



# ACNP Bulletin

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SPECIAL EDITION – ARVID CARLSSON, M.D., Ph.D. MEMORIES

Throughout my career in Neuropsychopharmacology, Arvid Carlsson served as an inspiration, a scientific muse, and later as a mentor and friend.

The inspiration was derived from the truly remarkable body of research that laid the foundation for his award of The Nobel Prize in Physiology or Medicine 2000. Not only did these findings demonstrate clearly that dopamine was a synaptic transmitter in the brain and not merely a precursor to noradrenaline, they also provided key insights into its vitally important role in the initiation and modulation of movement, thereby paving the way for the translational research that led to the use of L-DOPA therapy in the treatment of Parkinson's disease. Subsequent research in the early 1960's postulated that dopamine receptors provided the mechanisms of action of the so-called 'typical neuroleptic' agents that were just beginning to transform the treatment of schizophrenia. The importance of this approach of applying scientific discovery to unmet medical needs was but one of many lessons I gained from a close appreciation of this exemplary career.

As noted in his Nobel Prize Lecture, Arvid derived great satisfaction from the fact that he went from being a "nowhere man" whose cogent arguments for the roles of catecholamines in key brain functions were derided initially by the opinion leaders of physiology and pharmacology at the dawn of the 1960's, to a leading figure in neuropsychopharmacology, all within the space of only 5 years. For myself, this story has served as a constant reminder to always trust one's data no matter whose pet theories they may call into question.

The opportunity to finally meet this inspiring figure came in 2002 when Arvid Carlsson and his fellow Nobel Laureates, Paul Greengard and Eric Kandel kindly accepted my invitation as a member of the local organizing committee, to be Guests of Honor at the 23rd International College of Neuropsychopharmacology (CINP) World Congress in the newly refurbished

Palais des Congrès de Montréal. Arvid cherished his involvement with CINP over the years, but I believe that the warm reception afforded to each of these outstanding scientists at this congress, occurring as it did approximately 18 months after the prize-giving ceremony in Stockholm, reinforced his connection with this College. In recognition of this special relationship, during his Presidency of CINP (2010-12), Hans-Jürgen Möller commissioned the creation of the Arvid Carlsson Medal for outstanding contributions to neuropsychopharmacology, a gesture that was greatly appreciated by Arvid. At the outset of my term as President of CINP (2012-14), Arvid graciously accepted my request to serve as the Honorary President of CINP. During this period, he provided sage advice on a number of urgent issues concerning the College including the challenges of maintaining investment in the development of new CNS drugs, a topic that was always dear to his heart.

Despite his absence, we can all take heart from the fact that as an active scientist until the very end, he provided a wealth of ideas that will guide the field for years to come. Personally, I can think of no greater legacy.

*Anthony G. Phillips, CM, Ph.D., FRSC, FCAHS*



**Dr. Carlsson at the Nobel Laureate Celebration**





Arvid Carlsson was a tremendous contributor to psychopharmacology. The year following when he, Erik Kandel and Paul Greengard won the Nobel Prize, I helped as the immediate Past-President of ACNP to organize a symposium in Washington that featured the three of them. They each presented on their work. The meeting was open to the public and we had an invited luncheon with a number of government officials—Senators, Surgeon General, etc. Arvid brought his hand done slides from years ago (no Power Point from him then) and the talk really captured his early contributions in a charming way. It was incisive and nicely highlighted his observations on dopamine in Parkinson's Disease and then segued to the development of antipsychotics. I always found Arvid a positive force in the field—interested in young people and innovation, providing helpful suggestions on improving research and supporting advancement of the field. He was a role model for young investigators and will be missed.

*Alan F. Schatzberg, M.D.*

Great scientists often have either a direct or indirect impact on generations of researchers that follow them. This was certainly true in my case.

I can't remember exactly when I first met Arvid Carlsson but it must have been at an international symposium (c. 1974) soon after Arvid had proposed a mechanism of action of antipsychotic drugs on dopamine neuron metabolism, i.e. that it was mediated, at least in part, by feedback pathways from the areas they innervated. George Aghajanian and I had published electrophysiological evidence that supported his proposal. He couldn't have been more enthusiastic, gracious or generous to a young whippersnapper just starting out on his research career.

We continued to meet at conferences and, on another occasion, soon after he had predicted the presence of autoreceptors on dopamine neurons, based again on pioneering biochemical studies, I remember his being excited about our research demonstrating the electrophysiological effects of dopamine agonists and antagonists upon them.

For years some of my research was predicated on his continuing studies of the biochemical functioning of dopamine systems which, in turn, led to stimulating discussions of how the two fit together, and a friendship that I will always cherish.

I, and I know many others, owe Arvid Carlsson a deep debt of gratitude, not only for his pioneering work that opened many new fields of endeavor for us to develop, but for the personal support that he gave each of us including, for me, help climbing the academic ladder and the recognitions I received.

*Steve Bunney, M.D.*

Dr. Carlsson was an active and contributing member of the American College of Neuropsychopharmacology for many years before his passing in 2018. He was awarded the Nobel Prize in 2000 for his research in the area of dopamine, particularly as it applies to Parkinson's disease. However, he worked actively on other brain disorders, schizophrenia in particular, where dopamine is known to be important; he was not only active, but generative around the questions he thought about deeply. It is always remarkable to have a person involved in discussions at the ACNP who has been awarded the Nobel Prize. He credits his start in neuropharmacology to Dr. Bernard Brodie, with whom he worked at the National Institutes of Health in Bethesda, making his research close to scientists in the US who were his peers and implemented familiar paradigms. He was a physician not only by training but also by temperament and used his basic laboratory discoveries to design better treatments for people with brain disorders. He will be sorely missed at the ACNP as a scientific contributor, a wise critic of the process of science, a key contributor to the field of neuropharmacology, and as a role model for accomplishing creative and contributory brain research.

*Carol Tamminga, M.D.*

I have many delightful memories of Dr. Carlsson when we would meet together at ACNP or other scientific meetings. He was a man of great personal charm as well as scientific acumen across multiple disciplines. I would update him on the latest clinical research, particularly on antipsychotics, and sometimes in a wider context. He showed a keen interesting feedback from the clinic and would also update me about his latest studies and other findings in the basic sciences and in terms I understood. His generous nature and extensive knowledge will be missed.

*John Davis, M.D.*

Arvid Carlsson's scientific stature is such that one could hardly touch it in such a short note.

Therefore, I would rather write about the cultural and personal thread that links Arvid to the pharmacologists of the Institute of Pharmacology, University of Cagliari. This thread started by way of Bernard Beryl "Steve" Brodie and the Laboratory of Chemical Pharmacology (LCP), NIH, Bethesda, where GianLuigi "Ghighi" Gessa, my mentor, spent few years as visiting scientist in early 60's. Ten years later, I spent there three years as post-doc, when Brodie just retired but was still in the lab. BB Brodie, the founder of modern pharmacology, did not get the Nobel prize, but at least two of his former collaborators, namely Julius Axelrod and Arvid himself, did. That was a time of great excitement following the discovery by Brodie and coworkers that reserpine depleted brain serotonin. Arvid spent only six months at LCP but enough to discover that reserpine depleted, in addition to serotonin, also brain catecholamines. This finding anticipated what, once back to Sweden, Arvid actually demonstrated, i.e., that the depletion of dopamine and the loss of its function, rather than that of serotonin, accounted for reserpine sedation. Although we never directly collaborated with Arvid, we much capitalized on Arvid autoreceptor hypothesis and provided in vivo evidence for it. Thus, we showed that antipsychotics prevent apomorphine and dopamine agonists hypomotility and that ablation of striatal dopamine heteroreceptors by kainic acid leaves intact the effects of dopamine receptor antagonists on in vivo dopamine metabolism. Later, the existence of D2 autoreceptors was unequivocally demonstrated, and although this line of research was not specifically mentioned as motivation for the Nobel, Arvid was particularly interested into the clinical applications of drugs acting on dopamine autoreceptors and this topic was his main line of research in late age. In 2002 I edited the book "Dopamine in the CNS" for the Springer Handbook of Pharmacology Series and Arvid accepted to provide his personal account of the dopamine saga, a document that remains a must to read. But this is not the only peculiarity of that book. The other one is that it contains the personal account of the dopamine story by another giant, Oleh Hornykiewicz. It was not easy to put these two cocks in the same henhouse. When they discovered to be, back to back, in the same book, one of them threatened to withdraw his contribution. However, I managed to find a solution that was accepted by both of them. I have had many occasions to meet Arvid, particularly at those extraordinary meetings we organized in the beautiful Forte Village resort in Sardinia. I will never forget, at the dinner of the "Non Striatal Dopamine" meeting, in the centenary olive field of Villa D'Orri, the image of Arvid, the cold Swedish, raising his glass full of a 15 degrees Cannonau, towards Susan Iversen who, standing over a table, would shout at the top of her lungs "God save the Pound".



**Arvid Carlsson with Gian Luigi Gessa during the lunch break of a joint meeting between the Institute of Pharmacology of the University of Cagliari and the Pharmacology Department of the Karolinska Institute, in Stockholm (1995).**

*Gaetano Di Chiara, M.D.*

I first met Arvid when I was a post doc at Gothenberg. I was not in Pharmacology but Anika Dalhstrom and he had mapped amine pathways and thus I made an effort to meet them, ended up playing tennis with Anika and kept meeting Arvid over the next decade at meetings. In the 80's we worked together closely in planning a Dahlem conference on Schizophrenia. Ken Davis and Danny Weinberger were also involved. The planning meetings were just Arvid, Tim Crowe and myself and we met three or four times in Berlin before the meeting. From that time on, Arvid and I stayed in touch. He came to the Central Institute twice to give talks and I remember vividly one dinner (fish) in Mannheim with my wife and Arvid, we spent a wonderful 3 hours. Upon my retirement, Arvid was one of the main speakers in an "Abshied" (farewell) symposium. Over the last decade we only saw each other at ACNP meetings and an occasional ECNP meeting. He was a very humble and straight forward person, who never postured or acted superior, he was unfailingly kind to students and young scientists. A fantastic scientist and more importantly a truly fine human being.

*Fritz Henn, M.D., Ph.D.*



I have had the great privilege knowing Arvid Carlsson over a number of years. I first met him during the lively debate over the elevation of dopamine D2 receptors measured by PET, that occurred between the Hopkins / Danish team and the Karolinska in the late 1980s. As a dopamine pioneer, he was very supportive and interested in our findings although he was a Swede but not from Stockholm as he kindly reminded me. Later, we along with my former mentee and long-time colleague, Gerhard Gründer (now Director of Molecular Imaging in the Central Institute of Mental Health in Mannheim) had the opportunity to collaborate on the therapeutic mechanism of dopamine partial agonists in Schizophrenia. Arvid was working on his own Dopamine partial agonists “OSU-6162” in parallel with our work on PET occupancy work with aripiprazole (Yokoi et al *Neuropsychopharmacology* 27: 248-259, 2002). He subsequently wrote a joint commentary with us (Gründer, G, Carlsson, A, Wong DF. Mechanism of New Antipsychotic Medications: Occupancy is not just Antagonism. *Archives of General Psychiatry* 60: 974-977, 2003).

He was always most gracious with his collegiality, mentorship and understated demeanor. I will deeply miss his wisdom, engaging conversations and warm friendship especially at ACNP and CINP meetings.

Dean F. Wong, M.D., Ph.D.



Joint Panel Presentation

His discovery of the neurotransmitter dopamine in the brain and providing the first observations on its role in the actions of levodopa in the treatment of Parkinson's disease and of anti-psychotic drugs in treatment of schizophrenia gave him the Nobel Prize in 2000.

I met him for the first time in the early 1960s while working on my thesis (1963-1965) entitled “Evidence for the existence of central monoamine neurons in the CNS” in the Department of Histology at Karolinska Institutet. The reason was that my teacher Dr. Nils-Åke Hillarp, who was the chair of the Department, had a productive collaboration with Arvid Carlsson and his group. It was a pleasure and honor to meet Arvid and in the subsequent collaboration with him and his group in the 1960s he introduced me to the exciting world of neuropsychopharmacology.

So, I have known Arvid Carlsson over 50 years and am genuinely grateful for his dedicated and important help at Karolinska Institutet in the period 1965-1968 after Hillarp's death in 1965.

It feels strange that he is no longer with us. Almost every year we met at the conferences somewhere in the world, sometimes at the ACNP meeting, and interacted in a friendly and fruitful way. We always enjoyed his crystal-clear lectures that helped us understand monoamine pharmacology. He defended his work in an outstanding way if a scientist raised critical questions after his lecture. In addition, Arvid had a great fighting spirit. He also had a unique analytical capability that we admired and appeared when reading his papers. We are proud that Arvid was from Sweden and one of the leading neuropsychopharmacologists in the world over several decades.

Being gone he leaves an empty space that no one can fill.

With highest respect to a great scientist.

Kjell Fuxe, M.D.



Paris at the European launch of aripiprazole, June 2004

I will never forget an inspirational lecture about proving dopamine was a neurotransmitter and how he had to fight through the establishment in order to have his voice heard and wait 40 years for a Nobel Prize – all delivered in a beautifully clear, humorous, and gracious manner. Meeting him at the 2002 European College of Neuropsychopharmacology and subsequently at the European launch of aripiprazole, I was struck by his humility, warmth, and kindness. His work has made a huge difference, not just to research, but, more importantly, to a great number of people's lives.

Katherine Aitchison, BA(Hons), MA(Oxon), BM BCh, Ph.D., FRCPsych



**Arvid Carlsson and Herb Meltzer in Meeting in Corfu in 1980.**

meeting with him and Ferrosan scientists who had synthesized it and supported the funding of basic and clinical research with melperone in my lab and clinic at Case Western Reserve that provided additional evidence for its efficacy, including in treatment resistant schizophrenia. That molecule and related work lead to my formulation of the '5-HT<sub>2A</sub>/D<sub>2</sub>' hypothesis of 'atypical' APDs, in 1989. Arvid embraced that idea, even as many challenged it, especially Seeman and Kapur whose published work led to the cessation of melperone development in the US, because it mistakenly claimed that clozapine's efficacy was based on its D<sub>4</sub> receptor antagonism. Memorably for me, Arvid told me at an ACNP meeting that "I got it right" referring to the role of 5-HT in the mechanism of action of APDs and going on to integrate it into his thinking about the role of 5-HT in schizophrenia, of which he was an early proponent. Arvid and I championed monotherapy with a selective 5-HT<sub>2A</sub> antagonist, e.g. M100907 and SR43469B, leading us to have a private meeting with the head of Hoechst Inc (now Sanofi-Aventis) to urge him to go forward with clinical studies, but we were unsuccessful. This opened the door to my work with Mark Brann of ACADIA to develop pimavanserin, a selective 5-HT<sub>2A</sub> antagonist, which was the first approved non-DA dependent APD.

A memorable interaction with Arvid occurred in 1980 in Corfu, Greece, at a meeting he organized to discuss SSRIs, and, in particular, zimelidine. Like him, I studied both 5-HT and DA intensively, in both depression and schizophrenia. I reported the first case of an SSRI-induced extrapyramidal side effects in man, which was the major impetus for my initial work on the 5-HT-DA interaction noted above. This picture shows Arvid looking intently as I lectured. Based on our numerous interactions, I believe he was listening with genuine interest, as he showed to so many in the field.

Arvid Carlsson, a remarkable man and scientist who all who may read this and millions of people with neuropsychiatric disorders owe an enormous debt of gratitude to.

*Herb Meltzer, M.D.*

I've searched in countless storage bins and folders for any remnant of a picture where I stood by Arvid in group photos. Yet, I found none despite there being many visual photos within the memory centers of my brain gathered over the last 40 years. It was always a glimpse of Arvid standing across from me counseling and encouraging me about the development of the journal *Schizophrenia Research* on which he actively played a role as senior Editorial Board Member; or then later when strategizing about the building of bridges internationally by forming the *Schizophrenia International Research Society*. We were always in lively discussions, whether at board meetings or scientific sessions, discussing science or just expressing thoughts about American politics. There were countless past international meetings on schizophrenia and we were both there together listening to each other. I was honored to know Arvid and have those meetings and personal encounters. He was clearly a mentor that tremendously influenced my career and how I approached science. I will most of all remember his humble words of wisdom urging me on. He was a truly great and unique mind and one that will never be forgotten.

*Lynn E. DeLisi, M.D.*



My Ph.D. mentor, Bob Roth, was a postdoc with Dr. Ulf S. Von Euler at the Karolinska Institute in Sweden (the dates shall not be revealed). While I was in Bob's lab at Yale (1981-86), Bob would tell us stories about the history of catecholamine research in Sweden. Fascinated by the scientists who drove this research, we made our own science ancestry chart (we called it the loop chart) long before Neurotree existed. As a young scientist working on the regulatory properties of dopamine neurons, I particularly idolized Arvid Carlsson. Unfortunately, I was never able to visit Sweden as a Ph.D. student. However, during my postdoc with Greg Kapatos, I was invited to present our work on flow cytometric isolation of dopamine terminals at the European Society for Neurochemistry meeting in Göteborg, Sweden (1988). I was so excited that terror was only a secondary emotion. When I got up to the podium and saw Arvid Carlsson sitting in the second row with a pencil and a notepad, the idea of Arvid Carlsson taking notes on my scientific work was so mind-blowing that I decided it would be absolutely fine if I died then and there. Of course, I didn't and I later had the privilege to get to know him scientifically and socially. He was kind and attentive to me on that very first day in Göteborg and remained exactly the same over many years. I have heard similar stories from other people of my vintage. Such consistent generosity of spirit is extremely rare. I was fortunate to also experience it with Bob Roth. This is a standard that I aspire to emulate in my own career.



**ACNP Annual Meeting, San Juan, 2004.**  
**L-R Pradeep Nathan, Kjell Svensson, Frank**  
**Lotrich, Arvid Carlsson, Matthew Galloway**

*Marina Wolf, Ph.D.*

The death of a colleague notice I received from ACNP concerning the death of Arvid Carlsson came as an extreme body blow. These announcements are always hard to take but in this case, it concerned not only a colleague but a good friend as well.



**Arvid Carlsson after dissertation**  
**at KL in 1965**

I met Arvid on the first day he arrived in Dr. Brodie's laboratory at the NIH in 1955. We were awaiting the arrival of two visiting scientists that day, one from England and one from Sweden. When Dr. Carlsson walked into my lab and started talking to me, I thought he was the scientist from England. He spoke much better English, than my Brooklyn version.

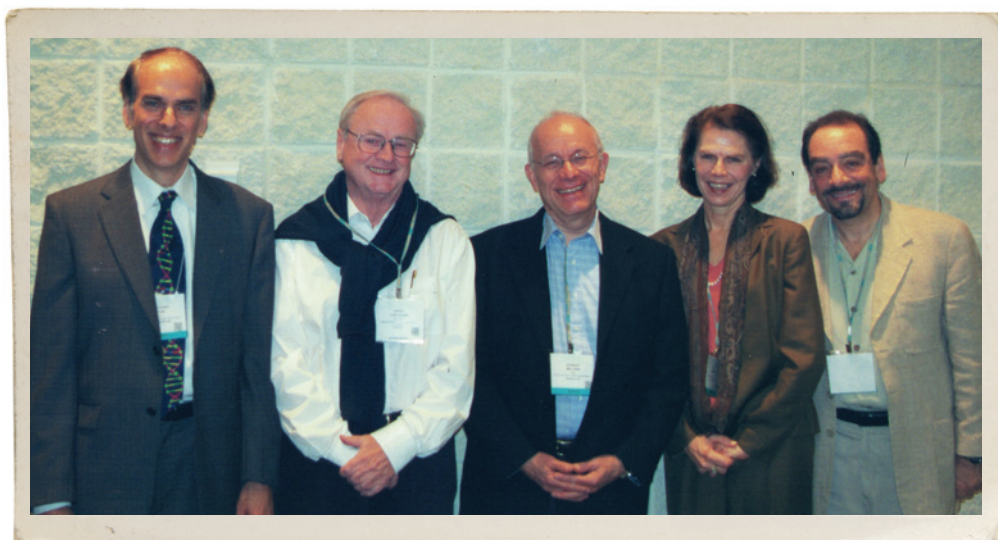
We shared a lab together for the better part of the year, working separately, on the role of serotonin, norepinephrine and from Arvid's point of view dopamine in the brain. Even this early, he thought dopamine was a hormone in its own right and not merely involved in the synthesis of norepinephrine. I am extremely proud to be the co-author on a review article with a future Nobel prize winner. Shore et al. N.Y. Acad. Sci. 66 609-615 1957 on the role of serotonin in reserpine action.

Arvid accompanied my wife and me on one of our monthly trips to the Big Apple. He was great company, on this five-hour ride, and I remember it fondly. We then met periodically over the next 35 years at various meetings and symposia. The last time I saw Arvid was at a birthday celebration we had for Dr. Brody in Stockholm in about 1990.

He will be missed by all who knew him, respected him and considered him a good friend.

*Ronald Kuntzman, Ph.D.*

One of Dr. Carlsson's less-publicized predictions became one of his greatest medical successes. He reasoned that because activation of the dopamine auto-receptor decreased dopamine release, and that too much dopamine stimulation of the D2 class of dopamine receptors contributed to schizophrenia, a partial agonist at the dopamine auto-receptor would treat schizophrenia. Such a drug would not only suppress dopamine release in the brains of schizophrenic patients, it might also bind to and lower post-synaptic D2 receptor signaling at the neuron targets of dopamine. These combined actions might have antipsychotic properties like the potent D2 receptor antagonists that at the time were the mainstay of treating psychotic patients. But this new class of drugs might not have the side effects D2 antagonists were becoming infamous for, such as creating symptoms of Parkinson's disease.



**Dr. Carlsson and ACNP friends before SFN 2002 symposium**

The first drugs that were made with Arvid's partial agonist concept in mind appeared in the early 1980s. Like those that I worked on at that time and tested in the clinic with Dr. Carol Tamminga, these early drugs produced too much agonism at the D2 receptor, and some that were tested in patients actually worsened their psychosis. This reinforced Arvid's dopamine overactivity hypothesis of schizophrenia, validated the D2 receptor as the likely target, and told us that even lower intrinsic D2 agonism was needed for the ideal drug.

Such a partial D2 agonist drug, aripiprazole, was created by chemists at Otsuka Pharmaceuticals over a decade later. We at Otsuka also discovered a similar action of aripiprazole at the serotonin 5HT<sub>1A</sub> receptor. In a collegial and productive collaboration with Otsuka and its new development partner, Bristol-Myers Squibb, Dr. Carlsson proposed the term "dopamine-serotonin system stabilizer" to succinctly describe Aripiprazole's mechanism of action. The dual D2-5HT<sub>1A</sub> partial agonism of this drug was concrete support for this description, and the term resonated with psychiatrists.

Aripiprazole was approved by the FDA in 2002 for the treatment of schizophrenia. Its dopamine-serotonin stabilizing mechanism also supported trials and FDA approval for patients with bipolar disorder and depression, making it the first-in-class partial agonist and the biggest selling drug worldwide in 2014.

Arvid's description of his theory for partial D2 agonists and culmination of the theory with Aripiprazole, now marketed as Abilify, were featured in an all-ACNP member symposium, "Novel Approaches and Effective Treatments for Schizophrenia", along with Tony Altar, Herbert Meltzer, Carol Tamminga, and Daniel Weinberger (Left to right, color photo) at the 2002 Society for Neuroscience meeting. For all of us participants, Dr. Carlsson's gentle nature and elegance of thought made a life-long impact as we strive to emulate, and hope to achieve, similar progress for patients.

*Tony Altar, Ph.D.*

I had the opportunity to interact with Arvid on many occasions early in my career. I greatly appreciated his insightful comments related to my work. I was very impressed that someone who had achieved so much in his career was still interested in interacting with, learning from, and supporting someone who was just starting their career. His behavior was a model that I have attempted to emulate.

*John H. Krystal, M.D.*

Dr. Carlsson was an inspiration for my generation of scientists. He was a careful and clear thinker.

*Michael J. Kuhar, Ph.D.*



How are Arvid Carlsson's outstanding achievements in the field of neuropsychopharmacology best explained? First, he had, needless to say, a genuine talent for scientific thinking: like few others he could detect a pattern in apparently disparate observations, disregard current dogmas and come up with truly novel explanations and ideas. Second, he displayed a never-fading interest in the scientific problems at stake, which throughout his life made him avoid both leading positions within the faculty and prestigious but time-consuming honorary assignments, so that he – during the 70 years he spent in our field – could always focus on science. Third, he had an extraordinarily entrepreneurial ability to get things done. And fourth, he had sufficient self-esteem to believe in his ideas, and to defend them with stringency and vigour, also when meeting resistance. Instead of anxiously adapting to the most recent hypes and trends in science, he created trends that others came to follow.

Progress in neuropsychopharmacology is inevitably based on clinical observations and preclinical discoveries closely intertwined. More than anyone else, Arvid illustrates the benefit for a basic, preclinical neuropsychopharmacologist to always keep an eye on the clinic, and to focus his/her endeavours on important clinical problems. By doing so, Arvid managed to pave the way for a number of clinical breakthroughs. His basic studies revealing the role of dopamine for locomotion led to the introduction of levodopa as treatment for Parkinson's disease, his discovery that antipsychotic drugs act as D2 antagonists enabled – with important contributions from his own laboratory – the development of partial D2 agonists for the treatment of schizophrenia, and he was also the first to introduce a selective serotonin reuptake inhibitor for the treatment of depression. By bringing vastly improved life quality to millions of patients around the world, he provided proof of concept for the societal utility and importance of basic neuropsychopharmacological research.



**Arvid Carlsson at Nobel Laureate Celebration**



**Photo of Dr. Carlsson taken by Johan Wingborg**

While not overly humble in defending his ideas, Arvid never displayed even the slightest trace of conceit. Throughout his professional life, the intellectual issues – never prestige or position – remained central for him. In private encounters, he was friendly and easy-going, yet always intellectually stimulating. Young PhD students who turned to Arvid to discuss scientific issues were greatly encouraged and inspired by such encounters, not least because he seemed to put as much value on them as the junior interlocutor did. Numerous colleagues throughout the world, who have met him at ACNP congresses or similar venues, have similar experiences.

Having had Arvid as a teacher, colleague and friend was an outstanding privilege. But also the entire international society of neuropsychopharmacologists should be grateful for his services. Without him, our branch of science would clearly not have been the same.

*Elias Eriksson, Ph.D. and*

*Torgny H. Svensson, M.D., Ph.D.*



I was very fortunate to have Arvid Carlsson as a Ph.D. mentor at The University of Gothenburg from 1981-1986. Arvid had early on realized the importance of a close collaboration between medicinal chemists and neuropharmacologists for successful drug discovery. He worked closely with chemists at drug companies including ASTRA and also Uppsala University. Together with ASTRA Pharmaceuticals, Arvid played a key role in the discovery of the first SSRI zimelidine. Arvid's own Medicinal Chemistry group at The Department of Pharmacology discovered several key tool compounds that helped identify novel drug targets and also further our understanding of central dopamine and serotonin pharmacology. In the early 1980's he discovered the first partial D2 agonist (-)-3PPP (preclamol) and published a series of key papers around the importance of dopaminergic tone for optimal behavioral effects of partial D2 agonists. (-)-3PPP reached early clinical testing both in healthy subjects and schizophrenics. Pharmaceutical companies then searched for decades for new more drug-like partial D2 agonists and eventually Otsuka identified aripiprazole (Abilify) for psychosis. During the mid 80's Arvid's group discovered the dopamine D2 autoreceptor-preferring antagonists (+)-AJ76 and (+)-UH232 where the latter compound reached phase 1 testing. From 1987 to 1994, Arvid initiated a very productive collaboration with The Upjohn Company in Kalamazoo, MI, and I was fortunate to join his lab again after post doc training to lead the pharmacology group. During this project, the D2 autoreceptor-preferring antagonist, (-)-OSU6162, also called dopamine stabilizer was discovered. This compound progressed to clinical testing in both neurological and psychiatric indications. In the early 1980's Arvid discovered the first 5-HT1 selective agonist 8-OH-DPAT. Later during the Upjohn collaboration a highly optimized 5-HT1 agonist with drug like properties progressed phase 1 testing. After this project ended, I joined the CNS drug discovery group at Upjohn where my wife Sue worked as a medicinal chemist, subsequently we joined Eli Lilly. After leaving Sweden, we would often stop to visit Arvid and his wife Ulla-Lisa when in Gothenburg.

Arvid's scientific brilliance and enthusiasm for dopamine receptors as a drug target inspired me immensely and meant everything for my career in CNS drug discovery. Arvid was a scientific giant but treated his students almost as equals and he would always prioritize scientific discussions and lab meetings. As a mentor, he had a hands off approach that helped the students develop their innovative skills and independence. Arvid understood the importance of enthusiasm and energy and would always find space for a student that showed interest in joining the lab. Arvid really enjoyed having a good time and socializing with students and colleagues across the world. I have many fun memories from conference dinners and excursions, in particular boat cruises in the Gothenburg archipelago during warm evenings in June. I really appreciate the opportunity to have Arvid as a mentor and I will always remember our friendship.

*Kjell Svensson, Ph.D.*



ACNP Annual Meeting, San Juan 2004. Arvid Carlsson



ACNP Annual Meeting, San Juan, 2004.  
L-R Pradeep Nathan, Bernadette Cortese,  
Frank Lotrich, Arvid Carlsson, Kjell Svensson.

Dopamine (DA) neurochemistry was the major research focus in Bob Roth's lab at Yale where I was a postdoctoral fellow in the early 1980s. It is also fair to say that the leading centers of DA research excellence in the 1970s and 80s were New Haven and Göteborg. Thus meeting the "King of DA", Arvid Carlsson, in 1983 at the 5<sup>th</sup> Catecholamine meeting in Göteborg was a professional and personal highlight.

European scientific meetings were strong on planned social interactions (the ACNP annual meeting reliably follows that template) and Arvid ensured the success of 5-CA social activities by handing the responsibility to his trainees at the time, including Stefan Hjorth, Kjell Svensson, Maria Carlsson, and David Clark. Of the numerous Yale neuroscientists and trainees (e.g. Tony Grace, Dennis Charney, Marina Wolf) in Göteborg that summer, few will forget Arvid's hospitality, especially the chartered boat trip to Marstrand and dinner at the Carlsten Fortress.

My interactions with Arvid's trainees at that meeting led to longstanding relationships as we developed our careers in academia and pharma. For example, in the early 1990s Kjell worked at Pharmacia-Upjohn in Kalamazoo and through his ongoing scientific endeavors with Arvid, we were very fortunate to have Arvid as the keynote speaker at the Michigan Chapter of the Society for Neuroscience scientific meeting. Despite his scientific stature, Arvid was genuinely warm and friendly with our small group of Michigan neuroscientists at that meeting. Similar to the opportunity I had a decade earlier, the graduate students in my lab had the unique opportunity to meet a supportive mentor and the soon-to-be co-recipient of the 2000 Nobel Prize.

At the 2004 ACNP meeting in San Juan, Arvid was a keynote speaker in a symposium on "The Discovery of Monoamines in Neuropsychopharmacology"; joining Arvid on the dais was a veritable list of catecholamine luminaries, including Julius Axelrod, George Heninger, Irv Kopin, Annica Dahlström, George Aghajanian, and Bill Bunney. After the symposium, Arvid joined us at the canonical ACNP reception.

Besides establishing in the 1950s that DA was a neurotransmitter, one of Arvid's most impressive scientific discoveries was elucidating the neurobiology of DA-D2R partial agonists, first focusing on the enantiomers of 3-PPP (Clark, Hjorth, and Carlsson 1985). Then, in conjunction with long term colleague Carol Tamminga (ACNP President 2004), Arvid was a driving force to translate his preclinical studies of DA-D2R partial agonism into the prototypical 3<sup>rd</sup> generation antipsychotic aripiprazole (Tamminga and Carlsson 2002). Arvid also had interests besides DA: For example, his timely research of serotonin as a neuromodulator of glutamate neurotransmission continues to influence leading theories of schizophrenia and OCD, elegantly promulgated by his daughter and collaborator Maria (Carlsson ML *et al.* 2004). Arvid Carlsson was a gentleman, a leader in biological psychiatry, and a superb neuroscientist whose innovation spanned 5 decades, from defining the origin of homovanillic acid to conceptualization of DA stabilizers.



**ACNP Annual Meeting, San Juan, 2004.**  
**L-R Matthew Galloway, Arvid Carlsson, Kjell Svensson**

*Matthew P. Galloway, Ph.D.*



The Nobel Laureate in Medicine or Physiology of 2000, Arvid Carlsson, has left us at the age of 95. He was active during 70 years and published his last paper in the same month that he passed away.

Arvid Carlsson was born in 1923 and grew up in Lund where he also studied medicine. After his Thesis (1951) on calcium and bone tissue, he worked during some time in Bernard Brodie's lab at NIH which made him change his field of interest to the new field of brain neurotransmitters. In 1959, he became professor of pharmacology at the University of Gothenburg where he came to stay for the rest of his career.

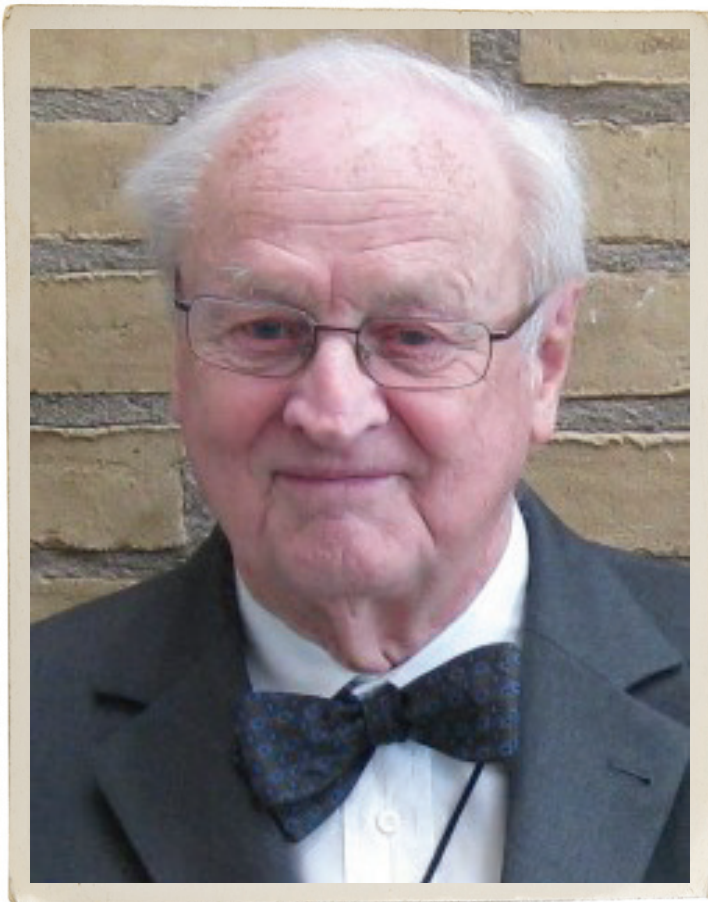
Carlsson established close collaboration with Nils-Åke Hillarp, who introduced the Falck-Hillarp immunofluorescence technique to dept of histology at Karolinska Institutet (KI) when he accepted the professorship at this institution in 1962. Hillarp's first student at KI, Kjell Fuxe, managed together with Carlsson's group in Gothenburg, Tor Magnusson and Georg Thieme, to get the fluorescence method working in brain slices, enabling the mapping of brain monoaminergic neurons together with Annica Dahlström. The mapping, first published in 1963-64, together with Arvid's group, N.-E. Andén, demonstrated elements too small to be viewed in the light microscope, and in many cases forming structures unnamed. After Hillarp's death in 1965, Kjell and I had the "mission" to travel and lecture about these formerly invisible neuronal elements, and I remember initially meeting much distrust and skepticism from older neuroanatomists and histologists around the world.

During the time after Hillarp's death, Arvid Carlsson was a strong support for our group at KI, which was needed in a surrounding where no senior researcher really knew enough about the new technique to give scientific support to us, many young students, "The Hillarp Family". Carlsson's pharmacological research supported our findings of alterations in fluorescence intensity (transmitter content) by quantitative experiment, and Arvid always was generous in giving advice and suggestion as to pharmacological tools that could be used in order to under-stand the possible function of the fluorescent structures we could demonstrate.

The mapping of the different kinds of monoaminergic systems, together with Arvid Carlsson's pharmacological research, has strongly contributed to our understanding of different diseases, like Parkinson's disease, depression and also schizophrenia. Carlsson's pioneering research, especially on Parkinson's Disease, awarded him the Nobel Prize in Medicine or Physiology in 2000. But his research also regarding schizophrenia, depression, anxiety syndrome, premenstrual tension and, lately mental fatigue must be added to his achievements. By collaborating with chemists and industry he "constructed" molecules that he theoretically felt would be active on receptores and autoreceptors. In many cases he was right and he followed with intense interest the results of the clinical studies with the drugs created. He was a pharmacologist from molecule to clinic, true translational research. It is sad that Carlsson did not live long enough to witness the outcome of the ongoing clinical trials where the dopamine stabilizer, OSU6162, is being evaluated for its proposed effect on mental fatigue.

Arvid Carlsson had a good self-esteem, and firmly believed in his ideas, He often defended his stance in scientific matters with stringency and vigour, sometimes a bit scary to a young student. But while feared as opponent in a debate, he was very friendly in private, discussions with him often contained joke and laughter. I am very lucky to have worked with and known great men and scientists like Arvid Carlsson and Nils-Åke Hillarp, both great personalities.

*Annica Dahlström, M.D., Ph.D.*



**Arvid Carlsson during celebrations of the Prize in 2000.**

I have known Dr. Arvid Carlsson since the mid-1960's when we attended an annual meeting hosted by Dr. Nathan Kline (a past-President of the ACNP). Invited speakers were asked to give 2-3 hour presentations of their research to a relatively small group of approximately 15 internationally renowned scientists. These meetings lasted a week, were held in the Caribbean and continued for 30 years. During this period, Arvid and I developed a long-lasting professional relationship. It was at one of these meetings that Arvid suggested that my wife, Dr. Blynn Bunney, and myself collaborate with him on a review paper on the actions of glutamate in schizophrenia (Bunney BG, Bunney WE Jr, Carlsson A. Schizophrenia and glutamate. In Psychopharmacology, The Fourth Generation of Progress, FE Bloom and DJ Kupfer (eds), Raven Press, pp. 1205-1214, 1995). I was honored that Arvid listed our chapter as one of 17 publications supporting his Nobel Prize nomination.

Arvid was a truly outstanding and dedicated pioneer in his field. For these reasons I nominated him for the Japan Prize which he won in 1994 for his "discovery of dopamine as a neurotransmitter and the clarification of its role in psychiatric and motor functions." The Japan Prize is awarded annually to scientists and engineers from around the world who have made significant contributions to the advancement of science and technology. Japan Prize laureates receive a certificate of merit, a prize medal and a monetary award equivalent to \$440,600 (50 million yen).

Six years later, I had the honor of being one of the scientists to successfully nominate Arvid for the 2000 Nobel Prize in Physiology or Medicine that he shared with Paul Greengard and Eric R Kandel.

Most recently I invited Arvid to serve as a member of the Brain and Behavior Foundation's Lieber Prize Committee for outstanding achievement in schizophrenia research. I am Chair of this committee and Arvid was an active member for about 5 years.

Arvid was a unique and gifted individual who helped set the standards for exemplary research in the challenging field of schizophrenia. On a personal level, Arvid was gracious and was a close colleague that I highly respected.

*William E. Bunney, M.D.*



**ACNP Annual Meeting 1997. Hawaii Anthony West discusses his research with Arvid Carlsson**



**Arvid Carlsson**