists, at one time it was nice for Uli Hacksellto have UH, but then the other chemists didn't like that, so they said "why not call it Organic Synthetic Unit because it's not any particular name." So, OSU 6162. We had beautiful preclinical data, we were at that time sponsored by Upjohn, but practically all the development, both chemistry and pharmacology, was done in our group, so what Upjohn really did was to spend the money on us. We had beautiful preclinical data showing that this is a stabilizer in the same sense as a partial agonist, but there was not very much in vitro binding, and then Upjohn said no, there must be in vitro binding.

DH: Because they wouldn't be able to market it?

AC: Well, then you don't have the mechanism. The mechanism was at that time, and still is, I think, a mechanism that can be shown in the test tube. If you don't have a mechanism demonstratedin the test tube – no chance of getting it through.

DH: Really? Even if you put it into people and show that it …

AC: But you see that's the problem.

DH: You don't get to that point?

AC: You don't get the money for that. How we got the OSU to people: Upjohn did not spend that money, did not even spend the money on a toxicity. That was another very strange story. We were in touch with an imaging group in Uppsala, a very well-known imaging group. They got the molecule, and they had an interesting model where they gave radioactively labeled C11-labeled L-dopa to monkeys, and they studied the increase in radioactive activity in the basal ganglia, in other words the manufacture and storage of dopamine, as a measure of dopaminergic activity so to speak, and they found something very strange. They found that those monkeys that were high in activity, when they gave the drug, they came down in their radioactive activity, their dopaminergic activity. But some very calm monkeys, who were down, they came up, and they had never seen anything like that. So, they actually saw the stabilization in this model, and they became so excited that the next thing they did – because they had access to some monkeys which were Parkinsonistic, they had been treated with one such drug, such as to get rid of the dopaminecells – they were treated with L-dopa, and after a week, they do have the dyskinesias. So, they gave OSU to the monkeys, and sure enough, the dyskinesias disappeared without interfering with their voluntary activities. It was a dramatic thing. So, then Joachim Tedroff, who was a neurologist, but he was closely linked to this imaging group, said "This is fantastic. We must try that in Parkinson patients." There was no toxicity: Done.So, he went up to the little counterpart to FDA that we have in Sweden and

told them about this fabulous story and said "I would like to try that on patients."They said "alright, let's do a just little bit of toxicity." So, they did some very minor toxicity, maybe on a few monkeys and also on some rats. Then it was on his responsibility as a doctor, the old traditional responsibility, and he did it, and the same thing happened as in the monkeys. These were patients very seriouslyaffected with dyskinesia, they even hadtube down into their duodenum and the L-dopa was infusedsuch as to make it as stable as possible, to get as much voluntary activity without so much dyskinesia, and yet they had dyskinesia. They gave the drug, and the dyskinesia came down, and their voluntary activity was preserved. That was done in maybe eight patients, single doses, intravenous injection. And then the films were shown to Upjohn, and they said "ok." Now they started on it, and a decent toxicity was done, lots of toxicity, actually, but then they focused rather on schizophrenia. We then did in Sweden a study on schizophrenia, and that also came our beautifully. It was an antipsychotic action, no EPS. It was a small group, of maybe some 10 patients. Then Upjohn decided to go after all for Parkinson's, with dyskinesias, and they did a very clumsy study that came to nothing, so they said no, they turned it down, the whole thing. But also at the same time we had done Huntington patients, and also seen a lovely decrease in the chorea, and also some improvement in cognition. All this was there and it looked enormously promising, and Upjohn said no.

ES: This is two promising drugs that Upjohn has passed on. Why didn't you take these agents to some other company?

AC: They owned the patent.

DH: Could you nothave made variations on them?

AC: Well yes, but that is a big pharma project.

DH: Yes, yes, of course.

AC: But when we saw that Upjohn was not doing well, that was the reasonwhy we founded Carlsson Research. It was exactly what you said. We wanted to make another compound, a similar one, that is outside the patent. That was ACR-16.

DH: And this was when?

AC: We founded the company in 1998, and already at the end of 2000, in December, we submitted the patent for ACR-16.

DH: Right, ok. When did you do the first human work with OSU-6162?

AC: In 1994 our collaboration with Upjohn was terminated, and my guess is that our collaboration with the imaging group in Uppsala, and that switchover, was after – then they were out of it, otherwise they would probably have objected, even though after they saw the clinical data they were back, developing it.

[To around 2:46.50]

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