Interview with Dr. Arvid Carlsson
Interviewers: Edward Shorter and David Healy
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ES: Now, Arvid, I at least would like to ask you of your views about some of the diagnoses and some of the indications in psychiatry, simply because David and I would like have the benefit of your considerable wisdom in this area. You were responsible for the development of one of the great classes of antidepressants. Do you think that there is a fundamental difference between antidepressants and antipsychotics?

AC: Yes, in terms of mechanism of action, I think that is clear. All the antipsychotics that are on the market today have an action on dopamine, and most of them are dopamine receptor antagonists, and we have one that is a partial dopamine receptor agonist. The antidepressants have different mechanisms – and of course the SSRIs, that is a group where the mechanism of action is perhaps the best defined because they are selectively acting on the reuptake of serotonin. Most of the others are also reuptake inhibitors, but they are acting on not only serotonin but also on noradrenaline and to some extent on dopamine reuptakes. On the mechanism of action point of view, they are different, all the drugs that are on the market today.

ES: You know that many of the antipsychotics simultaneously serve as anti-depressants

AC: Yes, that has been known for a long time.

ES: But if the mechanisms are fundamentally different, and the diseases are fundamentally different, how would you account for this overlap?

AC: I think it's not easy to answer in a simple way because these disorders, we talk about psychosis or schizophrenia, we talk about depression – but if you look into that, these are not homogeneous groups at all. There are overlaps between the two diagnoses. Actually,

I hesitate to call them diagnoses, even If you think about diagnoses, if you look at polio, then you are on safe ground. Polio is polio. But what is schizophrenia? What is depression? These are labels, actually. From that point of view, it is not at all surprising that you have overlap in terms of drug treatment. By and large one can say, drugs do not respect at all the borderlines of psychiatry. The drugs couldn't care less.

ES: There is this tradition in psychiatry, going back to the Germans in the 19th century – I'm talking about *Einheitspsychose*, unitary psychosis. I suppose today, Herb Meltzer is best identified with this – what do you think of that concept?

AC: Coming back to what I said earlier, I don't think much of any of these concepts. You are dealing with a poorly defined group, and you are trying to put different labels on them. You can try to describe subgroups, but the whole thing is really very vague. It's a big, big grey zone, the whole thing today. Of course, one cannot say this is something that one shouldn't do because the psychiatrists need to put labels on their bottles so they know a little bit of what's in that particular bottle.

ES: The rule in medicine of course is there is no treatment without a diagnosis. But if the diagnoses are all inadequate, then that makes the treatments unsuitable. If the diagnoses are inadequate, then the treatments aren't specific in any sense.

AC: This is a major problem, as I see it. Still, if you look at the FDA and other regulatory agencies, they require that when you develop a drug you should put one of these labels on it. So therefore, these labels are not adequate. Therefore, I think in a way these diagnoses could be a hindrance to some extent also, so it's a serious matter. It would be much better if one could rather focus on symptoms perhaps, in a drug development project, to not necessarily call it that this is for treatment of schizophrenia.

ES: The FDA certainly won't allow that. They insist that drugs be indicated for diseases and not for symptoms. Now, is there, within industry, unhappiness with FDA's insistence, *grosso modo,* that official diagnoses be used as the indications?

AC: I cannot tell. I haven't discussed that so much with these people. But I think they are less critical than for example I am, with the diagnoses. I don't think people in the drug development field are so much aware of how poor these diagnoses are, so they pay some respect to this, I guess

ES: But It must be a nightmare for industry to have to develop drugs for major depression given that it's such a heterogeneous category and given the heterogeneity of it the chances of your drug beating placebo are really very much reduced. So, you would think if we're talking about spending billions of dollars on the development of drugs, this would be a major concern getting indications that represent homogeneous illness.

AC: Absolutely. Perhaps if one could look upon the whole thing a bit differently, and before they were aware of this heterogeneity of patient population that the endpoint shouldn't necessarily have a statistical significance between these two groups – the placebo group and the other one. But perhaps rather look for a subgroup that is of responders. As it is now I think you could have a subgroup, maybe 20% subgroup with good responders, and you would not be able to be successful with it. You will have to discard the whole thing because you are not reaching significance between the groups.

ES: It's like giving insulin to everybody who is tired.

AC: Yes, exactly.

ES: There is this tradition, I think it's mainly a German tradition, of impatience with big trials and impatience with using questionnaires in order to assess endpoints, and rather, to concentrate with psychopathology and to do exactly as you've suggested – look carefully at small groups of patients. Roland Kuhn, whom David and I interviewed many years ago, was very much convinced of that, that this was the way to go, and he hated the idea of assessing a large trial and questionnaires. Our friend Thomas Ban in Toronto is also sympathetic to Kuhn's position. How do you feel about this question of psychopathology

of small groups and individual cases as opposed to large groups assessed with questionnaires?

AC: I like very much the small group approach and with very competent and keen clinicians such as Roland Kuhn.

ES: Do you know him?

AC: I met him a few times. By the way, what they say, and somebody – was it Jules Angst? – was quite sure that Kuhn was not the one who discovered the antidepressants.

DH: (laughing) A real controversy.

AC: What do you think?

DH: I think he has overplayed his hand.

ES: When the zimelidine trials were set up, did you attempt to have your own views about the nature of the trials prevail?

AC: No, I didn't even try. I was rather sure beforehand they wouldn't listen to me. Well, the first one, Seevers, that was in his thesis, I was very much of course interested and followed it very closely. But that was not a very structured study so I don't remember. But I guess we discussed dosages and a little bit of that. No, I cannot say I played any role.

ES: Have you ever had direct input into a clinical trial involving any of your drugs?

AC: Yes, with minus-triple-P, I discussed of course that very much with Carol Tamminga. Actually, that was interesting from one special point of view. That is that the first individuals – humans – who got the drugs were not healthy volunteers. They were

Carol's schizophrenia patients. That was fortunate because afterwards when we did the healthy volunteer study they vomited. But the schizophrenia patients didn't vomit; they felt well. No problem with their appetite at all! Even though they were off drugs. Carol was always very careful to have them off previous drugs.

ES: Can you tell us a little bit more about your conversations with Carol Tamminga about minus-triple P?

AC: The whole thing started by a kind of mistake, actually. I was down in Germany, in Heidelberg, and I gave a lecture, and Will Carpenter, Carol's boss, listened to that and got the impression that minus-triple-P was already in the clinic. So he went back and called Carol, and she wrote me a letter immediately and said she wanted to do this. So I called her right away and afterwards she said she was quite shocked having this phone call from me. But of course I explained this to her; nevertheless she was keen to start on it. So there was a long, I think several months of correspondence with the FDA before they approved it. The first study was intra-muscular injection, single doses. So that was very carefully done, started out with single doses, and I don't remember from the beginning if there was placebo already at the outset, maybe not.

ES: Who got the IND for this agent?

AC: It was Carol's personal IND.

ES: So she dealt with FDA? You didn't deal with them personally?

AC: No. She did it entirely, and that was probably much better than if I had done it. But I had to produce all the data, of course, the chemical syntheses and all that. At Astra, they had abandoned the whole thing, but they had all this data that was very helpful. I also got a lot of compound from them actually. It was of course very exciting because she called me – she does not belong to those people who believe that you have to wait three weeks in order to see an effect. She looked for an effect within less than 24 hours. She could

see that yes, it's active. And they felt well, also, but it didn't last long. After a few days they were back, after a single dose, and after that we went on with oral, repeated doses. Dose finding and so on, it took a long time. It was a very careful study. Not any big numbers, but still, finally, there was statistical significance and so forth.

ES: Is Carol sensitive to this question of homogeneity within this huge diagnostic basin schizophrenia? Did she try to put together a more or less homogeneous subgroup, or was it just whatever happened to be in the clinic at the time?

AC: I am not so sure how she, what kind of criteria she had in her selection of patients. I guess it was a rather complicated issue. First of all, whether the patient would be at all willing, and the patients' relatives and family and so on. I think these matters are probably very important with such studies, early studies with new drugs rather than trying to get some kind of homogeneity in the group, I doubt that she did.

ES: Maybe the patients are just too hard to recruit to be able to afford that kind of luxury.

AC: Yes, I think so.

ES: Do you know Herb Meltzer well? Have you ever discussed this question of Einheitspsychose with him?

AC: Not so much Einheitspsychose, but rather his attitude in relation to the role of serotonin, which of course is something that he likes to talk about a lot. The major point he's making is that atypicality needs the additive effect on serotonin receptors. You need dopamine receptor blockade, but there must be an additional serotonin receptor blockade, 582. And that he has built that on comparison between different antipsychotics. He has done some kind of mathematics on the difference in affinity for the two types – the D2 versus 582. A kind of approach that doesn't convince me so much, I must say. It could be – after all he is working on the correlations, of course, and one should look for, but sometimes they could be more or less…–

ES: We are far away from that kind of German pathology in doing that kind of research –

AC: I have never really heard him talk about Einheitspsychose

ES: Well he has used the term in print, and I think he uses the term unitary psychoses as well since most people wouldn't know what Einheitspsychose was. But no, he talks about unitary psychosis.

AC: That seems to be a dangerous thing to go into, because that would be to try to – there is a kind of a statement that we are dealing with, that you could sort out a homogeneous group.

ES: Well, psychose is psychoe

AC: Oh, I see, it's rather the opposite. Well, I mean, if you say it like that, that psychosis – that we could agree on. You just define which criteria are needed in order to say this fellow is psychotic. Alright. But what really does he mean? This is a new thing to me, that Einheitspsychose. What really does it mean?

ES: It means there is one single psychotic process. It doesn't matter whether it's in the context of depressive illness or non-depressive illness.

AC: Well, that doesn't seem likely. In view of how the brain looks, and all the circuitries that we have in the brain, that a certain phenomenon such as psychosis always should rest on one and the same basis, you have to define this basis very vaguely and generally.

ES: I guess I realize that's a bit of a leap.

DH: How about a slight different variation on this one: Of the people in the field, who are the major psychiatrists who you think <u>are</u> speaking the right language? Are there people

whose views you felt are better in terms of the neurobiology or the drug development that you bring to the picture?

AC: Well, of course I am biased, because the clinician whom I talked much to is Carol Tamminga, so my feeling is that her view on this is attractive and rather similar to what I think. So when she is studying the brain in schizophrenia she is almost entirely looking at regional differences in changes in activity and there are certain areas that then show up, such as the gyrus cinguli and so forth. She has some ideas about how the different circuitries in the extended amygdala – it's another concept of Leonardheimer, all these nuclei and how they interact subcortically, and of course the striatum – but I think she has a rather, it's not very precise. She certainly believes very much in the limbic system being involved somehow. One cannot really get very far at this time to define what psychosis is. You have the phenomena of course, added up, they build up to – alright, we say this is psychosis. You can see certain changes in the brain that perhaps most people would agree on, dealing with certain especially limbic parts. I haven't talked so much in depth with clinicians. I think some of the Germans seem to me also to be reasonable such as Hanns Hippius, a humble approach or opinion. I think one has to be very humble in trying to come up with any statements about what psychosis is. You have the phenomenon, and you can describe certain changes in the brain in imaging, and certain of course gross anatomical changes which I am not so much impressed by. That's about it.

ES: You mentioned Carol Tamminga as one scholar whose work you admire. In Europe you mentioned Hippius in Germany – are there other European psychiatrists whose work you admire?

AC: Well of course some are specializing, you have such a person as Heinz Häfner, but he is now retired., like Hippius. He is very much involved in the early stages and in the early symptomatology – how the disease develops in the early stage. A lot of epidemiological descriptive data – probably a good work I think.

ES: Ok, he's certainly a well-known name. How about Jules Angst?

AC: Oh yes, but he is very much of course in depression, and not so much in psychosis.

ES: Ok, I see what you mean. We were talking about psychosis, that's true. To expand the discussion to mood disorders, are there other names that –

AC: Of course Angst is very well known. His long term studies on the history of depression are I think very well recognized. He is a very precise and demanding researcher.

DH: But are there people whose views, like Kielholz's views, seem to map onto the things that you were doing? Do you think that there any people out there whose views– that maybe aren't being heard at the moment – that seem to be more suitable to you for the kind of things that you are doing?

AC: That's an interesting question, yes. I had the feeling that people would not have the courage anymore to do what he was doing. Kielholz, he stood up, and he had his views, and he could do that more readily at his time. Now with all that has come in terms of perhaps some kind of science, or perhaps pseudo-science, rather, with all these DSM, with all the numbers after it

DH: If you don't have a number, you can't talk anymore (laughter)

AC: I think that is probably a very good thing to have, in order to have a good description of the population of patients that you have. On the other hand I think it's kind of dangerous because it's not at all scientific. To me it seems to be – let's take a very great example of this kind of approach. Linneaus when he described all these plants and their sexual system, that was an entirely descriptive system – it had nothing to do with biology or the evolution. From that point of view it was poor. But it was a description that made it possible by means of a certain procedure to define what kind of a species this was. But otherwise it was useless.

ES: Well, this is a good description of DSM.

AC: I think so. In a way, a hindrance – there could be people like Kielholz who would like to stand up and give his subjective views on the whole panorama, but that is not considered to be science. Kielholz – that kind of people, they don't exist anymore, do they? I'm not sure, and that is a pity.

ES: Well, Don Klein.

AC: What I think is that many good psychiatrists, in their actual practice, I think it is quite possible they are in fact like Kielholz. But I don't think they like to stand up and say this. Because in a way the Kielholz approach in actual practice is like what you are doing in the kitchen – try to add a little bit of this and that, taste it and see if it's a good taste. In other words, to have this *fingerspitzgefuhl* [sic], so I guess that there are very good clinicians who can really do this. Some people say this is polypharmacy, that's no good, but after all the drugs are just as different as the different spices, aren't they? So just as you do with different spices and compose something using different spices, maybe that is what the clinicians actually do. But I don't think they like to talk about it, because it's not scientific at all.

ES: Well, in American psychiatry this kind of polypsychiatry is making a big comeback now using combo-therapy and combo-treatments, even though they aren't supposed to. The official organs still frown on this and believe in single agent treatments, but out there in the trenches there has been a big revival in combos. Do you have an opinion on this?

AC: I think one of the real pushes in the US and here has been schizophrenia and cognition. In that I think they have had an impact and that even the FDA listened to them, this is the matrix organization. What they say that is something that I am not sure if it is necessarily absolutely true, but that the concept as I understand it, is that for the treatment of psychosis you need a certain pharmacological mechanism dealing with dopamine, and most people then say add serotonin. But this is a treatment of psychosis, but not of

schizophrenic patients who have a problem with a cognition, and that is a different mechanism. Therefore you must look for drugs that you could use as add-on drugs to the anti-psychotics and that will lead to something very important because the general feeling is that the problems with cognition are enormously important in schizophrenic patients for the patient really to be able to be in society and live as a free person in society.

ES: From the viewpoint of drug development, does it have any sense to think of developing drugs to be used in combos with other existing agents?

AC I think so. It is not only the matrix group, they also have something called the TURN, which is actually supported by NIMH. What they say is that if you can come up with a molecule – well there is a reasonable clinical background to state that this could be good for improving cognition and could be combined with conventional antipsychotic treatment. They would even support clinical studies, with a lot of money actually. That's a program that's quite interesting. It's quite possible that it could be successful, even if I am coming back of course to the stabilizers. What I believe is a stabilizer could have not only an antipsychotic action but also have cognitive action.

ES: Stabilizers were introduced as single agent treatments, were they not?

AC: Yes. Single treatments such as ACR-16 and OSU-6162 -- and actually there are cases, that's a good example really, of coming back now to heterogeneity of the populations. In one of the ACR studies for example, which was actually ACR 16, the biggest one in schizophrenia – which was not very big, maybe altogether some 20 patients – what they found – and that was a placebo control – was that half of those patients who received active drug didn't respond at all. The other half had a very clear cut response. In one of them there is an interview by a very clever, very experienced psychiatrist, Leif Hinstrom, you probably know of his name, where he interviews this patient. That is enormously interesting, because this was a patient who really could describe things. So he describes such things as: Before treatment he had actually a part-time job and he could drive a car, but he had lots of problems when he was driving the car if he was feeling somebody was

behind him or after him, also there was a cousin of his who was talking to him, that was very unpleasant, and when he came to job the people there they looked rather hostile. On treatment, well, he didn't care that much about these guys, he didn't hear this cousin anymore. Then he said, "look, when I come to the job, they look so kind and friendly, maybe it's me who has changed!" And also he said, "I think I'm well now."

DH: Do you have a transcript of this?

AC I have it in Swedish. That may have been translated into English.

ES: Was this with ACR 16?

AC: That's ACR 16, yes.

ES: What an interesting story.

DH: When you talk about that, and when you talk about the first clinical work you did with minus-triple-P, it's easy to see from here that these were key moments for you. In the whole stabilizer story, what are the key moments that stand out for you? Forget the theory of the thing, but what are the moments that you think about in terms of the people or the event?

AC: I think the first experience was with minus-triple-P and how Carol describes – I also talked to some of these patients. It was that the psychosis came down and the patient felt well. They felt much better than on previous drugs. And also Carol has been very optimistic regarding the cognition enhancing effect. She has been talking about how "we must get back more of this compound, minus-triple-P and do a cognition enhancing study like the one in the TURN project." But we don't have the compound and we don't have the money – maybe we could have it now actually, it could be possible to raise the money to do that. That was very – also to Carol. She was very much impressed by what minus-triple-P was doing.

ES: Who synthesized the compound originally?

AC: That was Astra.

ES: Does Astra still have a supply of it, or is it all gone?

AC: No, no, we managed to get the last milligram of it.

ES: Oh, how exasperating. You would think that Astra would respond to entreaties from you and Carol to produce some more for further trials.

AC: No, I don't think so. We would have to raise the money in different ways. Of course there is in the US the possibility to get federal money for the synthesis of compounds that could be scientifically interesting, and potential drugs. So that is one possibility. Otherwise one could – we have some money now in our funds, and that would be another way. But of course at this time we are very much concentrating on OSU-6162, because that will be number one for us: To get it back from Pfizer, and also to have our relations with Neurosearch settled in such a way as to allow us to do studies. Maybe they will also take part in these studies, and then of course then Carol Tamminga will come in again. So that it will be number one. Because with the experience – I can tell you another story, these are anecdotes

DH: These are the key things?

AC: Yes, because actually, the most striking effects of these drugs do not show up in the ratings. You would have to look at the patient and see how they behave. So this is a story from the OSU study. I think it was three patients. They came for a pre-trial interview to settle their status. They were coming at the same time and were sitting on the bench or maybe on chairs in a group. They didn't talk to each other, they were just sitting there, one after the other. After maybe three weeks of the drug, the same patients

came for another interview, and then they talked to each other. One got up and asked "would you like a cup of coffee?" These things do not show up in any ratings, but it's a very dramatic change. With coming back to ACL-690 the principal investigator, Sven Nyberg, he describes one patient who actually got a job while on the drug. He could stay on the job, had been on this job for a long time. So there was a very dramatic change with this person. There are things that easily can be discarded when you look upon it from a statistical point of view – "you see, here is nothing" – but at the time there were very dramatic things happening.

ES: It's a beautiful illustration of the importance of psychopathology.

DH: I don't know if it's psychopathology, I think it's probably looking at things. The problem with ranking scales is: We take you out of your group and put you in a room with me, and we are just looking at particular bits of behavior; I miss the larger picture.

ES: But classical psychopathology is looking at the detailed observation of the patient.

DH: Phenomenology more – it's not – are they deluded? Maybe they are, but now they're making tea and coffee for each other.

AC: I think this is semantic problem, whether the term is phenomenology or psychopathology, because they're pretty close to each other.

DH: Looking at the patient.

AC: Another thing is that in the psychosis scales, I am sure they have been designed knowing about the response to Haldol. So that became rather obvious with M-100907, a 582A receptor antagonist.

DH: Like ketanserin, it would be that kind of thing

AC: Yes, but it's one step further, because ketanserin was both A and C – 582A and 582C – this compound was 582A and hardly C at all. That was done, and of course they had the Haldol scale, if we can call it that – and it turned out to have an antipsychotic action, they concluded, but it was not as strong as Haldol. Of course it was not, because the scale was designed to pick up Haldol.

DH: Of course. That was M-what?

AC: M-100907, and that was the company Aventis, which is now Sanofi-Aventis. We had collaboration with them for many, many years but then it had a very different name. I have almost forgotten the name of it – Marion Merrill Dow was the name, when we started the collaboration, and then it changed names several times, with all the takeovers, mergers, and so forth.

ES: Just to talk about things German for one more second. Are you familiar with the whole diagnostic scheme of Karl Leonhard? Does this even ring a bell?

AC: Not much, no. Can you tell me a bit about it?

ES: Leonhard was the professor of psychiatry in Ehrfurt and then at the Charité in East Berlin. He was a student of Karl Kleist's, and he came up with what is actually quite a complicated nosology involving systematic versus non-systematic psychoses. It was Leonhard who first distinguished between unipolar depression and bipolar depression, for example – although nobody knows this except David –

AC: In Sweden, the man that pioneered that was Perris.

DH: Yes, Carlo Perris. But he took his ideas from Leonhard.

AC: But of course we never learned about that in Sweden.

ES: Jules Angst was a student of Leonhard's. So was Frank Fish. So Leonhard has had selective but considerable influence. But what I wanted to know was your views, but since he's not a familiar figure, then the question is sort of idle.

Could we talk about DSM for a second? This must have impinged on your own research to some extent, the use of DSM diagnoses that the FDA generally insists on. Do you have some general thoughts on DSM?

AC: Well, we talked about it, and I gave my opinion about it, that it's a useful way – it's like the Linneaus sexual system. It's useful in actual practice, but there is no depth in it. It's just a description of all these various symptoms, and how constellations can end up in the conclusion of a diagnosis, I guess. I must admit I have not done any detailed examination of the DSM because to me it looks not at all attractive. It's not science, this. So it's probably useful for different clinicians to communicate such as to have an idea about what kind of patients either one of them has.

ES: Some people are critical of DSM because it leaves out biological tests of any kind, and also because it's quite indifferent to family history and genetics. Do you have any thoughts on that?

AC: Somebody told me that in the last edition, version of DSM they have taken into consideration how drugs act in a rather – which they probably did all that before, but say deliberately more – I don't know if that is true, that there is a little bit of that included in the latest version.

ES: David, do you know about that?

DH: I don't know.

AC: Somebody said that.

ES: You mean, distinguishing among clinical entities on the basis of drug response?

DH: Would they be thinking about it for DSM V?

ES: I can't think of any distinction in IV that involves drug response.

AC: I just heard it, some clinician saying that. I didn't ask about in what respect it showed up

ES: The diagnosis bipolar disorder is virtually epidemic now in the United States. Probably that's the case here in Sweden too. What do you think about bipolar disorder versus unipolar disorder, or do you see these as fundamentally different?

AC: I doubt it very much. How can you be sure, because all of the sudden a unipolar patient after maybe 20 years, all of a sudden becomes bipolar. If that can happen, isn't that just more or less how severe – I mean, bipolars are more severely ill, aren't they, than unipolars?

ES: I'm not sure that that's true.

AC: Maybe not.

ES: I think if you are going to accept bipolar illness as a separate illness, then you have to say that the depression of bipolar depression is different from the depression of unipolar depression. Otherwise all you've got is unipolar depression plus the occasional episode of mania, which you could say is really a different disease. So is the depression of bipolar illness really more serious than the depression of unipolar illness? I don't think there's really any evidence for that.

AC: Oh, I see. Maybe you are right, but I have gotten the impression that if you look at some very seriously ill patients that they are more likely to be bipolar than unipolar – but maybe not, I'm not sure.

ES: If we are dealing with the category of melancholia, melancholia and worse, I don't think there's a difference. That's my own view, but David may have another opinion.

DH: I think we should get back to Arvid. (laughter).
You talked about some high points in the development of antipsychotics and antidepressants. What are the low points that come to mind? The points where you thought to yourself "oh, it's not worth the effort – these people in Astra," or wherever?

AC: I have encountered so many times Big Pharma coming to me saying "we must stop it, it's not worthwhile." And that never turned me down, because I believed in this, so I just went on. For example, in Astra I gave back the minus-triple-P and I turned to Upjohn and they took it on for a while, and then they said no. But we believed in it all the time. Of course one of the reasons is as I said, the problem that somebody like me has with Big Pharma is the NIH problem: "not invented here." It's a very serious problem, because you are always with a drug in the phase of development, all the time there are doubts, reasonable doubts, maybe this is going to fail. And then you always have the difference between your drug and drugs that are in development and that originate with the drug company itself. And then of course the NIH impact is enormous. First of all those bench people who are very close to the thing and actually have been perhaps involved in the very early development of a molecule, these molecules are their babies, and they would hate to have my molecule coming in instead of theirs. Then if you go further up in the hierarchy, they are listening more than at the lower step, but still they have their information from the bench people. In addition, of course, they know that if two drugs – one from the outside and the other from the inside – look about the same in terms of uncertainty of being promising, of course you have from an economic point of view you have a drug where they will have to pay royalty – my drug – but the other one is theirs. Everything speaks against somebody coming from the outside. So that is what has happened all the time. I have been struggling – it was the same thing with the concept of partial agonism, of course. At Astra they really didn't think that was anything. And then at Astra the concept of serotonin uptake inhibition, they really didn't believe so much in it – because when this side effect came, they didn't want to hear about serotonin

anymore. To be outside Big Pharma and be involved in the development of drugs, that is not easy. And yet I must say that I have been more successful that many of the Big Pharmas lately.

DH: Both Ned and I have been wondering at times – there are drugs in the past that have done awfully well, whole drug groups that have then been eclipsed, and we don't know why pharmaceutical companies don't go back to them, like the amphetamines and the barbiturates. You have to figure there are drug actions in there that possibly deserve to be revisited, and there could even be further drug groups, because people in the 1950s and '60s tried a bunch of different drugs, very much like the barbiturates but weren't barbiturates, very barbiturate-like or amphetamine-like but weren't actually amphetamines. Are there drugs you are aware of, or drug principles that you are aware of, that perhaps we should revisit – and why don't we? Is it this NIH syndrome?

AC: Not necessarily. If they develop a new molecule that they have full patent-protection for, then the NIH problem is not there – but of course, if you take the word 'barbiturate' then you also have to consider the marketing people, and they would say that would be terrible to try. Because you had the barbiturates, and after that you had the barbiturate-free drugs. And then to come back to the barbiturates? From another point of view, maybe if you change the – I mean, the barbiturates were very extensively done in terms of synthesizing the variants.

ES: I don't understand that

AC: They varied the structure so much, so I think that it could be…

DH: It's been mined out

AC: …. and also if you look at it from a patent point of view, it may not be possible really, to have anything where you are not going to have a patent problem because there are so many molecules they could bar something. But of course you could start out from the

barbiturate molecule, and then you would have to do something rather drastic to the molecule so that it's not going to be a barbiturate anymore.

DH: But there are a whole bunch of drug groups from the 1950s and 1960s – prophenadiols, phenyls, glyconadols, hydergine, and so on

ES: Dicarbamates

AC: If you say hydergine, that is also an area, these ergolines, they have been really done. Well, of course, you can depart from the ergolines, such as the drug that actually we were involved in for patent liability, the GSK compound which could be looked upon as a variation of an ergoline.

ES: Peroxydine?

AC: No, no – the names of all these drugs – oh, it's used in the treatment of Parkinsonism, and it has an ergoline-like structure but it has departed from it, so it's really not an ergoline anymore That was part of this patent issue – whether it wasn't after all an ergoline – and it was not

ES: I am not familiar with this term. An ergoline?

AC: Ergoline – it is a general structure with an indole in it. You have a six-membered ring and then an indole and then you have certain substituents on the ring system, and that will give you an ergoline. They have been so – LSD is one. A lot of the antiparkinsonian drugs are ergolines.

ES: Oh, an ergot derivative, I see. I understand.

AC: Hydergine is an example. Following hydergine, you have this enormous number of molecules that the drug companies have been doing. Part of the problem here one cannot

disregard is the patent issue. You have to do it very carefully to look through carefully which compounds are not known, and could not be claimed to be too similar to what is already known. It's not easy.

DH: I've probably underestimated how much some of the big drug companies have gone and patented hundreds and thousands of the molecules.

ES: I'm sure that's true, but these patents all expire in 20 years time, and so the older patents will now be inactive.

AC: The patents are inactive but the compounds are known, so that is the problem. It's not the patent itself. It's the fact that the compound is known. That's something called prior alt. You always have to look at prior alt. Do you have a molecule that is a new molecule, and it is sufficiently different from the known molecules. And then in addition it must have some level of innovation that is clear-cut. So that could probably be part of the problem, of a certain area reaching saturation and being left. It's not only the aspect of not liking the barbiturates anymore, but that is part of it.

ES: That would be theoretically possible, but in fact I don't think that's why the barbiturates were left. They were left because people were very concerned about suicide in overdose, because they were otherwise such effective drugs.

AC: Absolutely! But I think what David has in mind here is that one would modify the molecules to get rid of all that aspect; and also there was very much abuse of these drugs as well.

DH: The minus-triple-P story really goes back 100 years, and more, to apomorphine and drugs like that. Are there older drugs which contain ways forward that we're just not looking at?

AC: One could say that when I managed to have a group of medicinal chemists – actually the first one was only one person – we started out with apomorphine. The first idea was very simple. It was to try to modify the molecule in such a way as to increase its oral availability. So we tried to bar the OH groups. The OH groups are necessary, but maybe you could find some protection on them, such as too late after it has gotten into the body to get rid of that, and then you have apomorphine. In other words, you are working for a pro-drug – that didn't bring us very far. Then the next step was to modify the molecule. That goal was when I got more medicinal chemists, more clever medicinal chemists into it – then the goal was to have a drug starting out from apomorphine and then have a better oral availability, but not that much of emetic action. It was that project that brought us to minus-triple-P. So it became something else – well, not entirely different, but still, sufficiently different to make it worthwhile

DH: Can you think of any leads other than just the apomorphine lead?

AC: Yes. But that kind of approach that we had, of course many others had at that time. So therefore in the apomorphine area, you again have I think reached a very high degree of saturation in terms of structures that are patentable and still have those properties of apomorphine.

ES: How about some other historic compound?

AC: I am sure there are such things, but …

ES: Choral hydrate?

AC: Yes, well, possibly, but that is such a simple molecule. Many of these things have been carefully done, because chloral hydrate was such an important drug at one time, so I'm sure drug companies have been working on that to try to – maybe not.

ES: There seems to be such a mania for innovation that going back to these historic drugs and giving them a second glance or synthesizing congeners of them, I'm not sure that this has been widely done.

AC: Possibly, yes.

DH: The German industry between the wars probably did an awful lot of these things, though. They were the first ones to gear up really large scale.

AC: It's impossible to know about any of these things unless you go into the patent literature and see what is there. If those who tried to develop something starting out with chloral hydrate didn't have any success at all, that is not the same thing as to say they didn't try. There could have been huge number of molecules that are there already, but that it was not possible to bring forward. But I am sure there are many, many molecules that have been – especially more recently – have been discarded because of the poor screening systems we have now. It's a terrible thing, also from that point of view, this high throughput screening, it's really a way of destroying molecules because you put them through a useless selection system, and then you destroy them because they are known compounds. They are in patent, and that's it. And some of them could be the most marvelous drugs! It's more or less similar to what we are doing to our environment today. We are destroying our environment by producing so much useless stuff. So that's what it is done also in the pharmaceutical industry.

ES: We talked about the barbiturates. Did you ever have any experience with the amphetamines?

AC: Well I had taken it once, maybe 16 or 17 years old. It was a small dose; I didn't feel anything. Otherwise of course in those days when I was a youngster, it was very popular among students for when they were doing before their exams in order to stay awake which was of course not at all useful. And also at parties. I still remember, phenadrine was one of the names – phenadrine is just another name for amphetamine – it was a party

and the spirit was not terribly high. Then one guy came in and said "anyone here have a tablet of phenadrine?" "Yes, I have." "Why don't you take it?" Because to elevate the spirit a little bit, so that was used. This is my experience. In our preclinical pharmacology, amphetamine, and also methamphetamine and dexamphetamine, these are very important drugs, they are key drugs in our science, actually. As one of the best in order to produce an increased release of dopamine especially. But then you have some variants that also get into serotonin and cause release of serotonin. These are very important tools, actually. They are part of, I would say, if we have new molecules, they will be combined with amphetamine to see how they interact with amphetamine.

ES: The whole subject of suicide in antidepressants is of considerable interest, certainly to David, and also to myself. Do you have any thoughts on this?

AC: My general thinking about it is that, first of all I have been impressed by the statistics on Sweden, dealing with the SSRIs, if we start with them. The suicide rate has gone down by 25%, that has coincided with the market introducing these SSRIs on the market. I think a lot of psychiatrists in Sweden are convinced that there is a causal connection between these two phenomena.

ES: Is there a subgroup for which the relationship goes the other way?

AC: Yes, I think so.

ES: Are there some SSRIs that induce suicidality?

AC: Yes, I think so. I don't think that is anything new, really, in principle, because that was also said at the outset about the tricyclics.

ES: That they induced suicidality?

AC: Oh sure, absolutely! It was said, that was agreed upon. I don't know how much serious literature there is on this, but certainly psychiatrists in general agreed that there is a stage maybe following two or three weeks after starting tricyclic that what they call the inhibition is lifted but still the mood is low. So therefore they start to do things that they wouldn't have done otherwise. But they keep the low mood, so therefore there is a risk of suicide. That was agreed upon by everybody. It was considered to be a fact. I don't know how the scientific literature looks on it. But everybody agreed on this, so I believe in it. Therefore, why shouldn't the same thing happen with SSRIs, even though SSRIs are perhaps not quite as anti-inhibition as some of the tricyclics. Those are more on the noradrenaline side in Kielholz. The secondary amines might perhaps be more dangerous, so from that point of view SSRIs might be less dangerous. But they could very well have it. Actually, one of my old collaborators, going back seven decades, a cofounder of causal research, he had depression episodes, and the next to last episode, he got on an SSRI and responded nicely. Then about a little more than a year later he got it back because he stopped treatment. So he came back, and then he started on SSRIs, and sure enough after about three weeks he committed suicide. He took potassium cyanide.

ES: I am asking about a slightly different phenomenon. We have been talking about a kind of window of suicide in people who are already very ill, and as they become animated again, as they climb up out of the trench, there is a kind of window in which they have more energy but their mood is still the same, ok? What I'm asking about is a little bit different, and it's really David who should be asking the question, because he's now associated with this in the literature. It's for patients who maybe are not so ill, who don't have any suicidal ideation at all, but have just a reactive depression, let's say, who take an SSRI and become acutely suicidal, whereas they weren't at all before. There does seem to be a subpopulation that this description corresponds to. Although this is very controversial, and I'm wondering if you have any thoughts on this.

AC: It wouldn't be at all surprising if this kind of thing happens because the serotonergic system is very complicated. You have pathways of serotonin in the brain that I think are functionally opposite to each other. It's quite possible that there could be individuals

where the baselines of the different serotonergic path lines are different from most people and where this kind of thing happens. That wouldn't be at all unreasonable.

ES: Is akathisia in any of the serotonergic pathways that you are familiar with?

AC: That could be, yes, one cannot exclude serotonin there, even though akathisia is mainly connected with dopamine. For example, I remember Herb Meltzer, in one of his first studies with Prozac, it so happened that a couple of them had Parkinson symptoms, and akathisia is part of the Parkinson's symptom complex. That's another kind of thing that can show up, yes; in some, rather few patients, I would say. We are very different even as normals, so it's quite possible that if you give this kind of drug – I think we are so different. We know, for example, how we respond to alcohol – in normal people there is an enormous variation in the way we respond to alcohol. Some people get very high, others get sleepy. We have some ideas about this, we say that those that are strong in dopamine, they get high, and those who are weak in dopamine but rather strong in GABA, they go to bed.

Actually, we did a study on alcohol after giving alpha-methotyrosine, such as to reduce the synthesis of dopamine. And we needed another blind. We had parties in the department, and we had the conventional thing in Sweden, you eat herring, have the Schnapps, and we would take a fairly big amount in 45 minutes, of alcohol. The alcohol was not double-blind, I can tell you, but the alpha-methyltyrosine was. There were some sober observers in the party. I was also in there. The response was very different in different people. But certainly some individuals and I belong to those – when I was on placebo, plus alcohol, that was fine. When I was on alpha-methyltyrosine I could hardly, I could notice weakly, an effect on alpha-methyltyrosine which was taken for about 24 hours before. For example it was easier to go to sleep the day before the party, because I had already started the first dose before going to sleep, the day before. But when I was on alpha-methyltyrosine plus alcohol, we could feel in beginning, the first 15 minutes or so, "well, it's coming, it's going to be ok." But then it started. Several of us left the party and tried to find a place where one could lie down. But that was in some, but not in

others. Others went on happily drinking, some of them didn't even obey the feeling of dosage so they got very high, and one of them got really depressed.

DH: Healthy volunteers and clinical scientists are a lot less likely to stick to the protocol than patients.

AC: Yes, we are so different, and I think it's very hard to – if there are such observations, some doctors have had it, others have not had it, and even if those doctors who have seen it are in the minority, one couldn't disregard it. It's quite possible. You cannot predict how any one particular individual is going to respond to a certain drug.

ES: This is true and very controversial within psychiatry, this question of the SSRIs inducing suicidality. Maybe none of this controversy has reached Sweden?

DH: Oh, it has it reached Sweden, alright.

AC: Yes, it has. What I think is not appreciated at all is the very likely possibility that you can have a drug that can reduce the suicide rate in depressed people, and yet this drug could induce suicidal behavior. There's nothing special about that; it's quite possible. Something of course that's very important to know about and be aware of.

ES: Whether this side effect should appear as a warning on the label has been extremely controversial.

AC: I think it should. If there are enough – even if it's a minority of doctors that claim to have that experience, I think it should be in.

ES: Ok. Let's talk for a moment about Joe Schildkraut and the catecholamine hypothesis. Did you know him personally?

AC: Yes – I didn't really know him, but I met him at several meetings.

ES: In retrospect, what is your view of the impact of catecholamine hypothesis, or its accuracy for that matter?

AC: That was the catecholamine hypothesis of …

ES: Depression. Depression was caused basically by a deficiency of norepinephrine.

DH: When the hypothesis came out in the mid-sixties, what was your view of it then, as opposed to what your view of it now would be?

AC: That's an interesting question. If I remember correctly, I was invited to comment on that first article.

DH: Oh really?! By the journal? Oh, were you?

AC: By the editor, I think I did. You can find it. I think I did it, actually. At that time I was certainly not enthusiastically for it, but neither did I reject it. I was probably wrong in many of my comments.

ES This was 40 years ago, it was a long time ago.

DH: The reason that you wouldn't have been awfully enthusiastic about it was, did it just seem too simple?

AC: Maybe I have been a little bit against – part of the evidence that he had was pharmacological, wasn't it? I don't remember exactly. I guess at that time in the US especially, the tricyclics were thought to be mainly acting on noradrenaline, not on serotonin. I have always been against extrapolating from a drug effect to an hypothesis dealing with pathogenesis. For example, when I had been involved with that 1963 paper, where we proposed these antipsychotics acted on dopamine and noradrenaline receptors

and perhaps also serotonin receptors, but I wouldn't dare from this to propose that there would be an aberration in the function of either of these amines as an important pathogenetic factor. These are different things; they should be kept apart. If you take a drug like curare, and you get paralyzed, you wouldn't say that polio is located at the same place to block the same peripheral transfer of signaling from the motor nerve to the muscle. And yet they get paralyzed; they have the same endpoint. There must be more to it before you can really come up with an hypothesis of pathogenesis. I guess probably I had that kind of point of view in my comment.

ES: The norepinephrine hypothesis seems to have had a significant impact on drug development, though.

AC: Yes.

ES: Did this influence your thinking at all about drug development in the '60s and '70s? The drugs you developed went along the serotonin pathway, which is very different. But before that time, was norepinephrine prominent in your own thinking?

AC: From the point of view of pathogenesis – or of drug development?

ES: Yes, drug development.

AC: I don't know when I started to look at Kielholz, but that was certainly in the late '60s we had a picture of Kielholz' scheme and we had our own data, and that certainly did not favor noradrenaline as the most important factor.

ES: Did you think, "aha, the catecholamine hypothesis is overturned, Shildkraut was wrong," or was that just off your radar?

AC: I never was a strong believer in Schildkraut anyway, for the reasons I mentioned. I am not sure if I even had Schildkraut in mind when we were into this in the late '60s. I don't remember what year Schildkraut –

ES: '65.

AC: Well, I was never really impressed by this hypothesis, one can say. It was of course one possibility, and it still – noradrenaline could very well be an important factor in principle. But there are so many others, presumably.

ES: Could we just step back a pace, and talk about Swedish psychiatry and Swedish psychopharmacology in general. Are there important ways in which Sweden has gone in a different direction than western psychiatry and western psychopharmacology as a whole?

AC: I don't think so. I would guess that before the Second World War we were perhaps more – I am sure – psychiatrists were very much influenced by continental psychiatry, German and Swiss. Then the Anglo-Saxon countries became more influential after the Second World War. But I doubt that there was anything special about Sweden, otherwise. We had the controversy between of course the psychotherapists and those people who are enthusiastic about the drugs. That was, if we compare with the U.S., in the U.S., when would you say the real shift came such as to become those who believed in drug treatment and started to pay less attention to Freud and psychotherapy.

ES: In the trenches, I think it was the 1970s.

AC: That did not happen in Sweden. I think in Sweden the psychotherapists have remained very powerful and are still powerful. So from that point of view, Swedish psychiatry has not been able to really show any impact or strength at all. They have not had a great reputation, and there is still a great problem with Swedish psychiatry in that context. We have had all these terrible things, you know, with the foreign minister, Anna Lind, getting

murdered, and a couple of children getting killed by a psychotic patient who just happened to be there, didn't know anything about this child, and then killed the child. It happened the last time only maybe a month ago, and similar things had happened before. One person who drove in Stockholm in the Gamlastad, the old city, a car right into people, killed several people. These kind of things are happening, and then when you try to find out about these people, they are psychotic and have tried to get help from the healthcare and have been rejected. They have no time, they are asked to go somewhere else. Swedish psychiatry is in a very poor condition I would say.

ES: If I had asked you the question about Swedish psychopharmacology rather than psychiatry, would your answer have been any different?

AC: Yes. I think as a science Swedish psychopharmacology has been doing well. But perhaps not been as strong as it used to be, but of course I am biased.

ES: I am struck that over the last two days that many of the names that have come up in our discussion in scientific matter have been Swedish names, and it's not just because they are personal friends of yours. Why aren't there any Portuguese names in this story? Why does this story have so many Swedish names in it?

AC: I think there is some kind of tradition, I guess; but of course we had von Euler, who discovered norepinephrine as being in the peripheral, sympathetic system. But he was not really building a school. He was the kind of person who, when one of his closest collaborators became professor at the veterinary school or something, and they had been working closely on norepinephrine together, he said "from now on, when you go to the veterinary school, you stop work on norepinephrine. That's mine, that's my work." So he didn't form a school, as you can understand. (Laughter) School-building I don't think is – well, of course Sweden has a high, if you compare with Portugal, scientific standard generally was higher, more than Portugal. So that's one thing. Maybe these things could also be looked upon a little bit as stochastic things. It just so happens. How could we predict, even if we looked backwards, that we look at one place – let's say Brody's place

– that that would become such an important lab? It simply so happened that a person that had this opportunity, and there was this level of knowledge where he could have an input. There was something he could fill that was a vacuum, and he could go there and fill it because of his knowledge and because of his talent. So these are things that I think one shouldn't try to analyze too much of course because it's too complicated. When something scientific happens, it should be looked upon as not just …

ES: I think there are national moments of genius. Germany experienced one of those in the late nineteenth and early twentieth centuries, I believe. I don't think that was a stochastic moment.

AC: What do you think then?

ES: It arose from the particular structure of the German universities – the fact that you had 23 German-speaking universities, each of which was well-funded and competitive against the others, in contrast to France, where there was only one university. There is a system of national honors in Germany, Herr Hofrat, for example, that is also conducive to scientific excellence. Those are two national factors, for example, that distinguish the Germans from other countries.

AC: Yes, I am sure you are right. The opportunity for a breakthrough depends very much on the kind of thing you are mentioning. If you have one country with a large number of universities there is a high level, of course, it increases very much the likelihood of a breakthrough.

ES: Were there comparable structural factors here in Sweden, or in Denmark? We can expand the discussion a little bit to Scandinavia, because there have been lots of important Danish accomplishments, too.

AC: Well, I guess that our school system and our universities were high-level. There is no doubt about that – comparable to, I think, Germany.

ES: Before the war, because they aren't high-level today, really.

AC: I am thinking about before the war, yes. This of course is a very important question. What Leeds did is: how should we optimize the possibility for a breakthrough of some kind? And now in Sweden – and I think it's true of many other countries, in the U.S. I'm not sure, and in Britain I'm not sure either – but certainly in Sweden, there are two things that have happened in the Swedish university and school system that are very unfortunate. One of them is that there have been erected a number of small universities, and this has been simply that it's part of the regional politics to support all regions. It has nothing to do with an ambition to improve the level of knowledge, at the higher kind of level. They rather favor the lower level all over the country. If you don't add funds to the same extent, you will reduce the funding for the old universities, and therefore reduce the standards.

ES: National mediocrity. This has happened in Germany; it's one of the big problems in Germany.

AC: Yes. In addition to that, they have done one more thing in combination with the other thing which is very unfortunate. That is to go for the so-called centers of excellence, which I think is a serious mistake, for the very reason that when we think about breakthroughs, they should be looked upon as stochastic phenomena. You are right when you say that the general level of opportunity should be there, but if it happens in Heidelberg or in Berlin or wherever in Germany, you cannot tell beforehand. Because these I look upon as stochastic phenomena, the particular place where the breakthrough will be. Therefore, if you concentrate your resources to a few centers of excellence, it is therefore through statistical reasons very unlikely that these will be the ones where this is going to happen, the breakthrough kind of thing. But what you do by this kind of policy is that you reduce the possibility of a breakthrough anywhere. There is not a lot more of a chance for a breakthrough in a so-called center of excellence than anywhere else because the center of excellence is in a certain area, and it's quite possible that the next

breakthrough will be in a different area that is not at all supported. This is a serious mistake. I think Sweden is going in a very bad direction.

DH: It's happened in the U.K. as well, and I think it's a mistake.

ES: That is the end of my questions. David, do you have final questions?

DH: Well, just points that were the highpoints and points that were the low points. Just the stories, the anecdotes.

AC: Low points. Of course, one could think about many different aspects, and let me say perhaps a little bit facetiously used to say is that what people have said about me many, many times is that "what Carlsson did five years ago and before that was okay, but what he's doing now is not so good." That has been the same. I've always been doing something wrong. There is a funny letter, a joke, from Sid Benner, he got the Nobel prize a few years ago. He wrote about how you should be in relation to the wave. It's no good to be in the wave. One should be either before or after. I think what he called the stampeding halls, how something is all the sudden is in, something is fashionable. Most of these waves turn out to be red herrings. There is so much of red herrings around. When the peptides came, then they said, "well, these amines, those are old hat.". Now it's the peptides. And the peptides came, there was a wave, and the peptides went away. And then the amines were still there. That kind of thing I have been through many times. And then molecular biology. "How come you have not started on molecular biology?" Why should I? That kind of thing. Also, there have been things like that, when there was a pharmacology position vacant and to be replaced here in Gothenburg, they said the person to get should be knowledgeable in molecular biology – I mean in a technology that's stupid. Of course I must admit that the successful aspects of my work has been closely linked to new methodology. But it's not necessarily so, and I think one of the best examples where you can make really a breakthrough on the basis of very old technology, that is Isaac Newton. The data that Isaac Newton used to come up with gravitation theory was based on Kepler's laws. Kepler's laws were based entirely on

Tycho Brahe's observations on the planet Mars. That was almost one century – and Tycho Brahe did not use a telescope. He was watching with his naked eye – not only himself, of course, lots of other people helped him – on the island of Hven outside Skåne, and it took more or less a century. So it was observations with the naked eye that were more or less the basis for Newton's gravitation theory. That I think is a good example, that one couldn't place too much emphasis, not a decisive a role, on the methodology – because in this case in was really obsolete data from a methodological point of view that formed the basis. The entire basis of Newton's gravitation theory was Tycho Brahe's observation with the naked eye on the planet of Mars. That I think is very impressive. People are very much exaggerating the role of methodology, in the sense that when a new methodology comes, everybody should start on that. It could be that your problems are not that kind of problems. You must take a different path because with the methods you have, there are still a lot that remains to be done and that could lead to important progress. Many times they have let me know, "this is old hat what you are doing."

DH: If we had your wife here, and not you, and we had asked her what had been the high points and what had been the low points of your career, what would she say?

AC: I can go back then. When I started –

DH: One of the other ways of asking that particular question would be, who does she hate of the people that you know?

AC: That's an interesting question. I have to go far back. My school time was no problem. I came through easily. My first studies when I got into medicine were ok, and when I headed the exam in pharmacology, the professor asked me to join his group. All that came through very smoothly. By the way, this professor is another interesting– I must say – example of what we have already been through, the stochastic aspects. This man, this mentor, was a candidate for the Nobel prize. It had to do with what has to do with tissue respiration, the very the first time that you could take out tissue and put it into the tube, and see that it consumes oxygen. He was very successful there, but then, at a very

young age, he became a professor of pharmacology, and after that he didn't produce anything. He tried certain things, but they didn't come out successfully. So that was the department where I did my work. He was considered to be a failure, more or less. And yet, he was good. I consider him, in retrospect, more than at the time, as having been a very good mentor for me. But he was not considered to be a great scientist, of course. And yet a lot of people defended their theses there and came into good positions of different kinds, professors, doctors, and so forth.

ES: What was his name?

AC: Ahlgren. He is actually mentioned in this. So people really looked down at this Institute. Two major things came out from the people whom he had been teaching. One Nobel prize, that was me. The other one was Alwall, who was one of the few pioneers in the world of the artificial kidney. He is mentioned in the Nobel prize book. His work on the artificial kidney led to the foundation of Gambro, which is a global, major, very successful company in the health care area. So if you compare with the other departments, this department was doing well, really, not badly at all, but doing better than most. That was an institute that was considered – if you think about centers of excellence, I can be sure this institute would never be considered a center of excellence, and yet that shows this stochastic phenomena. It so happened that this man who was a mentor, a very special kind of mentor, and there happened to be a couple of people who could develop under his mentorship, such as to become very successful. It is impossible really to understand how this came about.

So let's come back to the story. He put me on one rather trivial, but not bad, project. I did that and it was a publication, it was conventional pharmacology. Then he wanted me to switch to calcium metabolism because radioactive isotopes and commercially available instruments were there. So I started on calcium metabolites, and that became my thesis. When I had the thesis – and now we're coming to a low point – the great man in Scandinavia in calcium metabolism was a Norwegian, Nicoliasson. So I met him at the meeting and I said "I am going to defend my thesis in the near future. Would you like to become my external opponent?" "Oh, yes." So I sent him the manuscript and he sent it

back, "no, this is no good. I don't want to go to become your external opponent." So then I was lucky enough, there was Sune Bergström, who later got the Nobel prize for his discoveries regarding protoglandins. He used to be a good advisor when I had problems. So I told him about this disaster, and he said "ok, I will read it." So he read it, and he said, "it's ok." So I came through alright. We were rather successful. I had a couple of students who defended theses and later became professors, one in orthopedic surgery, the other in pediatrics. The whole thing came out nicely, and I was recognized by international people a little bit also. And then I applied for a professorship, or associate professorship, whatever you call it, and I didn't get it. The expert committee let me know "what you are doing" – and I got it second hand, of course – "what you are doing is no good for a pharmacologist. This is not centrally located in pharmacology." I was already a pharmacologist, so what could I do?

DH: Which work was this that you were doing that they didn't regard highly? Was this the early amine work?

AC: No, Calcium metabolism. At that time calcium was not considered so important as it became later. Then again, I went to Sune Bergström and said, "look, I must change here because what these guys are going to be my experts the next time I apply for a professorship, so I have to switch. And I want to go to a lab that is a pharmacology lab that is chemically oriented and it should really be at the top level." He had a tremendous net of contacts. So he wrote to a friend of his at the National Institutes of Health, Witkop, a chemist. He handed it over to Udenfriend who in turn handed it over to his boss, Brodie. That's how I came to Brodie. That's how the whole thing started.

ES: So you got to Brody by escaping from calcium metabolism?

AC: Exactly.

ES: Have you ever told this story before?

AC: Oh, yes, indeed. It's in there.

ES: It's a wonderful story.

AC: So that's how all this happened. And just so happened that just a few months before I came they had made this breakthrough discovery researching the depletion of the serotonin store. This was also stochastic; these are stochastic phenomena. I happened to come there, in this atmosphere of organic chemistry, not knowing that much physiology or pharmacology. That's how I could go on. That was a good platform for me to go on, on my own. That was a good thing. Let me see…. The next low, I'm thinking about the next time: The professor of physiology, J. George Carlsson, he would be the one that my wife would hate. He said when I applied for the professorship in Gothenburg here, he tried to become a member of the expert committee, because "now, at last, I should put this little, what would you call it? chicken cock …"

ES: Upstart, I think is the word

AC: "Now I will put him in his place." Fortunately he did not become – that's another stochastic phenomenon. If he had been there I would never have gotten this position here. I would say of course the disaster in London was a kind of disaster, but even though we …

DH: The London meeting which you look back on with pride, really, at the time, you felt quashed?

AC: Yes. For example, when this expert committee, what they told me was right! I should switch to something else. Even though my work in calcium metabolism was not at all bad, that's for sure, but nevertheless, it probably wouldn't have been successful as it now became, because this particular phenomenon at this place was absolutely the perfect place for me to go to. Well, I had a lot of fights here in Gothenburg with the associate professor, but that, of course, was not a major thing. Let me go further on. Well, in a

way, I felt very disappointed when I was sort of squeezed out of the discovery of the histochemistry, in terms of the methodology even though they compensated me by being the first author – even though that was by it being in alphabetical order– of the discovery of these systems in the brain. In a way that was a disappointment, but I didn't feel so bad about that. Let me see, what would my wife – that's a good question, you know, thinking about her.

Of course, lots of things have not gone so smoothly. In a sense, some of the worst disappointments have been in the present century, which I have mentioned to you already. The Institute, the Arvid Carlsson Institute, that became a disaster, and simply a method to use my name for purposes that I didn't like at all. Actually, we haven't been into that, but perhaps I should say a little bit about that. Because in this Arvid Carlsson Institute they focused on stem cells. I started to study that, and they more or less squeezed me out, and also my daughter and her group out of the Institute. Finally it came to an end; it had to be stopped. It was stopped now on the first of January this year. That made me look at the stem cell research, and that is, insofar as the central nervous system, that is a red herring. That is really, I am 100% convinced, nothing will come out of that. Well, something trivial will come out of it. The relationship between the input and what will come out of it is absurd. There is an enormous input into stem cell research, and there are very good data. First of all, if you take Parkinson's disease and the transplantation, there were some promising studies that came from Lund, from Berglund in Lund, and Lindvahl in Lund, and looked very promising – but then the follow-up was in two very careful American studies where they did it actually in a way that when I heard about it first was a bit shocking because they did it double-blind. In other words, they had an equal number of patients, one that got active material, which was now fetal dopaminergic cells transplanted into the striatum, and the other group got, they thought they had it, but they just did a little bit up here and nothing else. They didn't even go through the skull. These studies showed there was no benefit at all. These transplants didn't do anything good. But it caused side effects. It caused dyskinesia, which makes a lot of sense from the point of view of our present knowledge about circuitries and their feedback systems. If you put in cells to replace cells that were located in a different part of the brain because those that were lost were down in the brain stem and now you put

them into the striatum in the terminal area. If that was 20 years ago when the Swedes started on this, that wouldn't look so bad, but with our present knowledge, that looks absolutely stupid. We know how careful these circuitries are, how carefully they are designed in fetal life. These two studies were showing exactly the same thing – no benefit, but side effects. In addition, they showed – which was also very interesting – that was a very strong effect of the sham operation. One of the studies showed that first of all those patients who got through this procedure, many of them had an opinion about whether they were on placebo or on active cells. And what turned out was those who believed they were on active cells, they improved, and they not only improved subjectively, but also objectively they improved. Whereas the other ones – regardless of whether or not they got active material – that didn't matter. What mattered was what they thought they had received. I think that is very striking and interesting. That part of it to me looks so discouraging, and actually both these groups in America, their conclusion was that at the present time is that we cannot continue this kind of treatment. Actually, there were some patients who were still being planned to have treatment, and they stopped it for ethical reasons. That was very clear. Then what do these guys do, who are in this and have invested enormously into it? What they say is "what we are dealing with here is a lack of sufficient materials. The cells that we can get, the fetal cells, is not enough. Therefore we need to grow cells. We start with stem cells, and then we will manipulate the cells such as to make them be able to produce dopamine, and then we will do the same thing, and then we will have enough cells." What is wrong in that reasoning is that apparently the cells were viable, and they did produce dopamine because of this dyskinesia. There was nothing wrong with that, that was not the problem. The problem was, you cannot do this kind of thing. You must put in order for the transplanted neuron to become functionally active, you first of all – of course the neurons should take contact with the subsequent functioning of the relevant neuron – but in addition, it should receive from the cerebral cortex the input such as to bring it into a feedback control system. The whole concept is fundamentally wrong. And yet, they go on with a tremendous success. They still collect enormous amounts of money, draining from others. That is a typical example of a red herring, one of these waves that one should avoid, according to Sid Benner. Very typical. Like before, the peptides; and you

also have gene therapy is another thing that was very big. There is not much left of that now. Of course there may be a few instances of gene therapy, but not much. These are the waves and these are what one has to fight with. I am now a little bit involved. We have a website which is called brainmessenger.com, where all the stem cell story is in and where I give my straightforward opinion. But they go on and they are making new discoveries they say, which are not really good, it's like the emperor's new clothes, actually. All this, I am sure, will become a scandal, finally. I am actively involved in this as a sideline. So that was that. Therefore my wife hates those people from the Arvid Carlsson Institute who did all this bad stuff to me.

DH: We do have the wrong person here to interview, you know that – we should have had your wife here. (Laughter)

AC: And the next one to mention, that will be those people who kicked me out of Carlsson Research. It was the people on the board, but in addition, the man who is now the CEO of NeuroSearch Sweden, Nicholas Waters. I can tell you – as an example to bring in my wife, here – of course from the point of view of economy and also prestige, of course, I was kicked out of the company, then it became sold. I was the second biggest controller or owner of the company, so that means I have become a rich man. Not only myself but also a foundation that I mentioned yesterday that had owned shares. But my wife is not perfectly happy about it., and that is because Nicholas Waters, he has now also become rich, and she hates the idea of him becoming rich.

ES: Who is the largest shareholder in the company?

AC: That was the pension fund. Among the founders, I was at least the biggest owner. Controlling together with my family and my company, Carl Albert, and Maria, who was also one of the founders, controlling over a little bit more than 20%. If the whole thing comes through successfully, it's going to be a lot of money. It's going to be maybe something like, before tax, 160 million Swedish kroner. You divide by 7 to get the dollar. It's a lot of money. But my wife is not perfectly happy; she thinks all the time

about Nicholas Waters because he will also get rich. And also some other guys. He is probably the one – the two people who did the bad things to me in the Arvid Carlsson Institute and Nicholas Waters. They are the three on top. She would probably like to see them dead, I guess. (Laughter) Otherwise I am not so sure about, other things that have been – By the way, I should have said, this fellow, Nicolaisson, the one who sent back my thesis –

DH: Did you ever meet him again?

AC: I think I did. I went up twice to Oslo to talk to him, because that is what Sune Bergström advised me to do, but I couldn't convince him. He was partly right in his criticism, but he was fundamentally wrong, but partly right. Later on, he admitted that had made a discovery regarding Vitamin D. So he even talked about the Carlsson effect of Vitamin D – not so bad! That had to do with Vitamin D having a direct effect on the catabolic aspects of bone growth, in other word, the breakdown. In other words, when the bone grows of course, there must be a breakdown for the bone to keep its shape, of course, and Vitamin D is actually stimulating this.

ES: It stimulates the osteoplasts.

AC: That is correct. That part was also good of course for me, that he changed his mind from that point of view. Well, let me see if there are any other people that my wife would not like so much….

DH: One of the other questions to ask you (and your wife) is that yesterday, over lunch, you painted a very vivid contrast between Hässle as it was when you went in there first to consult and put to them the idea that maybe they wanted to think about an SSRI-type drug, and the pharmaceutical companies now. On the one hand, you had a small group of people, and now you have these huge glass and steel corporations with tens of thousands of people. Are there any other contrasts like that, between how things were during the '60s when it worked, when all of these actions came together and worked quite well, and

now, when things aren't working so well? I guess one of the other contrasts would be, say, the meeting in '65 which seemed to be a place where people actually came to exchange ideas and there was a lot of open kind of debate, and the kinds of meeting that you would get at the CINP these days, which are run completely by the corporations. There is no debate of any sort. Nothing moves forward at the meeting.

AC: Yes, there is of course the balance between pharmaceutical industry and academia has changed dramatically. In those days, Hässle was very small, and we were the ones who had more resources in academia. We had more competence and so on. This switch I think is a general phenomenon, that the pharmaceutical industry has become so much more powerful as an enormous accumulation of financial strength. The additional bad thing is that it has had a negative impact on academia. Very clear, because in academia not so much in the U.S. as in Sweden, the resources given to the individual researcher have come down enormously. If I compare when I was coming back from Brodie's lab, what resources I had in Lund at the time, that was not bad. I had two chemical engineers, one very skillful and experienced lab assistant, and two younger lab assistants, and two Ph.D. students. It was a good group. I was a little bit about 30 years old and I had of course no – in the field I was at that time, I had no printed publications. And now, those people who are in the same position as I was, they could have maybe one lab assistant, possibly. Many of them actually have to apply for funds not only for the lab assistant, but also for their salaries. It's such an enormous change – in the wrong direction. It's very serious.

ES: To get back to CINP for a moment. Today you wouldn't go to CINP to get intellectual stimulation from colleagues, unlike the way it once was. Where would you go today? What international forum would you go to today if you wanted intellectual stimulation and collegial conversations?

AC: CINP, I would at least partly agree with you. I might go to a CINP meeting; it's not all that bad. But if you compare with ACNP meetings, it's at a higher level. ACNP is absolutely worthwhile to go to. These programs are well-planned, and of course

especially when they are in Puerto Rico in San Juan, that adds to it of course in December for a Swede. Nevertheless, the program is good, it's absolutely worthwhile, regardless of having the sun free of charge. My favorite meetings in the past few years have actually been the ACNP meetings in San Juan. Otherwise most of the meetings, apart from that one, the meetings I go to are meetings where I have an invitation to give a talk. But I go to ACNP even if I have no invitation. I would hardly go to CINP if I don't have an invitation. Any more questions?

DH: I think the stories are the key thing, to make the whole thing live. So if you have any more vignettes, they'd be useful.

AC: I will think about that. I am sure there are. I can e-mail to you.

ES: This is why it's so useful for us to have access to your correspondence because the stories are in the correspondence, and they are fresh there.

[discussion on accessing archival materials]

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