Interview with Oleh Hornykiewicz, MD
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Barbara W. Sommer, Interviewer

OH: Oleh Hornykiewicz
BWS: Barbara W. Sommer

Analog Tape 1, Side 1
BWS: Would you give your name please?

OH: My name is Oleh Hornykiewicz.

BWS: And I am Barbara Sommer. I am doing an interview with Dr. Hornykiewicz for The Movement Disorder Society. It is February 9, 2007, and we are in a conference room at the Toronto Western Research Institute at the University of Toronto. Thank you.

OH: I am pleased to meet you. Let us start with the interview.

BWS: Will you tell me a little bit about your background. I know you have written about this. About being born in the Ukraine. Your father was a Catholic Ukrainian priest, as were your grandfathers. Will you describe a little bit about your family prior to moving to Vienna?

OH: As you mentioned, I am the youngest son of three boys born into a priestly family which traditionally was Greek Catholic, Ukrainian, and parish priests. Then, of course, the youngest years I spent in that atmosphere, which was a very warm atmosphere. The family was a very large one. We were three boys at home but I had, altogether, counting all my first [degree] cousins, I had something like 40 of them. I still remember when I was a small boy – I know – those meetings on the long summer vacations, the family meetings for birthdays and saints name day celebrations, it was like a little village – such a gathering of all the family. Some of my cousins, being so much older than I was, they could have been my parents actually. It was a very, very warm feeling and I still – I think that that had also an effect on my attitudes toward life. It made me somehow an optimistic person. I think that I am an optimistic person that always tries to see something

good in the world around me. That is what I would like to say about my background. It is important and I still have very warm feelings about that.

BWS: That optimism must have served you well, because at the age of 13 things changed for you with World War II and the invasion of Poland by Germany. It was a difficult time for many people.

OH: Yes. I think that was kind of good for survival. When I say survival, I mean the mental survival and the attitude that one had during that time. When the war broke out, as you mentioned, I was born in a part of central Europe which was Polish at that time, having been part of the Hapsburg Monarchy before, before the First World War – and when the Second World War broke out, we then moved to Vienna mainly because that part of Poland became a part of the Soviet Union and my father [was immediately dismissed as a college teacher of Catholic doctrine and church history and] lost all means of existence because of that. We moved to Vienna where my father's brother lived permanently. So we had a base. We moved – leaving in order not to be under the rule of Stalin, we moved into a part of Europe, Austria, that was German under the rule of Hitler. [laughs] Of course, my background, that background of also the spiritual attitude that I received because of my family background, it actually protected me from many things. Bad things, I think. I could have become enthusiastic about the new movement, the Hitler movement, and such things.

Maybe you are interested in one little thing. When I came to Vienna with my family, I didn't speak any German. I had to learn it really from scratch. I was sent to school nearly immediately after we arrived in Vienna. My father, he spoke German, he was from the old Austrian times when my birthplace was still under Austrian rule. So he spoke German. But he wanted to, as he said, improve it a little. To polish it a little up. They gave us, since we were new arrivals in Vienna, some political figure gave us – every family that arrived in Vienna received a copy of *Mein Kampf*. So my father started reading it. He used, in the evenings, to read it aloud so that we could also hear something German. He always said, "Well, I am trying to improve my German by reading *Mein Kampf*." But when he came to those parts which were really very, very extreme politically and ideologically, he would then stop and give a short exhortation to us boys, saying, "Look, that is what Hitler has written about that and that. Beware of that." And I think my father was one of the few people, even including politicians and so on, who really had read *Mein Kampf* from cover to cover. And when he finished with it, he said, "You beware of that ideology. That is not our attitude toward life and way of living." So, I think that my background and my father, who became very much aware of what the ideology was like, that they protected me from many, many bad things.

BWS: Vienna was a real hotbed [politically], wasn't it? Was there a great deal of political pressure to conform and accept this ideology – the new order?

OH: I guess it was the same as everywhere. The Hitler regime really exerted a large pressure on people. And many people became even enthusiastic. But I was lucky, when I came to Vienna, I was again lucky. We lived in a district that was formerly populated by

Jewish people. I went then to a school, I was sent to a school that was formerly, before Hitler occupied Austria, three-quarters a Jewish school. The pupils were dominantly Jewish boys. By the way, Sigmund Freud also went to that school, some hundred years earlier, of course. That was not a Nazi school because the teachers that remained – the Jewish boys were all, of course, already gone, not there, but the atmosphere remained. The teachers were still, to a large extent, the same teachers, and the atmosphere was not at all that of a Nazi ideology.

BWS: Intellectual?

OH: It was a very good school. I liked it very much. And I still like to remember those days because I had good teachers. You see an incident, for instance, what the attitude of the teachers was. I didn't speak any German. So my father then went, at the beginning of my school days, to the teacher of German and told him that that boy doesn't speak German because it was not the language at home. But from now on, "we will start speaking only German at home." The teacher of German said, "Don't do that because he will forget his Mother Tongue. Leave it to us to teach him German at school." That was something that I still remember. He was very right, of course. We continued speaking Ukrainian at home and I have not lost my Mother Tongue that way. It was a very good school.

BWS: The Realgymnasium?

OH: The Realgymnasium in Sperlgasse, Wien Zwei, Vienna Two – "two" for the second district of the city of Vienna.

BWS: Your brothers were at school with you?

OH: Only the elder brother. My eldest brother was already in medicine. He finished medicine during the war, at the beginning of the war, and was then a doctor.

BWS: Did your father continue to serve as a priest?

OH: Yes. My uncle, his brother, was also a priest. He was the parish priest of the Greek Catholic parish in Vienna. There was only one such church in Vienna. My father then became a chaplain to that church. That way he somehow continued.

BWS: Were you thinking of science or medicine at that point in your life? Were you expecting to move on to the university in the medical field?

OH: Of course, I expected to move on to university studies. But many people, including my eldest brother, whom I admired very much – I wanted to be like him somehow, he was 7 years older than I – he felt that I should maybe study languages, probably because I had so quickly learned German. Everybody was a little surprised how quickly I somehow found my way through all that labyrinth of German language. Very soon I became one of the best German pupils at school. But I admired my brother very

much and I wanted to be, as I mentioned, something like him. Since he studied medicine, I chose medicine. I think that was one of the most important points for my decision. But there was another aspect of that. That was, I finished school at the end of the war and the post-war times were very uncertain. Studying languages was an uncertain thing. I wouldn't know if I would be able to make a living just studying some strange languages and grammars and so on. So medicine was something that, of course, could be practiced everywhere. It was an internationally accepted thing that would be useful everywhere since I didn't know, after the war, whether we would stay in Vienna or move on to the United States as many people did at that time. But we remained in Vienna and I studied medicine. And that was how I came to do all those things that followed.

BWS: Why pharmacology?

OH: That was because of my student days. The teacher in pharmacology, the professor of pharmacology, was an exceptional person. Professor [Franz von] Brücke. He was from a family of scientists, rather well-known, famous scientists. His great-grandfather was the founder of physiology in Vienna. Came from Berlin, from Germany. It was originally a German family but they settled then in Imperial Austria. By the way, also, a cousin of Brücke's was Ludwig Wittgenstein. So he was related also to the philosopher Wittgenstein. It was really kind of an amusing thing – about 10 years ago or so [in 1993] I received in Vienna the Ludwig Wittgenstein Prize [laughs], and [when I started my career] the head of the pharmacology department was Brücke, his cousin, at that time [in 1951].

To come back to your question, Brücke was an excellent lecturer. I was fascinated by his knowledge and the way he taught us pharmacology and made us really enthusiastic about what can be done with chemical compounds to help the patients. So, after finishing my medical studies [July 1951], I immediately went to him and asked him whether he will accept me. He accepted me, but he gave me a position without salary. That was, at that time, customary because there were so few positions. It was after the war. There was no money for research. Pharmacology was a research department in essence. Therefore, I had to accept such a position without salary. But I worked half-time in the hospital to earn a little money at least. It was not much, but it was better than – it helped. That was the reason why I started in pharmacology.

The second reason was still my brother, my brother's influence, because after his medical degree he started doing some research, too. He was sent to Germany at that time, during the war, as a doctor to one of the cities that were heavily bombed. So they needed doctors, of course, and so he was sent there. But he started doing some research. And as I mentioned, I wanted to be like him.

BWS: You were thinking about doing research early in your career?

OH: When I joined pharmacology, that was with the clear understanding that I would then start doing research. What, I didn't know. But there was one maybe important influence that later – at first subconsciously – that decided about the direction of my

research in pharmacology. And that was again the influence of a teacher. That was the teacher of neuroanatomy in the first years of medical courses. His name was Friedrich Ehmann. He was an exceptional teacher, again. Completely different from Brücke, whom I only later encountered during the studies. Ehmann was a very dry kind of person, but he was so exact and so clear. He explained the human brain so well that it made me again enthusiastic about learning everything about the anatomy of the brain. And I was very good at that as a student. He would also explain the development of the brain. He also gave lectures on the evolution of the brain, starting with frog brains and even lower species, and go up and up and up to the human brain. To show us how actually things were added all the time during evolution to the brain and how it became the human brain. And that way, the anatomy became understandable. It had a function. It received the functions through his explanation of the evolution and development of the brain. I was also enthusiastic about that. So, at the first occasion that offered itself to me in pharmacology research, I did something that was already a little in the direction of what later became my field of research.

BWS: You started in that direction?

OH: My first post-doctoral work was about a protein that occurs in mammalian blood, [also] human blood, but we studied it [only] in human blood. This protein later became known as ceruloplasmin. That is a copper-carrying protein in our blood plasma. We studied the enzymatic activity of that protein which we sort of felt that we discovered this. [laughs] But we later discovered that it [the protein] was already somehow known by other people. But its enzymatic activity was a new thing. It was completely new. Ceruloplasmin was just at that time recognized as a protein [of physiological importance] in human plasma. Since it was a copper protein, it was responsible for copper metabolism in the body. It occurred to us that there was a neurological disease that was caused by too much copper deposition in the brain. That was Wilson's Disease. It was called Wilson's Disease after a British neurologist, [Samuel Alexander] Kinnier Wilson, a very famous neurologist in the 19th century. That is a disease that destroys the basal ganglia in the brain. At that time, it was a logical thing to look for the copper-carrying protein, for its enzymatic activity, in the blood serum of Wilson's Disease patients. So we obtained blood from Wilson's Disease patients by cooperating with neurologists. That was my first cooperation with neurologists [in 1953]. I measured the activity of that ceruloplasmin enzyme in the serum of Wilson's Disease patients and I found that it was low. I was not surprised about that somehow.

BWS: Why were you not surprised?

OH: Because [of] the copper deposition [that] occurred [in Wilson's Disease] – because the blood could not retain the copper properly because there must have been some failure of retaining the copper properly in the blood and the copper transport was [obviously] disturbed. That was [at that time] somehow suspected. You see, ceruloplasmin [dysfunction had already been postulated to be involved]–

Analog Tape 1, Side 2

OH: actually a disturbance [lack of] ceruloplasmin protein and that we also found to be the case [with our enzymatic activity]. That somehow was my first connection or experience with a basal ganglia disease. Of course, from my medical studies, I knew about basal ganglia diseases, but that was more a kind of theoretical knowledge. Here I examined the blood of those patients and I saw some changes. That may have also somehow influenced later on my path of research which became, then, as I mentioned, my main occupation.

BWS: You were asked, when you were with the pharmacological institute, to apply to go to England on the British Council Scholarship. Or that was discussed with you, was it not? Did this, the British Council Scholarship, occur about the time you were doing this research?

OH: It was during the time when I was doing the ceruloplasmin enzymatic studies on Wilson's Disease. My supervisor, his name was Professor Lindner, he suggested to me that I should go for a year or two somewhere to broaden my experience. But I think his motives also were a little selfish because I was one of the most useless of his post-doctoral fellows – because I did not like to work on the ideas that he would suggest to me which were some things that did not appeal to me. He was doing some endocrinological work and also some work on digitalis effects. I sort of did not really – that didn't catch my attention and interest, apparently because I subconsciously already wanted to do something with the brain, though I didn't know what at that time. So I applied to the British Council in Vienna for a research fellowship and a scholarship and I received it. That was the beginning, actually, of my interest then in dopamine.

BWS: Tell us why and how. This was 1956-1958.

OH: Yes, in late autumn of 1956, I came to Oxford to Dr. [Hermann] Blaschko.

BWS: Was he British?

OH: He was originally from Germany but he emigrated from Germany when Hitler came to power because of his ethnic background. He became in England, first in Cambridge and then in Oxford, the world expert, I would say, on the enzymes that form catecholamines, including dopamine. And also on the metabolism of the substances formed by these enzymes – so that is the metabolism of those substances, the catecholamines. When I came, he started talking to me about dopamine. Now, dopamine, at that time, was a new name. So he had first to explain to me what he meant by dopamine. I knew it only under the chemical name as 3-hydroxytyramine. It was in 1952 that Sir Henry Dale at a meeting of the Physiological Society, after a talk by Blaschko where he was mentioning always the name 3-hydroxytyramine, when Sir Henry Dale got up, somewhat angered, by saying. "Why do you call that substance 3-hydroxytyramine? It has nothing to do with tyramine. It is a direct product of the decarboxylation of levodopa, L-DOPA, so call it dopamine." And that was how the name dopamine was made and became then accepted. Henry Dale was a very - sort of the leading figure in British pharmacology and physiology – so everybody started calling this substance

dopamine. And dopamine was, at that time, regarded as a mere intermediate in the formation and the biosynthesis of noradrenalin from dopa, from L-DOPA. Blaschko was actually one of those who postulated that pathway in 1939. So if you want to refer to the first people who postulated that pathway, Blaschko must be always quoted as one of the first.

But by 1956, he started believing that dopamine might have some of its own functions in the body which were independent of noradrenalin. So – independent of its being a metabolic precursor of other catecholamines. And he asked me to do something about it.

BWS: Were you aware of Blaschko's work and did you want to go and work with him in Britain? How did that occur for you?

OH: I was aware of Blaschko's work. The British Council asked, "Where do you want to go?" I was very biochemically minded and so my pharmacological interests were in the biochemical direction. That was, again, because of my teacher in chemistry for medical students, Friedrich Wessely, who was an excellent teacher. An admirable teacher again. You see how much good teachers have influenced my later interests in research. So I applied to Sir Hans [Adolph] Krebs, the discoverer of the famous Krebs Cycle, which is a very biochemical, metabolic, affair. But Krebs – of course, I had to send in my few little papers and a C.V., Krebs probably thought that I was completely useless for him as a scholar. But Krebs was a good friend of Blaschko's from the time when they both were in Germany. Krebs also had, because of his Jewish background, to emigrate from Germany. They were good friends even from their German times. Krebs was also in Oxford, the chairman of the biochemistry department which was close, just practically next door, to pharmacology. So Krebs passed on my application to Blaschko. And Blaschko accepted me. And that is the way I came to Blaschko. Had Krebs accepted me, I would never have done anything with dopamine, I am sure, because that was not a topic of research in biochemistry.

BWS: Blaschko had done work on this, asking questions about lowering blood pressure and the role of dopamine.

OH: Blaschko referred me to a work by Peter Holtz in Germany, published during the war in 1942, on dopamine. Holtz was the discoverer of the enzyme dopa-decarboxylase which forms dopamine from L-DOPA. So Holtz was doing quite a bit of work on dopamine, too, because it was the product of decarboxylation by his enzyme, so to speak. And he observed that also dopamine was, like noradrenalin and adrenalin, in most species increasing the blood pressure. But in the guinea pig, it actually produced a fall in blood pressure. Holtz was very surprised about that and he produced an explanation which, to Blaschko, appeared very improbable. Holtz felt it was the metabolites of dopamine by monoamine oxidase, which are aldehydes, that produce the fall in blood pressure. Aldehydes were known to produce some such effects in animals. So he postulated that. And Blaschko didn't believe it really. Blaschko was an expert on the metabolism of catecholamines and he knew that it was an improbable explanation, so he asked me to repeat those experiments of Holtz. But I used, in addition to what Holtz had done, I used

the first in-vivo-effective monoamine oxidase inhibitor, iproniazid, to block the metabolism, the break-down of dopamine [to the corresponding aldehyde] by monoamine oxidase. The idea was that if Holtz was right, that it was the break-down product by monoamine oxidase, then inhibition of the enzyme should abolish that lower blood pressure, the fall produced by dopamine and dopamine should then produce like adrenalin and noradrenalin a rise in blood pressure. So I repeated Holtz's experiments in addition with treatment with iproniazid and I found that iproniazid not only did not abolish the fall in blood pressure by dopamine but even increased it [the fall]. So that was clear evidence that the effect of dopamine on the blood pressure in the guinea pig was its own physiological effect independent of its being converted to some metabolic products or to noradrenalin and adrenalin or anything like that. So that was the first such evidence that dopamine may have its own function in the body. Of course, it was in the periphery. At that time, dopamine was not known to occur in the brain. The brain dopamine story proper starts actually a year later, in '57.

BWS: Did you expect this result from your work? Dr. Blaschko had asked this question and the results were very clear to you.

OH: I was aware of this, that it was something of interest. Actually, Blaschko, when I left Oxford and returned to Vienna, Blaschko gave me the advice to continue with dopamine research. I started immediately in Vienna doing some pharmacology of dopamine. First, still on the circulation and cardiovascular system, but very soon, nearly immediately, I changed to the brain.

BWS: You have written that the decision was quite easy for you to go from the periphery to the brain. Why was that?

OH: It was during my experiments at Oxford that dopamine was discovered to occur in the brain. That was by Kathleen Montagu in London in the summer of 1957, published in *Nature.* That was the first time that the substance with which I did the blood pressure experiments was found in the central nervous system. Dopamine was until then only known to occur in peripheral nerves probably, presumably, as a precursor of noradrenalin. Then, while I was writing up the results for publication in the *British Journal of Pharmacology*, there were made several discoveries, especially about L-DOPA, L-DOPA's effects on the central nervous system. I knew that L-DOPA was a precursor of dopamine. I had done also experiments in guinea pigs, on the blood pressure that used L-DOPA and found that it behaved just like dopamine and also was potentiated by iproniacid, by an inhibition of monoamine oxidase. So I was interested in those compounds [and this problem]. Then Peter Holtz in maybe September or October, '57, showed for the first time that L-DOPA produced excitation in animals, in mice, especially when they were treated with iproniazid, a monoamine oxidase inhibitor.[1] Then a month later, Arvid Carlsson in Sweden found that the D,L-DOPA had antagonized the

[1] Holtz, P., Balzer, H., Westermann, E., Wezler, E., 1957. Beeinflussung der Evipannarkose durch Reserpin, Iproniazid und biogene Amine. Naunyn-Schmiederberg's Arch. Exp. Path. Pharmakol. 231, 333-348.

tranquilization by reserpine.[2] Holtz also showed that the L-DOPA had an awakening effect in barbiturate-treated animals. So that was an interesting pharmacology for me.

In December of the same year, '57, Alfred Pletscher, in Switzerland, showed that levodopa increased the catecholamine levels in the brain.[3] Holtz actually postulated, as the only one, that the L-DOPA effect which he observed in mice, must be due to the dopamine formed from dopa in the brain. Whereas the other researchers were not clear – did not make a clear statement about that because L-DOPA is the precursor not only of dopamine but also, via dopamine, of noradrenalin. So, the effect could have been due to either of the amines. But Holtz who knew all about the [kinetics of the] formation of dopamine from L-DOPA, he apparently felt that it must be the dopamine that was responsible for that central effect of L-DOPA. That, of course, was an interesting statement. And Carlsson's findings that dopa antagonized the reserpine tranquilization was in that context even more interesting because we knew all, at that time it was general knowledge in pharmacology, that reserpine is a Parkinson-inducing agent. Patients treated with reserpine, which was, at that time, used as a drug for high blood pressure and also in psychiatry – it meant that those patients would develop a reversible Parkinsonian syndrome.

BWS: That led you to the brain.

OH: That made me change immediately to the brain. I started measuring the influence of centrally-acting drugs on the dopamine metabolism in the brain, in the rat brain. Among the drugs that I used was chlorpromazine, which was the first effective treatment of schizophrenia. Chlorpromazine, like reserpine, also induced Parkinsonism-like conditions in patients. So I became, of course, aware of Parkinsons, and the drugs in question became very familiar to my thinking. But then, in January of '59, came the decisive publication. It came from Sweden, from [Ake] Bertler and [Evald] Rosengren, who were Carlsson's Ph.D. students at that time.[4] They found that the dopamine was localized specifically in the basal ganglia in the dog brain. To connect all those findings and produce the working hypothesis, what to do next, it came to me like a flash, I would say. Since it was easy for me, then, to connect the findings that reserpine removed – and, by the way, at the time also it became known that reserpine removed the dopamine from the brain and that L-DOPA could restore the concentrations of dopamine.[5] So, I put all those things together in my mind. I didn't have to do anything. It all fell into place, I would say, by itself, in my mind. And I immediately started collecting Parkinsonian brains, brains of patients dying of Parkinson's Disease, to see whether there was a change of dopamine or not. To me it appeared much more logical to do this than playing around

[2] Carlsson, A., Lindqvist, M., Magnusson, T., 1957. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature 180, 1200.
[3] Pletscher, A., 1957. Wirkung von Isopropyl-isonicotinsäurehydrazid auf den Stoffwechsel von Catecholaminen und 5-Hydroxytryptamin im Gehirn. Schweiz. Med. Wschr. 87, 1532-1534.
[4] Bertler, A., Rosengren, E., 1959. Occurrence and distribution of dopamine in brain and other tissues. Experientia 15, 10-11.
[5] Carlsson, A., Lindqvist, M., Magnusson, T., Waldeck, B., 1958. On the presence of 3-hydroxy-tyramine in brain. Science 127, 471. Weil-Malherbe, H., Bone, A.D., 1958. Effect of reserpine on the intracellular distribution of catecholamines in the brain stem of the rabbit. Nature 181, 1474-1475.

with animals and with reserpine which was not an ideal drug because it did all sorts of other changes to brain monoamines – we knew that already at that time. So it was – there were the controversies about how it [the reserpine] worked and what the important change was – I felt the best thing was to go directly to the human brain and see whether there was a change in Parkinson‘s Disease or not.

BWS: Did you go to Carlsson’s lab? Visit his lab?

OH: No, I did not. At that time, I didn’t know him personally at all. I knew of his publications, of course, since there were only a few publications in that area and we all knew each other by publications, by reading the papers. But I didn’t know him. I met him for the first time in Prague or Milan something like 3 or 4 years later.

BWS: Not in Sweden?

OH: No, I have never been in his lab in Sweden. He worked at the time of the first papers in Lund but then moved to Göteborg. I have never been in his lab or in Sweden at that time.

BWS: Was this what you would call your Eureka moment? Things coming together for you?

OH: Yes, that was the moment. After reading the Bertler-Rosengren paper, it became quite clear to me. Since Bertler and Rosengren already in that paper made the suggestions that dopamine may be involved in the Parkinsonism produced by reserpine. That was logical, of course, because it was known already that reserpine removes the dopamine from the brain and levodopa restores the concentrations of dopamine and also abolishes the reserpine signs, its central effects in animals. So they [Bertler and Rosengren] suggested that, but they did not mention Parkinson’s Disease at all, so I immediately had that idea and we started about 6 weeks after we read that paper – we started already Parkinsonian studies.

BWS: Why do you think they did not follow that path?

OH: That is a question that I have very often thought about and I could not find an answer to that. Because you see they were students of Carlsson’s and Carlsson, of course, also knew all the literature. He contributed to it so much. Bertler and Rosengren immediately analyzed also human brains. But they did only controls. Only normal brains. Their next publication was published only a few months [June 1959] after the first came out about the localization of dopamine in the basal ganglia of the dog. And they did the same thing in human brains. But they don’t mention anything about that it would be interesting, maybe, to study also Parkinson brains. Nothing at all. So in Carlsson’s lab, apparently, that was not a question of interest or discussion. Because otherwise they would have done it. It was so suggestive.

BWS: You have described this as the all-decisive step.

OH: Yes, but I should have maybe also added that after the Bertler and Rosengren paper, which had described the dopamine localization in the dog brain –

Analog Tape 2, Side 1

OH: Very soon after the Bertler and Rosengren paper, one would have to say simultaneously, in Japan, Isamu Sano and his colleagues examined the normal human brain and found also that the dopamine was concentrated in the basal ganglia, which is not surprising, of course. But that was a simultaneous discovery in the human brain. And again, Sano mentions, as a conclusion of his communication, that apparently dopamine is concerned with the functions of the extraperamital basal ganglia system. But he does not mention the name Parkinson's Disease. So it was really interesting, somehow, that none of them really thought of that at that time. I did it simply because I thought it was the best thing to do. Just to decide the question.

BWS: I know that you have done this a number of times, but will you please talk through – "why the basal ganglia?" There were influences from your early teaching and that was coming back, that was part of your thinking in moving into the Parkinson's brain?

OH: I think that one of the reasons why I so quickly conceived that idea of going to the Parkinson brain was because of my first post-doctoral study on the ceruloplasmin in blood serum of Wilson's Disease patients. I knew, therefore, that there was a basal ganglia disease, the Wilson's Disease. And basal ganglia became something familiar to my thinking. And I guess that it was subconsciously – that idea to do something with Parkinson's brains which I knew had a disturbance of basal ganglia since that was known at that time. That was what neurologists expected – there was a disturbance of the functioning of the basal ganglia. Since dopamine was concentrated – most of the brain dopamine was localized in those basal ganglia, and reserpine removed the basal ganglia dopamine and produced Parkinsonian symptoms – then it was very logical to conceive the idea that we should examine that situation in Parkinson brains. I was very surprised that it was not done by anybody else who was involved in those dopamine studies. By the way, I should mention that when I did those studies, and I had reprints of that work, and repreints of the consecutive studies, which were about the dopa experiments in patients, I sent the reprints to Sano in Japan. And because he was the first to analyze dopamine in the normal human brain, so I sent him the reprints. And I received a letter, that was in 1962, back from him where he congratulates me on the findings and says that they are something "I would have liked to do myself, but have not done it." Only later it became known that he actually started doing those studies. He also studied one Parkinsonian brain in 1961, '60 probably. And found lower amounts of dopamine in the putamen, which is part of the basal ganglia. But as he states in his letter to me, he was in doubt whether that was a real result because of the post-mortem changes of the brain. He did not analyze another Parkinson brain anymore and gave that up. He published those results only in Japanese, in a Japanese journal. In 1999, that paper, where he published it, was translated into English and became accessible to the Western readers. He didn't publish a real paper on his finding but included it in an overview talk about catecholomines in the

brain. He also tried levodopa in Parkinson patients and he describes his experiments in the letter to me. But he was not really interested in the effects of levodopa on the movements in Parkinson's Disease. So he had his patients lying on the examining table and he was trying to see the side effects of levodopa, which were vomiting and such things. And he did not test the effect of levodopa on the motor activity of Parkinson's patients. He did not let them walk around to see whether they could move better or not. His conclusion at the talk, which he gave in Japanese, was that levodopa was not a drug for Parkinson's Disease. So it was a tragic end of a very good start. He could have also discovered independently the dopamine deficiency in the Parkinson brain and the levodopa effect. But he simply gave it up and did not believe that it was of any consequences.

BWS: Were you looking for a way to use L-DOPA – when you started this study, were you expecting some of these results?

OH: I think chronologically speaking, I started the dopamine studies in Parkinson brains without a thought about treatment. That was not yet on my mind, I would say. If I tried to reconstruct the situation really as much as possible in my memory. I wanted to see how dopamine behaved in the Parkinson brains. Whether the idea that it was low in Parkinson brains was true or not.

BWS: It was basic science, measuring the dopamine –

OH: Yes. It was at that time a great risk, I would say, because, you know, post-mortem material was not at all a part of basic research at that time. Human post-mortem material, brain material, was regarded as already too decomposed to be useful [for neurotransmitter research]. And the dopamine and the other catecholomines and serotonin, they were regarded to be unstable compounds post-mortem. So they would quickly be metabolized and disappear from the tissue. So the first thing was, mentally at least, to overcome the difficulty to use post-mortem material. Many people in the laboratory warned me about that. They said, "You are losing your time trying to use post-mortem material. The results will be inconclusive because you will always have low dopamine because it will be – also in controls it will disappear because of the post-mortem changes." I didn't listen to those things. I thought I should do that anyway.

BWS: Why?

OH: Because I was so sure that I would find something. [laughs] I wanted to find something. The second difficulty was, of course, to obtain the brains because there had to be some kind of procedure to obtain brains. So together with my collaborator at that time, Herbert Ehringer, we arranged with the pathology department of the university pathology to obtain, especially, control brains. Brains of controls. And we did ask the pathology department in one of the biggest hospitals in Vienna, on the periphery of Vienna, for Parkinsonian brains. They had a larger population of Parkinsonian patients in that place so we could then do the study. And then already the first Parkinsonian brain which we did sometime in April 1959, about 3-4 months after the Bertler and Rosengren paper

came out – the first Parkinsonian brain…. Of course, I had the special difficulty with the dopamine assays. I should mention that. Because the pharmacology department at that time was not biochemically oriented, they didn't have really modern equipment. They didn't have a spectro-flourimeter which was necessary for very sensitive methodology. So I settled on the colorimetric assay for dopamine which I learned in Dr. Blaschko's laboratory. It was a simple, not very sensitive, but it was a nice method. You could see the color of dopamine – pink, a nice pink color. I used that method already for my experiments on the brain dopamine in rats, on the effect of drugs on the brain dopamine. So I had it already, in my hands, that assay. And I simply changed [adapted] it to the human brain…. Already in the first Parkinson brain I remember that very, very clearly, when I did the dopamine reaction in the extracts of normal brains and in the Parkinson brains, the normal brain – normal basal ganglia – gave the nice pink color of dopamine which I could see before putting [the reaction vials] into the colorimeter. But the Parkinson brain was not at all pink. So I knew already before measuring, before getting the measurements, I knew already there was a lack of dopamine in the Parkinson brain. Then it was a matter of repeating the study several times to be sure about it. By the end of the year, of 1959, we had already 3 brains examined. It was a slow thing because in the beginning, we had difficulties in obtaining the Parkinson material. It was easier to obtain for us the control material.

By the end of the year, we had 3 brains showing that there was a deficiency of dopamine in the Parkinson brain. We suggested to the head of the department, Professor [Franz] Brücke, to publish it. We were excited. We wanted to publish it. But he looked at the results which we showed him and said, "No. You want to make really a far-reaching conclusion. Three cases is not enough. You have to continue and collect more cases." It took us 10 months to collect the additional 3 cases and then we published it at the end of 1960.[6] The paper came out with 6 cases of Parkinsonian brains, but in the meantime, we had plenty of time to collect also other materials. So we collected something like 20 control cases. We also analyzed 2 Huntington's Disease cases. That is also a basal ganglia disorder. And we also analyzed 6 cases of patients with basal ganglia symptomology but without known etiology. So we analyzed altogether 14 basal ganglia disorder brains, but only the 6 Parkinson cases showed the changes in dopamine. The other cases of basal ganglia disorders had normal dopamine which was very important because it showed that the loss of dopamine was specific for Parkinson's Disease. And that is what we already saw in the first publication – done with that very insensitive method, but a very nice method because it showed us the results before measuring even. We also included noradrenalin in our study because noradrenalin at that time was much more popular than dopamine. Dopamine was disregarded by famous people mostly. Famous catecholamine researchers didn't acknowledge the existence or importance of dopamine for many years to come. That was one of the difficulties of the Parkinsonian studies. And also the levodopa studies.

BWS: Why do think that was? You were following this path. Why were others not?

[6] Ehringer, H., Hornykiewicz, O., 1960. Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Ekrankungen des extrapyraminalen Systems, Klin Wochenschr. 38, 1236-1239.

OH: I came from a different direction. I was not at all burdened by the debates about what was the reason for the central effects caused by reserpine. That was a very heated debate between Bernard Brodie at NIH especially and his people and Carlsson, Carlsson's group in Sweden. Bernard Brodie believed that it was the effect of reserpine on serotonin that produced the central effects of reserpine. Carlsson was for noradrenalin. Carlsson was nearer the real facts, of course. Brodie was on the wrong path, one would say. Not really wrong because reserpine also influenced serotonin so it had an effect on serotonin function in the brain, but anyhow, somehow they started quarreling. These were very heated debates. Quarreling about whether it was serotonin or noradrenalin. And dopamine came in the middle of those discussions, but it was not a topic of those discussions. They seemed to push dopamine to the side because they were trying to decide the main question, whether it was serotonin or noradrenalin. So, dopamine became neglected that way. Which was good luck for me, I think. I could do my studies relaxed and not under pressure at all.

BWS: You were communicating with others about dopamine research? Did you have a role in the Brodie-Carlsson discussion?

OH: No, no role in that. But I knew there were maybe half a dozen people or labs that were doing anything with dopamine. One of the people was the laboratory at McGill Psychiatry [Canada] headed by Ted [Theodore] Sourkes. Actually I didn't know anything about Ted Sourkes' work when I did the dopamine study in Parkinson's brains, but when we published the paper on the dopamine loss in the Parkinsonian brain in December 1960 – it was published in a German-language paper in 1960 – in February [1961] I received a letter from Dr. Sourkes, from Montreal, saying that he has read the paper. Imagine that – 2 months later he had read the German-language paper without all the Internet communication or anything like that. He is very interested, he said, in the results because he has studied with [Andre] Barbeau the concentration, the behavior of dopamine, in the urine of Parkinsonian patients and found that it was low in the urine of those patients. That is how I learned that there was another group doing [dopamine] studies in Parkinson patients, but not in the brain, but in the urine. So we started communicating with each other and they even cited our paper when they published the urinary dopamine study in June the following year, '61, [in *Science*] and in the note "added in" proof, quoting our results. That was the first quotation, I think, of our study. [laughs] And Ted Sourkes then came to Vienna in the summer of that year [1961]and we started discussing the questions. And he became then very influential, very important, for the dopamine research, brain dopamine research.

And, of course, as I already mentioned, I sent the reprints then to Sano since I knew that he had – and I also sent reprints to Sweden, to Bertler and Rosengren and to Carlsson. I can't remember for sure if I sent it to Carlsson, but I know that I sent it to Bertler and Rosengren. We were so few, you know, that we tried to encourage each other to do something about dopamine because it was so much neglected by the big science.

BWS: Responses from the others?

OH: I received only a letter from Ted Sourkes and then from Barbeau, we also had communications with Barbeau who was a clinician, clinical neurologist, in Montreal. And Sano, of course. I received a letter from Sano, [and also many requests for reprints. But the real interest in our work came 1 or 2 years later, after the dramatic L-DOPA results in patients.]

BWS: Were you presenting at any meetings at this point?

OH: No, I was not at that time. I was not presenting it. We published the paper before any presentations, oral presentations, as far as I remember.

BWS: Were you at the – there was an international catecholomine symposium in 1959?

OH: I learned about it only when it was published at the end of June the following year [1959] – it [the symposium] was in 1958, at the end of 1958. I became aware of the presentations when they were published in June 1959 [in *Pharmacological Reviews*]. There was also Carlsson's presentation. A review article. He actually reviewed the results obtained by Bertler and Rosenberg in that paper. [7] That paper is generally quoted by Carlsson, especially by Carlsson – it is regarded as the one that suggested the concept of dopamine loss in the Parkinson brain. It takes, of course, the knowledge of our results to interpret what he says in the article the way he interprets it now, I would say. Without those results he would not be able to intepret [in the way he does now], what he says in that review article in '59. He mentions Parkinson's Disease and Huntington's chorea and he discusses reserpine Parkinsonism and L-DOPA. But he ends up with the statement: it is impossible to decide at the present the contribution of dopamine or noradrenalin to the effects of L-DOPA and of reserpine as the Parkinson hypokinesia-inducing agent. That is all that he concludes. Also, he mentions Parkinson's. I am surrpised that he does it without having asked Bertler and Rosengren to do, at the same time, a study of Parkinson brains – dopamine in Parkinson brains. It is a mystery. A little of a mystery. Anyhow, by the time these communications were published, in June of '59, we had already 2 of our 3 Parkinson brains analyzed and knew already that dopamine was low in the Parkinson's brains.

BWS: So you had moved ahead at that point?

OH: Yes. I was working independently of that paper since I did not attend the meeting on the catecholomines in 1958. I was not present. It was in Bethesda at the NIH. So I had no idea about what was being said. I only learned it when it was published.

BWS: Professor Brücke's presentation in Belgium in 1960 started this?

OH: Yes. After we showed him the 3 cases which we wanted already to publish in 1959 and he rejected that idea, advising us to do more cases, he included those 3 cases in

[7] Carlsson, A., 1959. The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacol. Rev. 11, 490-493.

an oral – in a lecture. He was asked to give a lecture in Belgium in February 1960, and he gave a lecture on catecholomine metabolists and other studies done in the pharmacology institute because there were other groups working on peripheral catecholomine metabolism, on the vascular effects and so on. And he included those 3 cases in a little paragraph; a mention of them. But he did not show any actual data. I mean, he did not publish them. It was mentioned in the publication that came out but there are no actual data there. But he had the slides of those 3 cases. That was the first time it was mentioned somewhere outside the insitute.

BWS: Your publication came out in December of that year.

OH: 1960.

BWS: That was when you were able to show your work?

OH: Before that time we were discouraged from giving any oral presentations by Brücke's judgement that these 3 cases were too few. We were silenced. We were condemned to silence. [laughs]

BWS: That must have not been easy.

OH: We accepted it. And I must say he was not wrong. It is like that. Sometimes nowadays when I see publications with 1 or 2 cases, I wonder whether they will survive the test of time.

BWS: You said that your equipment was not as sensitive as that in other places. Was that a factor, that you were developing studies with less – because of what you had available to you.

OH: There is one important point that depended on the sensitivity. That is the substantia nigra in the Parkinson brain. We quit analyzing the substantia nigra, which is part of the basal ganglia, which was already at that time known to be involved in Parkinson's Disease from pathological work. We could do the normal – analyze the normal substantia nigra for dopamine by pooling the number of different cases of the substantia nigra. It was kind of a collective value then. So we measured the dopamine in normal substantia nigra and knew that it was contained in larger amounts in substantia nigra. But we could not measure it in single Parkinson cases because our method was not sensitive enough.

<u>Analog Tape 2, Side 2</u>
OH: Our first publication on the dopamine loss in Parkinson brain does not say anything about the substantia nigra dopamine in Parkinson's Disease. But 2 years later, we already had more sensitive equipment. We finally acquired a spectro-fluorimeter. And then I changed to a more sensitive method for dopamine and I analyzed the dopamine in the substantia nigra of Parkinson's cases. And, again, against the advice of very famous – written advice, not personal advice – opinions of, say, famous people who didn't think it

was a good idea. In 1962, I found that the dopamine in the substantia nigra was just as much reduced as in the striatium, in the other parts that contained large amounts of dopamine. And that brought me to the idea that there may be a connection – a dopamine-containing connection between the substantia nigra and the nuclei that are called caudate and putamen that are involved in Parkinson's Disease. I, for the first time, suggested that the loss of neurons in the substantia nigra may be the cause of the loss of dopamine in the caudate and putamen. That was published in a local [Viennese] medical journal, again in German, in March '63.[8] I knew at the time that there were already people interested in that question, where dopamine was localized in the brain. Because until then, we didn't know the cells in which dopamine was contained. Was it contained in cell bodies of the striatum, caudate and putamen, or was it contained in the terminals coming from other areas? Was it contained in the glia? We could exclude all those things. And then we postulated in the connection between the substantia nigra and the striatum. I knew at that time there were 2 groups already trying to answer that question. That was Dr. Sourkes in Montreal who started a collaboration with a neuroanatomist, Louis Poirier, and they were lesioning the mid-brain. Different areas in the mid-brain in monkeys. Trying to reproduce Parkinsonian symptoms in those monkeys. So I knew that they were interested in that question. I sent them a reprint of that little German-language paper on substantia nigra in Parkinson brain. The second group were Annica Dahlstrom and Kjell Fuxe in Stockholm who were using the histo-fluorimetric method for dopamine and noradreline, for catecholamines, also, examining morphologically under the microscope the localization of the catecholamines in the brain. But at that time, they did not analyze the substantia nigra. They did the experiments in rats. It was known that dopamine is contained in the caudate and putamen in the neuropil, as it is called, diffusely distributed, not in cell bodies. But in the substantia nigra, nobody was looking at. So I sent also a reprint of that [paper to the] group in Stockholm and as you say it in English, "lo and behold," [laughs], a year later both Poirier and Sourkes in Montreal and Dahlstrom and Fuxe in Stockholm published papers showing that when you lesion in the primate the substantia nigra [Poirer and Sourkes] you have a loss of dopamine in the striatium which proves there was a connection between those two. And Fuxe and Dahlstrom published beautiful histological pictures showing the dopamine in the cell bodies of the rat substantia nigra. That was the birth, as I would call it, the birth of the now so famous nigrostriatal dopamine pathway, which is now the best-studied neurotransmitter pathway in the brain. That was also based on those Parkinson studies.

In a way, it was only possible because nobody else was doing anything. So we were not under pressure. You could stop and think properly. I started reading all the literature on substantia nigra to find out if it was a good idea to do the substantia nigra. And actually, it was not considered a good idea. It was not supposed to be a good idea because two famous people were opposed to that. [Derek] Denny-Brown was a famous neurologist in Boston at Harvard who was a world-leader in basal ganglia neurology and experimental neurology. He had a colony of monkeys where he did all sorts of lesions studying the – trying to reproduce the different extrapyramidal disorders and symptoms. He is considered the founder of modern American neurology. He stated at the same time, when

[8] Hornykiewicz, O., 1963. Die topische Lokalisation und das Verhalten von der Substantia nigra des normalen und Parkinson kranken Menschen. Wien Klin Wochenschr. 75, 309-312.

I decided to analyze the substantia nigra in Parkinsonian brains, he stated, again in an excellent monograph, he was an excellent person, [I am quoting this literally] "We have presented evidence against the common assumption that substantia nigra is involved in Parkinson's Disease." [laughs] He would have discouraged everybody except maybe me by that statement. The other person who was, somewhat irrationally, I would say, against my conclusion of the study was Rolf Hassler in Germany. He was a director at the Max Planck Institute for Brain Research in Frankfurt, a very influential person in the basal ganglia field. He was the first to really prove that the substantia nigra was [always] degenerated in Parkinson's Disease and that that was a specific finding for Parkinson's Disease. So he was not against substantia nigra, but he was against a connection between substantia nigra and the striatum for some reasons which, to me, have always looked a little irrational. Maybe it was a personal animosity against somebody who was in favor of that or something. It must have been something like that. So he wrote me years later [in 1967] when I sent him the reprints of my studies, he wrote me a letter that I am completely mistaken; my conclusions are completely mistaken and erroneous because I interpret the data the wrong way, because my results could be much better explained by assuming a connection between substiantia nigra and the striatum in the opposite direction. But not in the direction I was suggesting. I have the letter to this day in my collection of correspondence during that period of time.

BWS: It was an energetic and exciting period?

OH: Yes, it was very exciting because there were only a few people and they had strong opinions. It was always a kind of challenge to discuss things with them. But there were only a few – and, of course, we haven't yet mentioned anything about the levodopa treatment. Because the levodopa treatment came [in 1961] right after the [1960] publication of the results on dopamine loss in Parkinsonian brain. Actually, before that paper came out, I conceived the idea that one should try the levodopa in the Parkinson patient.

BWS: Why?

OH: That was again very simple, very logical. I knew all the literature on levodopa. It was a very small collection of information. I had done [in 1957] also my own experiments with levodopa in Oxford on the blood pressure and the specific effect of dopamine in guinea pig. And I found in Oxford that levodopa had exactly the same effect as dopamine. Then I already mentioned the results with L-DOPA (I call it levodopa at some times and L-DOPA; L-DOPA would be the correct one I think). I have already mentioned those studies in 1957 by Peter Holtz, Arvid Carlsson, and Alfred Pletscher showing that levodopa and D,L-DOPA increased the catecholamines in the brain – it had an anti-reserpine effect – and the earlier studies by Holtz showing that it had a temporally excitatory effect on locomotion. So I knew it all. And since I saw the deficiency of dopamine in the Parkinsonian brain, it was very logical to [try and] see what L-DOPA would do in the Parkinson's patient. There was already in the literature, actually in the same volume [of the journal in which] our results on dopamine were published in 1960, a human trial of L-DOPA in reserpine-treated psychiatric patients by Rudolf Degkwitz in

Germany. He found, not surprisingly, that it had an anti-reserpine effect – that was known from animal studies already. But he did not try to look at Parkinson's patients. He did not have that idea. He must have known that reserpine causes a Parkinson-like syndrome because as a psychiatrist he must have seen that in his reserpine-treated patients. And he actually tried, in those patients, to antagonize that reserpine effect and showed that it did antagonize it. But this neuro-psychiatrist, who should have developed the idea to try levodopa also in Parkinson's patients, he did not have that idea. It seems that that idea was reserved for – only for 1 or 2 people. I include Sano also, although he failed to really recognize the effect, but he, at least, tried it. I should also include the Sourkes group, of course. Sourkes in Montreal. When he analyzed the urine of Parkinsonian patients and showed that it was low, he then suggested to Barbeau who was the clinician, the neurologist, he suggested to use levodopa in Parkinson's patients. That was also in '61 at the same time when we started our studies. They gave orally the levodopa to Parkinson's patients and published a French-language paper in a symposium volume on the favorable effects of oral L-DOPA. Also, the effect was not as strong as our effect, the intravenous effect, in Vienna because the amounts given were small. We all used, at that time, very small amounts. Levodopa was a rare compound; you could not buy it anywhere. You had to ask drug companies to supply it to you. Synthesize it and supply it. But they [Sourkes and Barbeau] noticed a significant effect on the Parkinsonian symptomology.

But to come back to the beginning of our trials, I made the suggestion to use L-DOPA in Parkinson's patients intravenously. I had already the paper by Degkwitz who tried it also intravenously in his psychiatric patients. And [in November 1960], I gave the instructions and a sample of the L-DOPA which I had in my laboratory to Walter Birkmayer, a neurologist who was the neurologist of the Parkinsonian ward from where we had received our Parkinsonian brains earlier.

BWS: Had you known him?

OH: I knew him from one occasion only, before. And that may also be of some interest. Because when I asked Birkmayer in November, 1960, to try L-DOPA in Parkinson's patients, he did it only in June, July, 1961. There was a nearly 10-months delay. I urged him again and again. I asked him whenever I saw him at a meeting or so. "Why don't you do that? I gave you the sample. I gave you the instructions how to dissolve it for slow, intravenous injections." He would use excuses. He had other drugs to test now in his patients and he didn't want to interrupt his trials. And so on and so on. The reason was that he was actually not on good terms with me at that time. When I returned from Oxford with the idea to continue my dopamine research, he came [March 1958] to my lab. He was a clinical neurologist, as I mentioned. He wanted to persuade me to use Parkinsonian material from his patients, dying on his ward, to analyze the hypothalamus of the Parkinson patients for serotonin. I didn't see any reason why I should measure serotonin in the Parkinsonian hypothalamus. Birkmayer's idea was that Parkinsonian patients have a temperature dysregulation. Something that was not clearly shown anyway. No real literature on that. So I didn't see any rationale to do this stuff. So I sent him away. I said, "Look, I am busy setting up the laboratory. I have just returned

from Oxford. And I don't have a method for serotonin. I cannot measure it in those small quantities in the hypothalamus." I sent him away. He stopped all communications with me. For a year or two, he didn't even want to speak to me because of that. When I asked him, then, in 1960, 2 years later, to start a trial of L-DOPA in Parkinson patients, he was not very enthusiastic in doing it, you know. He wanted to repay me for my refusal to do the serotonin in the hypothalamus of Parkinson's Disease. He actually acknowledged that in a letter to me which he wrote years later [in February 1970]. So I have it in writing. [laughs] But that was later. Finally, he did it in the beginning of July, 1961. I still remember, of course. I was present at that time in the hospital and watched the results. It was a spectacular moment to see the patients who could not walk, could not get up from bed, could not stand up when seated, start walking. They all performed these activities like normal. Speech became better. Movements – the associated movements, the face expressions; they started laughing and then actually crying with joy. These were patients who could not be helped by any doctor. And then levodopa produced the effects. It was really very spectacular. We made a film of those patients and showed it very soon in a meeting of the Medical Society in Vienna. That was the first presentation, actually, where I presented all the dopamine results in Parkinsonian patients. And then Birkmayer showed the movie showing the clinical effects of L-DOPA. That was in November, 1961.[9]

BWS: That's a classic now, but how was it received at the time?

OH: That was received with a lot of skepticism. The reasons were manyfold. First, spectacular results were not liked at that time, I would say, in Parkinson's Disease because it was considered a completely untreatable condition. It was a progressive, neurodegenerative disease and it was assumed that those conditions can not be really influenced to any really significant degree by drugs. So that was that at that point. The other point was the selection of patients. One or 2 studies were unable to reproduce the effect of levodopa. But one study done in Vancouver in those days, for instance, used patients who were treated with neuroleptics. Parkinson's patients treated for some other reasons with neuroleptics. And we know that neuroleptics block the dopamine effect, so you would not expect any effect. This was a poor selection of patient material. People were not really very trained in doing such clinical studies before. So that it was only 5 or 6 years later, in 1967, when [George] Cotzias in New York decided to use oral levodopa, or oral dopa – he used a racemic mixture, DL-DOPA, actually, because it was easier to obtain in larger amounts – he more-or-less repeated the Sourkes-Barbeau experiments who did it 5 years earlier by giving L-DOPA to Parkinson patients orally. But he gave large amounts. Grams. Grams of DL-DOPA and every day. Not just one experiment, but every day. That is something we could not do with intravenous injections. Small amounts. Because it was impossible to inject all the time, levodopa, it has a short action. So, we could not really develop an intravenous treatment for levodopa. Cotzias was the person who accomplished that by giving high daily oral doses of levodopa. And he then showed that the effect was not only spectacular, but also sustained. That the patients

[9] *L-DOPA-Effekt bei der Parkinson-Akinese*, produced at "Lainz" in August 1961. The paper that followed is Birkmayer, W., Hornykiewicz, O., 1961. Der L-3,4-Dioxphenylalanin (= DOPA)-Effekt bei her Parkinson-Akinese. Wien Klin Wochenschr. 73, 787-788.

improved and sustained the improvement as long as you continued with oral L-DOPA. So that was the clinical breakthrough, I would say. When the neuroscience world realized there was really something new. That effect – you could not deny it anymore, just by being something like a skeptic.

There was also the idea that maybe our results in Vienna with intravenous levodopa, which were spectacular – our movie, I was asked to send out the movie to several people, in California, in England, in Sweden – that they somehow thought it might be a placebo effect of the intravenous injections. That was really a little – I don't know how to classify it – interesting, I would say. That idea, it showed they didn't read our full paper [1962] on the L-DOPA effect in Parkinson's patients where we treated the same patients who reacted so spectacularly to L-DOPA, given intravenously – in the same patients, we tested a series of chemical compounds related to L-DOPA.[10] I asked Birkmayer to test all the possible other related compounds to see how they acted on the patients. And none of these compounds had the levodopa like effect. Which excluded, of course, the placebo effect. But those people who doubted the L-DOPA effect didn't really – [they] disregarded those results. But in the end, it was the high oral dosage by Cotzias that convinced everybody.

BWS: You have called this the Dopamine Miracle?

OH: That expression doesn't come from me. It was the title of a talk that I was asked to give [in London, in 2001]. They gave me that title. I wouldn't have used miracle.

BWS: What would you have used?

OH: Good therapeutic effect.

Analog Tape 3, Side 1

OH: To some people, it seemed really very important. There were some people who really recognized it.

BWS: In 1965, you were invited to Columbia [University, New York City] to participate in the symposium on biochemistry and pharmacology of the basal ganglia. Will you talk a little bit about that?

OH: That was the first, to my knowledge – it was not the first symposium on the biochemistry of the basal ganglia, maybe, but the first one [in North America] that included our work. I was asked to talk about dopamine, levodopa, about our results in Parkinson patients. The symposium was organized by Melvin Yahr, the neurologist at Columbia, who was aware of our work. Also he did not really believe at that time, was not convinced of the levodopa effect. But he came to Vienna in '64 already and I showed him the movie and we had a chat. I even gave him levodopa for intravenous injections.

[10] Birkmayer, W., Hornykiewicz, O., 1962. Der L-Dioxyphenylalanin (=DOPA)– Effekt beim Parkinson-Syndrom des Menschen: zur Pathogenese und Behandlung der Parkinson-Akinese. Arch. Psychiat. Nervenkr. 203, 560-574.

He tried it in a few patients and couldn't see much effect and gave it up. He didn't pursue it. But he was aware of those findings and he invited me – he asked the other organizers to invite me to the meeting. That was the first time that I presented it to an international audience since it was a kind of international meeting with many speakers from other countries. There was also Carlsson there. Other people from other countries. Melvin Yahr then arranged a press conference for me and Carlsson where journalists were asking questions and so on. That is how the L-DOPA came into newspapers. For the first time, it was also in the American newspapers mentioned. After that meeting, I received also letters from patients from the United States asking me about whether I could treat them. But that was not a real treatment at that time. Low-dose intravenous injections were not practical as a treatment. The effect was too short-lasting. It was only 2 years later when Cotzias came up with the high-dose oral L-DOPA that it became a real treatment.

BWS: Did you become more active in the international community after this? Did things change a little in terms of understanding your research?

OH: That meeting was very important. I think it was for the first time it made people, neurologists and neuroscientists of that time, aware of that possibility. I know that that slim volume that was then printed of the lectures given at the symposium, it had to be reprinted several times because it went out of print immediately. It was actually the first volume published by a new publisher called Raven Press, which then became a very important publishing medium for basal ganglia disorders and Parkinson's Disease symposia and so on. That was the first volume they published. And it went out of print immediately. It shows that it was an important meeting that really made people aware of something completely new in that field of basal ganglia.

BWS: Were people starting to look at the brain differently at that point?

OH: No. That is, of course, interesting. But somebody explained it to me why it was so. I have been wondering that the first papers reproducing our brain dopamine results in post-mortem brain came out in 1970-1971. So actually 10 years after our paper came out. And one of them was from Columbia University by Stanley Fahn. The other one was in Finland, from Dr. [Urpo] Rinne. I have always wondered why it took so long to reproduce the results or why people were not reproducing them immediately. Somebody, I can't remember who it was, one of the colleagues, actually explained it to me. He said, "Your 1960 paper was so complete. It contained 20 controls. It contained 14 cases of basal ganglia disorder and 6 cases of Parkinson's Disease amongst the 14 cases. And it showed that [the dopamine loss] was specific, that it was reproducable, that it was everything. So that nobody really wanted to repeat the study because it was so complete." That may be the reason why it took so long. Actually Stan [Stanley] Fahn not just reproduced the paper, but he studied the sub-regional changes in the caudate nucleus of the Parkinsonian patients, so he added something to our original study. And Rinne also, in his paper, studied the effect of levodopa on the brain chemistry. Tried to find something out about that. So there were modifications. But still these were the first papers to reproduce also our basic results.

BWS: After that, it became the treatment. Not a cure, but alleviates symptoms.

OH: Still the same regimen. Of course, they have added several other details to the treatment. The real clinical treatment, like some inhibitors of dopa decarboxylics in the peripherary and some dopamine agonists can be used and so on. But that is only additional. Levodopa is still the most efficacious drug in Parkinson's Disease. And it can be safely stated that during the course of the disease, every patient at one time needs levodopa and receives it. That is still what is called the Gold Standard.

BWS: And a help to the patient.

OH: Yes.

BWS: I expect that is when world opinion began to change?

OH: Yes.

BWS: You have talked about the missed opportunities on the part of others. In 1968 –

OH: 1967.

BWS: Thank you. You had an appointment here [Toronto] as well as continued in Vienna. You have continued the same path of research.

OH: I was lucky to have a laboratory in the Clarke Institute of Psychiatry [Toronto]. They gave me a budget and let me do what I liked to do. So I continued those human brain studies especially. During that time, we have made several very important observations and contributions to basic knowledge about the human brain and Parkinson's Disease. We were the first to really show that there exists the dopa decarboxylase enzyme in the human brain. At that time, it was claimed there is no such enzyme in the human brain and dopamine is probably synthasized by a different pathway – making the human a kind of curious mammal, quite different from all the other mammals. But we proved that is wrong. If you do the right chemistry, enzyme chemistry, then you can prove that there is dopa decarboxylase in the human brain and that the human is not a curious kind of exception in the animal kingdom. It is just as normal as all the others. So we proved that.

We, of course, extended our research into other brain conditions. We studied Huntington's disease brains and showed that the dopamine was normal in those brains, or near normal. And we made also the first observation on the monoamines, especially dopamine, in Lesch-Nyhan Syndrome, which is an X-linked inherited metabolic brain disease. And showed that there was also a dopamine deficiency in the basal ganglia but no changes in the substantia nigra, which was something quite new at that time. Although now we have other examples of such [dissociation between striatal and nigral dopamine] – and that study became actually a kind of a reference, a reference standard for the animal experiments [on the Lesch-Nyhan Syndrome] with transgenic animals, since these [the

transgenic mice] are [good]models of genetic disorders. So we can reproduce in transgenic animals the results obtained in our studies and do a comparison against those animal studies. We then extended also further and we were the first to analyze the brain of dopa-responsive dystonia. The dystonia in children that responds to levodopa. Nobody really knew what the changes in the brain were. We analyzed such a case; we were lucky to receive it from Dr. [Ali] Rajput in Saskatoon. We showed the dopamine lack in the striatum and deficiency in activity of the tyrosine and hydroxylase and cyclohydrolase, the enzymes that are at the beginning of the synthesis chain of dopamine. Many of these studies were very rewarding. We enjoyed it all very much. When I went back to Vienna, we then established, in the Clarke Insitute, the Human Brain Laboratory, because we had so many brains in our freezers and we didn't want to lose them. I became, then, the Head of the Human Brain Laboratory in Toronto being, at the same time, the Head of Biochemical Pharmacology in Vienna. So I had 2 positions.

BWS: There is so much that you have done. If you were to think about the major advances in the last 50 years in the work that you have done, globally, what would you think they are?

OH: In my field?

BWS: Yes. What would you say?

OH: Since our work.

BWS: Your work was the break-through.

OH: You could call it that. As I mentioned, that is the general opinion. Levodopa is still the Gold Standard. The drug of choice for treatment of Parkinson's Disease. Of course, there are advances, let's say, in terms of discoveries of dopamine agonists and use of dopamine agonists so that you don't use levodopa then because they have a similar, identical, effect, but they are much weaker. So they are not satisfactory in severely-affected patients. Of course, a major advance was the neurosurgery. The rebirth of neurosurgery because, you see, neurosurgery was one of the treatments before levodopa. Levodopa simply killed neurosurgery. Neurgosurgeons were very unhappy about that because levodopa was a drug and the patient didn't have to be lesioned in the brain and so on. It was much simpler to use it. And neurosurgery went out of fashion. But then, people started thinking about it again and developed micro-lesioning methods. Methods that would lesion really very specific areas. The earlier neurosurgery was crude, in a way. They didn't have those refined instruments and machinery. They then discovered that with micro-lesions you could also improve Parkinsonian symptoms and reduce the need for levodopa. So that lower doses of levodopa would already be effective and the side effects of levodopa, especially the dyskinesias, could be minimized. So levodopa would be possible to use even in patients that formerly could not receive it because they had too many side effects. And the newest development in that area is the deep brain stimulation, of course. Of which Dr. [Andres M.] Lozano, the head of this department, is one of the masters. And deep brain stimulation is one step further from the lesioning. It is still in its

development, I would say. It produces amazing results but we still don't know exactly how it works. It is an interesting situation where you have a procedure that seems to help but still lacks the explanation why it helps. Which is just the opposite of what we had with levodopa. I mean at least I knew why it helps because it increases the dopamine levels in the brain.

BWS: Has your view of Parkinson's Disease changed over the years at all? How you would define it?

OH: I don't think anything essential has changed in that area.

BWS: A single disorder? A syndrome?

OH: There are different opinions on that, many different opinions. I still like to think that it is a single disorder. I have my own reasons for that which I think people disregard but I am not offended by that because it is normal that in research there are many different opinions. But I think it is a single disorder. It is probably caused by many factors which have a common final pathway. That pathway must be specific for Parkinson's Disease. So I don't think there are different syndromes. I mean we know that there are Parkinsonian syndromes that are not Parkinson's Disease; that is well-known and acknowledged and I accept that. But Parkinson's Disease proper is probably a single disease – but may be caused by different factors, environmental factors and so on, which lead then to a very specific changes, patterns of dopamine loss, in the brain. That is my opinion. I don't want to elaborate on that because it would take us too long.

BWS: Has the Braak changed the definition of the disease at all?

OH: The Braak paper is a strange one. It is apparently – is so strange that now symposia are held to interpret Braak. That answers, I think, the question.

BWS: In what ways can neurochemists tell us about new drugs for Parkinson's Disease? Best inform the scientific and medical community.

OH: Inform the scientific communities about the new progress on drugs? Well, it is symposia and papers. Publish good papers. I think good papers are always the best means of communicating the new results.

BWS: Now we have the Internet which moves things faster. Do things move faster?

OH: I don't use it. I don't use the Internet. I don't have an e-mail address. I can be reached only by mail or fax. With respect to the Internet and the information it offers, I try to store it all in my brain.

BWS: You talked about things moving quickly when you were doing your research. Has accessibility to information changed and has that had an impact?

OH: It probably has, but I am not sure. You see, my example shows that the opposite can also happen. Two months after we [had] published [in 1960] the dopamine paper in German, I received from Canada, a letter written in English already knowing the results and expressing interest in starting a collaboration. That was so fast; it cannot happen much faster with the Internet. I think if you are really alert to something, then you will find it sooner and don't need all those very sophisticated means that are actually overloaded with junk information. You have to select the proper things. I think real progress is made in a completely different way. It is not made by such media, communication media. It is made by having a good idea and doing the right thing.

BWS: A lot of people have asked you about the Nobel Prize in 2000. Carlsson was on the list. But there was world-wide support for your work. Do you want to comment on that?

OH: I was surprised because when I learned that there was such an action going on [the Open Letter to the Nobel Committee], I predicted that there will be maybe 10 or 20 people supporting it. [laughs] I couldn'think of so many. And there were something like 270 people supporting it and I was very impressed. And I was also grateful, of course, because it was an expression of the opinion of colleagues about what I have done. That is always – in research, that is the only recognition we really can expect – the recognition of the colleagues. That they recognize that what one has done is important. So that was very impressive.

BWS: It was quite an outpouring of support.

OH: I guess the main reason for such massive support was that they felt that it was somehow – that the prize committee somehow missed the essence of the discoveries. Somehow they did not recognize the connection between what Carlsson has done and what I have done and they didn't see that, of course, the one thing without the other couldn't have existed, so to speak. That each one by itself was not a whole. And what upset many people I know from personal conversations who have approached me and talked about that, was the Prize citation for the – it was strangely wrong because it created the definite impression that Carlsson actually made the discovery that dopamine was lacking in the Parkinsonian brain and also suggested the treatment for Parkinson's Disease. And that is, of course, wrong. And I don't think that Carlsson himself would ever say such a thing. I don't know why they worded the citation in such a way. There was no necessity to create that impression because Carlsson had so many merits on his side that you could clearly state his contributions without that ambiguous kind of wording that sort of tried to – it looked as if they tried to exclude me. [laughs] Well, you know, they have done it. They have achieved the purpose. But you see, as I stated somewhere in one of my recent comments, in research we don't work for prizes. And only a fool, only a fool, would work for a Nobel Prize. But there have been many fools that have received them also. [laughs]

BWS: There are many prizes in the world. You have received so many including the Wolf Prize. [And the Gairdner Prize]

OH: Are we still taping this?

BWS: Yes. I will send you the transcript when we are done to check it over.

Another question – do you see new therapies on the horizon? New ideas for Parkinson's treatment?

OH: Not really concrete. There are several hopes that something will come out of these new possibilities. They had put big hopes and expectations into the fetal transplants which actually failed, it can be stated. Now they are putting all their hope in stem cells which are essentially no different from fetal transplants. So there is not a high possibility [for success – there is also the] probability that they also will fail because of those uncontrollable mechanisms that will simply be involved like in the fetal cells. Growing into other cells. Growing in cancer cells. Over-producing the dopamine and cannot be stopped. And so on. These are very intricate things and we don't know whether we'll ever control those things. My personal opinion – I expressed it at a recent scientific advisory board meeting – if I had all the money that the granting agencies put into Parkinson's Disease, I would not spread it into dozens of different approaches. I would put all my money – my personal money, so I wouldn't have to ask anybody for reviews of my ideas – in growth factors. In neurotrophic factors.

Analog Tape 3, Side 2
OH: Neurotrophic factors if they really are real and if they exist and if they have the effects that they have been shown to have in the laboratory on the survival of neurons and the development of neurons – I think that this is the most likely approach to finding a treatment for Parkinson's Disease in the early stages where you could probably stop or slow down the progression of the disease. So that is my personal opinion, which is not really shared by everybody, I guess. But we always have different opinions. We have to accept that. There have been some studies done on the growth factors, GDNF, which were negative but they are not really very good studies, I don't think so. You still have to develop a good study and a good way of supplying them, the growth factors, and so on. But I think that would be probably the way to go. In respect to drug treatment, there is nothing clearly that would surpass levodopa. So it is all more-or-less multiplying the possibilities but not creating anything new.

BWS: If you were to look at your greatest achievement, somethat that would be your scientific failure or frustration, or something that you would do over again, what would it be?

OH: I wouldn't do anything over again. [laughs]

BWS: Differently?

OH: I think it was all fun and it was successful as people tell me. No, I don't see any failures in research. Of course, basic scientists, we start many projects, little projects,

ideas, which all end up in the waste paper basket. Whoever is not able to survive, to tolerate, 90% useless work that ends up down the drain, goes down the drain, is not fit for basic research. Those little things do not count. Otherwise what I have achieved is, I think, enough to satisfy me in a way. Parkinson's Disease, the dopa-responsive dystonia, the Lesch-Nyhan Syndrome, the dopa decarboxylase, all those things that were really crucial. I would say they were all very successful. I don't have anything to do differently.

BWS: How would you describe yourself? Are you a pharmacologist, a neurologist, a biochemist, a neuroanatomist? All of the above?

OH: You have left out philosopher. Not in the terms that – that this expression is used nowadays. That is actually contained in one of these little – not by me. That was written as a kind of, as I call it, an editorial by a colleague.

BWS: You are a philosopher, in your thinking.

OH: I like very much to think, you know. To think about nearly everything that comes to my mind. And in the Canadian *Who's Who*, the entry for me ends up with something like, Your Hobby. I have two hobbies listed in that *Who's Who* book. That is reading, mostly non-fiction, and thinking. That is the second hobby of mine. And they really printed it that way. I thought they would reject that. [laughs] But they were gracious enough to print that. And that, in a way, describes me – as I would describe my approach to whatever is seen in the world, whatever I do in research, and whatever I think myself – my private life – I like to be thoughtful. And try to see things in a kind of balanced perspective. But as to your question about those cited possibilities, I would say I am – formally I would call myself a brain researcher and now I would call myself a neuroscientist without really knowing what that all means. I have been trained as a pharmacologist, so my training is simple pharmacology. You know, experimental pharmacology. And I am still sort of – trace my research approach to that source.

BWS: Your background, and as a final question, going back to your father and his influence. There are many and continuing discussions and study of religion and science. I don't mean this to be a huge question, but in your thinking, is there anything you would like to comment on about religion and science?

OH: I think you could regard me or call me a religious person. That is not surprising, I assume. To me there is no antagonism between religion and science since they are on completely different levels [concerned with very different, but complimentary, ways of knowledge]. If you want me to elaborate, I could, but I don't think it is necessary. No, there is no collision at all. I am always wondering and surprised about those controversies and those things that happen in North America – those rather extreme views, [those religious views and some reactions to them]. I would call them merely pseudoreligious views. I don't think those people have the right ideas about what things really are [– religious things and scientific things]. They should think a little more.

BWS: Thank you.

For further information, please see:
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