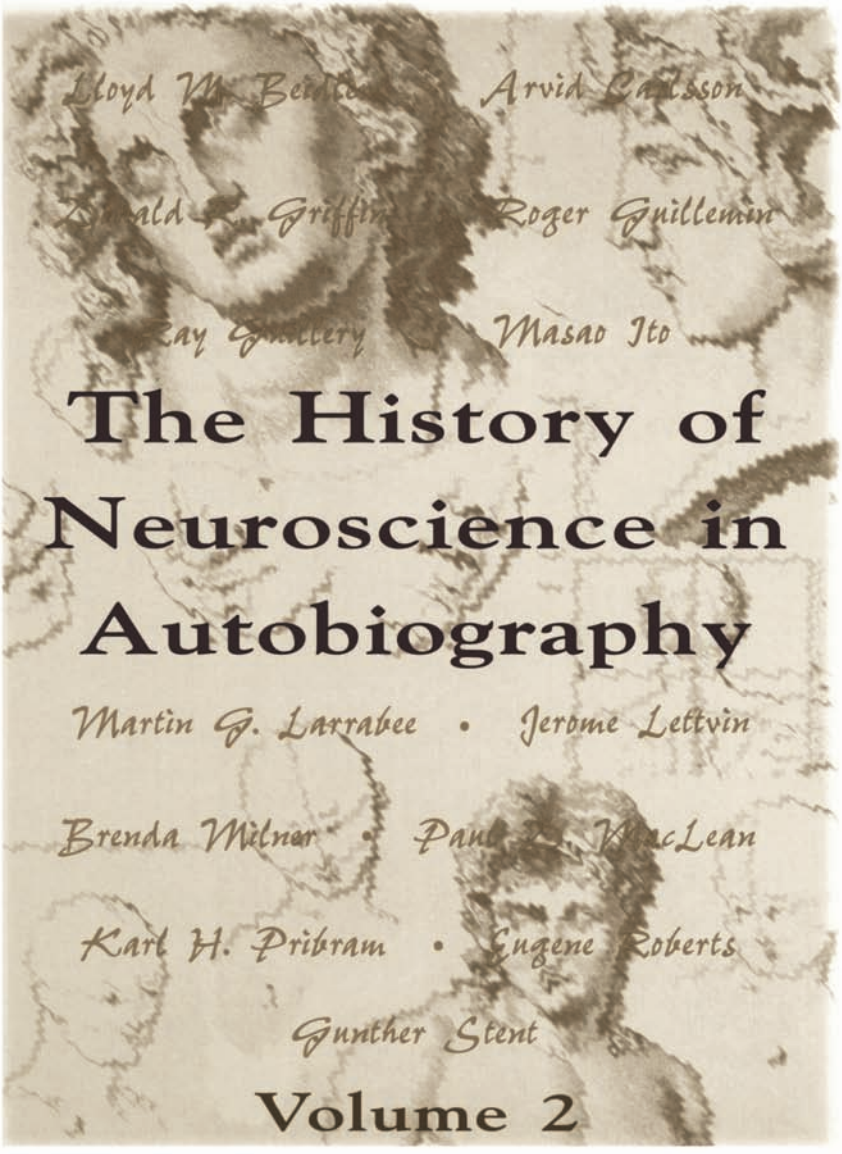

Edited by Larry R. Squire

The History of Neuroscience in Autobiography

VOLUME 2

Edited by Larry R. Squire

ACADEMIC PRESS

San Diego London Boston New York Sydney Tokyo Toronto

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Academic Press
a division of Harcourt Brace & Company
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
http://www.apnet.com

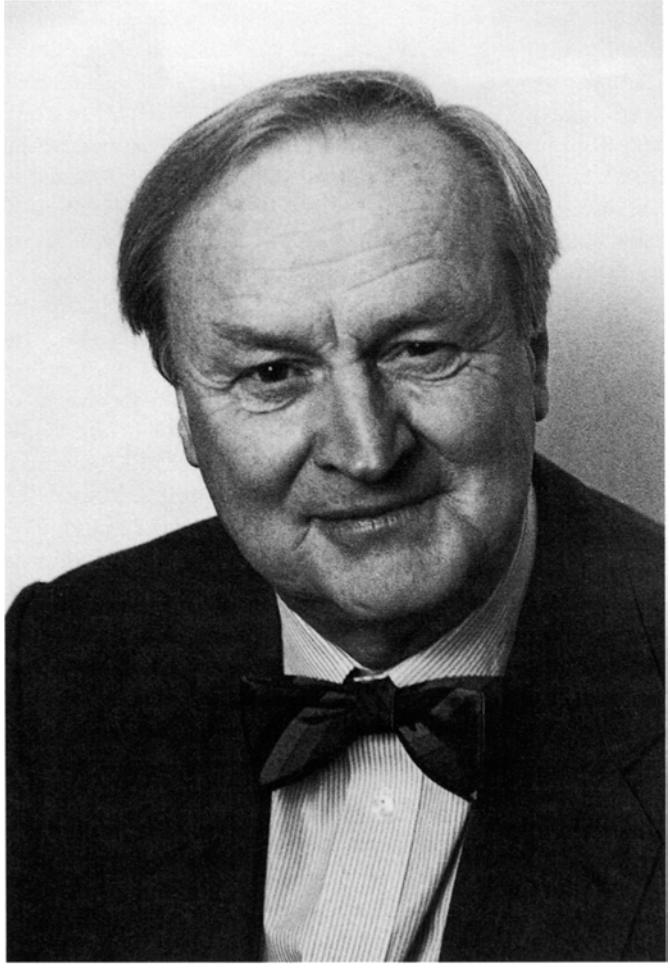
Academic Press
24-28 Oval Road, London NW1 7DX, UK
http://www.hbuk.co.uk/ap/

Library of Congress Catalog Card Number: 98-87915

International Standard Book Number: 0-12-660302-2

PRINTED IN THE UNITED STATES OF AMERICA
98 99 00 01 02 03 EB 9 8 7 6 5 4 3 2 1

Contents



Arvid Carlsson

BORN:

Uppsala, Sweden
January 25, 1923

EDUCATION:

University of Lund, M.D. (1951)
University of Lund, Ph.D. (1951)

APPOINTMENTS:

University of Gothenburg (1951)
Professor Emeritus, University of Gothenburg (1989)

HONORS AND AWARDS:

Royal Swedish Academy of Science (1975)
Wolf Prize in Medicine, Israel (1979)
Japan Prize (1994)
Foreign Associate, Institute of Medicine, National Academy of Sciences, U.S.A.

Arvid Carlsson made fundamental discoveries about the role of biogenic amines as neurotransmitters in the brain. He and his colleagues presented the first convincing evidence for dopamine as a central neurotransmitter and suggested that it plays an important role in the reward system. He also discovered dopamine autoreceptors and selective serotonin reuptake inhibitors, and he clarified the action of certain antipsychotic drugs in terms of their action on central biogenic armine systems.

The History of Neuroscience in Autobiography, Volume 2

Arvid Carlsson

I was born in Uppala, Sweden, on January 25, 1923. I grew up in an academic, middle-class family. When I was 3 years old, my father was appointed professor of history at the University of Lund, and moved my family there, from Uppsala. My father had earned his Ph.D. at the University of Uppsala and my mother had passed the master-of-arts examination. My mother kept a keen interest in research throughout her life but gave priority to raising her children and to assisting her husband in his research. However, when my father died at the age of 76 she, then 71 years old, devoted herself entirely to her favorite area of research, the legal status of Swedish women in the Middle Ages. She published a couple of books and a number of articles on this subject in Swedish, which earned her an honorary Ph.D. degree at the University of Uppsala, several years later.

We were four children in the family, and we all took academic degrees at different levels. We had a strong orientation toward the humanities. My elder brother and sister chose to study the humanities, but I chose medicine, as did my younger brother, who was 7 years younger than I. The reason for my deviating behavior was partly youthful opposition, partly some vague idea of science being more "useful" than the arts.

My childhood and youth were happy. I grew up in a stable environment with loving and supportive parents. I was probably average in my disobedience and escapades. School was endurable; I made very good marks without too much effort.

At age 16, in June 1939, I took a hitch-hiking trip to Germany for 2 weeks with a boy of the same age. This was to be my only trip outside the Nordic countries until I was 32. It occurred only two and a half months before the outbreak of World War II. We had the opportunity to talk to many Germans of varying social standing; most of them felt convinced that a war would begin as soon as the harvest was done, and they seemed to accept it, albeit reluctantly. In Berlin, I spent one night in a hostel which was run by an evangelic foundation and inhabitated by very poor people. I especially remember several Jews with long beards and sad faces, mumbling while they read a heavy book that could have been the Talmud, apparently searching for an answer and a solution in a desperate situation. Otherwise, I was not aware of the terrible actions against Jews that were probably going on around me.

My medical studies started in 1941 and went smoothly, apart from several interruptions for a couple of years of military service. Lund was, and still is, a small university town, somewhat reminiscent of Oxford. The quality of research and teaching, including that of the medical school, was good. Among the professors of the school are a couple of prominent names: Torsten Thunberg, professor of physiology, who had discovered "tissue respiration;" the dehydrogenases, and had developed a method to measure their activity. His work was simultaneous but independent of Warburg's research on the same subject, in Berlin. Warburg, but not Thunberg, was awarded the Nobel prize. Ernest Overton, professor of pharmacology, was famous for his revolutionary theories on the structure and lipid properties of the cell membrane and on the mechanism underlying narcosis. Overton had died before I started my medical studies, and Thunberg was already emeritus by then. Sadly, Overton became mentally ill in his later life; he was said to propose himself repeatedly for the Nobel prize, which he, like Thunberg, certainly deserved, but did not get. Among the most innovative of my contemporaries at the medical school was Nils Alwall, although his seminal contributions had not been generally recognized at that time. Alwall is one of the pioneers in the development of the artificial kidney. He successfully ran a department of kidney dialysis in the medical university's clinic. The internationally renowned Gambro Company was founded on the basis of this work. It is still quite successful in kidney dialysis and other biomedical technology. Another major innovation from the university was ultrasonar cardiography, which was developed by Helmuth Hertz and Inge Edler. Jörgen Lehmann was one of the most prominent among Thunberg's students. In the 1940s, in Göteborg, he discovered paraaminosalicylic acid (PAS) which, together with streptomycin, discovered by Selman Waksman, provided the first effective drug treatment for tuberculosis. Waksman, but not Lehmann, was awarded the Nobel prize for his discovery.

During the first 5 years of my medical studies, World War II was going on, rendering Sweden almost entirely isolated. During my first year, however, five Danish medical students were allowed to leave Denmark, which was then occupied by Germany, to do their anatomy studies with us, in Lund. I became especially friendly with one of them: Ib Munkvad. Among other things, we played chess together. Munkvad later became a psychiatrist with an orientation to biological psychiatry. He was instrumental in developing biological psychiatry in Denmark and is also known for formulating the hypothesis that the dyskinesias induced by dopaminergic agonists could make a model of psychosis.

Another remarkable contact with the war occurred during a few nights in October 1943, when thousands of Jews managed to escape in small fishing boats across the sound between Denmark and Sweden. This happened when one of the top members of the German occupation informed Danish authorities that a major deportation of Jews from Denmark to Germany

was forthcoming. Among the Jews who came to Sweden were a number of prominent medical researchers. They were immediately enrolled in our medical school and became important teachers and researchers.

An even sadder contact with the war occurred in the spring of 1944, when I was in my first year of clinical training. Count Folke Bernadotte, a member of the Swedish royal family, had managed to persuade German authorities to allow him to enter Germany with white buses and to pick up prisoners at concentration camps. Through Bernadotte's efforts, 30,000 prisoners, among them 11,000 Jews, escaped. Some of the prisoners were taken to Lund, where a big tent was erected in a park to house them. I was given the task of examining several of the prisoners. Many were children who suffered from malnutrition. Tuberculosis was not uncommon. However, most shocking was their mental status. They behaved like wild animals, obviously suffering from severe anguish and suspicion and they trusted nobody.

Starting in Pharmacology

At the outset of my medical studies I had decided to become a researcher, and in 1944, I was offered a modest position as *amanuens* (initially without salary), in the University of Lund's department of pharmacology, after I had passed a successful examination in that discipline. The head of that department, and at that time the only professor, was Gunnar Ahlgren. He had been Thunberg's favorite student and apparently had been an asset in the group around Thunberg. However, when he was on his own, he was not scientifically productive, but he managed to attract a number of talented students, who were to make successful careers in various medical disciplines. One of these people was Nils Alwall.

Ahlgren gave me and another student, Georg Theander, a topic to investigate: measuring the duration of action of pentylenetetrazol (Cardiazol), a convulsant that was then used frequently as an analeptic to wake up people who had taken an overdose of a hypnotic or sedative, and which was also used as a forerunner of electroconvulsive therapy. Nowadays this drug has a modest use as a diagnostic and experimental tool. To measure the action of pentylenetetrazol, Ahlgren proposed employing its awakening action against central depressants. At first we tried nitrous oxide, but to our surprise the drug was unable to antagonize its anesthetic action. We then added a subhypnotic dose of barbital and found that the combined action of barbital and nitrous axide could be antagonized, and the increase in partial pressure of nitrous oxide that was needed to inhibit the righting reflex could be used as a measure of pentylenetetrazol action. The result of this study was that the duration of action of pentyleneterazol was much longer than expected from observations on its effect in animals that were not treated with central depressants. We published our results (Carlsson

and Theander, 1946), and this first publication of ours was awarded a modest prize, intended for young medical scientists at the University of Lund. One might wonder why Ahlgren was interested in the duration of action of this drug. He never explained that to me, but when I told him about our results, he was obviously pleased, but not surprised. A plausible reason for this was that he had actually tried it on himself to antagonize a sedative and thus discovered its long duration of action.

Together with another pharmacologist, Folke Serin, I studied the action of another analeptic, nikethamide, and discovered a circadian rhythm in its lethal action. The publication of these findings (Carlsson and Serin, 1950) appears to have been the first to describe a circadian rhythm of a drug's action, according to a review article on chronobiology, which was published much later when this subject became fashionable in connection with space research.

Work on Calcium Metabolism

In 1948, Gunnar Ahlgren persuaded me to go into an entirely different area of research, calcium metabolism. At that time, radioactive tracers, among them ^{45}Ca, had become commercially available, and a Swedish drug company wanted us to test a number of calcium salts for their oral availability. I agreed to do this research. The testing of different calcium salts did not disclose anything of interest, but I used this opportunity to investigate the absorption of calcium as well as its metabolism in the skeleton by means of the new technique. That work resulted in my M.D. thesis (corresponding to the American Ph.D.) and in several subsequent papers, including the doctoral theses of two students of mine, Bertil Lindquist and Göran Bauer, who later became professors of pediatrics and orthopedic surgery, respectively. Briefly, what we found was that it is possible, contrary to the opinion at that time, to use tracer techniques to differentially measure the uptake (or "accretion") and the resorption of the bone mineral (for a review, see Bauer et al., 1961). Among other things, we discovered that vitamin D in physiological doses can stimulate not only the intestinal absorption and "accretion" but also the resorption of bone minerals. Our findings aroused some international interest and resulted in an invitation to a Gordon Conference in the summer of 1955.

Getting into Neuropsychopharmacology: Sabbatical in Bernard B. Brodie's Lab

In 1952, when I had an appointment as assistant professor and had applied for an associate professorship in the department of pharmacology, the expert committee instead appointed my competitor, Folke Serin, who later became a prominent specialist and academic teacher in internal medicine

and still remains one of my oldest friends. At the same time, the committee let me know that, in their opinion, my present research field, calcium metabolism, did not occupy a central position in pharmacology. I now felt that I had to make a choice, to either leave pharmacology and go into internal medicine (I had completed my medical education in 1951) or switch into a new research field. I decided to apply for a position as physician in the department of internal medicine of the university hospital. I worked for the whole of 1954 in that department. I found the clinical work interesting and I learned a lot during that year which, I believe, was useful in my subsequent career. However, I still found basic research too attractive to abandon. I thus contacted the professor of medical chemistry, Sune Bergström, who had proven to be helpful on previous occasions when I needed advice and support, and asked him if he could explore the possibility of my working in an American laboratory, studying chemical pharmacology. Bergström kindly wrote to one of his many friends in the United States, Bernard Witkop, a prominent organic chemist who worked at the National Institutes of Health. Witkop forwarded the letter to Sidney Udenfriend, who in turn forwarded it to his chief, Bernard Brodie. Brodie replied that I was welcome to work in his laboratory, the Laboratory of Chemical Pharmacology at the National Heart Institute, as a visiting scientist.

In late August 1955, after attending the Gordon Conference on Mineral Metabolism, I began work in Dr. Brodie's laboratory. The first day I had lunch in the cafeteria of Building 10 with Drs. Brodie and Udenfriend. I got the impression that Brodie had not yet made up his mind whether he would take me on or let me work with Dr. Udenfriend. He told me that he wanted me to work with him and Parkhurst A. Shore on the action of reserpine on the storage of serotonin in blood platelets *in vitro*. I started immediately on this project. Adequate equipment had already been acquired.

The following month I was frustrated because the results were entirely negative. Moreover, I was shocked to find that in this new environment, my competence as a scientist was by no means taken for granted. This was of course understandable but still shocking in view of the way I had been treated in my home laboratory. After a month of completely negative results the *in vitro* system suddenly started to work beautifully. The reason for this dramatic change was never fully clarified, but it coincided with the introduction of a new batch of reserpine. Thus, we could demonstrate a clear-cut and specific blockade by very low concentrations of reserpine on the storage of serotonin in platelets. This was the first demonstration of a direct action of reserpine on the storage of serotonin (Carlsson *et al.*, 1957a).

I can hardly overemphasize how lucky I was to get that opportunity to work in Dr. Brodie's laboratory during a very dramatic period, when drug research was undergoing a revolution and psychopharmacology was *in statu nascendi*. This was only 3 years after the discovery of the antipsychotic action of chlorpromazine and 1 or 2 years after the rediscovery of the

antipsychotic action of reserpine (reported by psychiatrists in India, three decades earlier). At this point I was introduced by Drs. Brodie and Shore to the most modern methods of biochemical pharmacology as well as to the hottest area of psychopharmacology at that time.

What kind of person was Bernard B. Brodie, the man who has played the most important role in my scientific career? It is difficult to answer this question in a few words. He was obviously richly gifted and had a lot of charisma. His background was in organic chemistry, but he had specialized in drug metabolism, which he had pioneered by developing a multitude of methods for measuring the levels of drugs and their metabolites in tissues and body fluids. At the time of my visit, the prototype of a new instrument, a spectrophotofluorimeter, had been constructed in Brodie's laboratory by Robert Bowman in collaboration with Udenfriend. This instrument was to revolutionize the measurement not only of drugs but also of several endogenous compounds of great physiological interest. It combined high sensitivity with specificity. For several decades this instrument played a dominant role in biochemical pharmacology. It has now been surpassed by even more powerful equipment.

Brodie had remarkable intuition. When he sensed that a research area was "hot" he did not hesitate to go into it, even if his knowledge of the area was limited. Thus, when he learned about the antipsychotic actions of chlorpromazine and reserpine and the finding that lysergic acid diethylamide (LSD) seemed to possess affinity for 5-hydroxytryptamine (5HT) receptors, he started to do experiments with these drugs in order to find out more about their relation to serotonin. Although some of these experiments were primitive and inconclusive, they culminated in experiments in which reserpine was found to have a dramatic effect on the storage of serotonin in tissues. This seminal discovery was made only a few months before I joined Brodie's group.

Back to Sweden: Work on Reserpine, Dopa, and Dopamine

After spending 5 fruitful months in Brodie's lab I returned to Lund, having been recently appointed as associate professor of pharmacology. Before my return I had contacted Nils-Åke Hillarp, who was working as associate professor of histology at the University of Lund. Hillarp was an ingenious scientist. At that time he had already made a number of remarkable contributions to neuroscience as well as to endocrinology. Hillarp and I worked together until his untimely death in 1965. In the mid-1950s Hillarp's interest focused on the adrenal medulla, where he had discovered that cell organelles store the adrenal medullary hormones and discovered the role of adenasine triphosphate (ATP) as a counter-ion in the storage complex. With Hillarp I discovered that reserpine caused depletion of the adrenal medullary hormones (Carlsson and Hillarp, 1956), and soon afterward I

discovered, together with my students Åke Bertler and Evald Rosengren, that similar depletion took place in other tissues, including brain (Bertler et al., 1956; Carlsson et al., 1957b). These findings offered a possible explanation of the hypotensive action of reserpine. This was confirmed by experiments where stimulation of sympathetic nerves no longer caused release of the neurotransmitter noradrenaline following reserpine treatment (for a review and references, see Carlsson, 1987).

These discoveries excited us, but at the same time, they placed me in an awkward position with my highly esteemed mentors, Drs. Brodie and Shore. Our results challenged their interpretations in two respects. First, our data indicated that the action of reserpine should not necessarily be interpreted as due solely to its effect on serotonin; second, our results argued against their proposal that continuous release of the putative neurotransmitter serotonin onto its receptors is responsible for the action of the drug. Rather, our results suggested that at least the hypotensive action was due to an effect on catecholamines and that this effect was caused by depletion rather than release. Unfortunately, this divergence of opinion was to place my mentors and me in different camps for many years to come and led to a many sometimes intense debates, in writing as well as at various meetings. This was especially unfortunate, because despite these divergences, we were on much more common ground than a great number of other workers in this field.

To resolve the issue of the mode of action of reserpine my colleagues and I administered 3,4-dihydroxyphenylalanine (dopa) to reserpine-treated rabbits and mice and discovered the central stimulant action of this amino acid as well as its ability to reverse the akinetic and sedative action of reserpine. Because the serotonin precursor 5-hydroxytryptophan was not capable of reversing the action of reserpine we suggested that depletion of catecholamines, rather than serotonin, was responsible for some important behavioral effects of reserpine (Carlsson et al., 1957c). However, when we analyzed the brains of the animals treated with reserpine and dopa, we found them still fully depleted of noradrenaline. Further analysis revealed that the behavioral action of dopa was closely correlated to the accumulation of dopamine in the brain. Moreover, our studies disclosed that dopamine is a normal brain constituent and is released by reserpine, as are noradrenaline and serotonin. The data suggested to us that dopamine is not just a precursor to noradrenaline, as was generally believed at that time, but is an endogenous agonist in its own right (Carlsson et al., 1958). This received further support when Bertler and Rosengren (1959) shortly afterward discovered the marked difference in regional distribution between dopamine and noradrenaline, the former being largely accumulated in the basal ganglia. We could thus suggest that the Parkinsonism induced by reserpine is due to dopamine depletion, which can be restored by L-dopa, and that dopamine is involved in the control of extrapyramidal motor

functions. This was further supported by the finding that the motor disturbances in Huntington's chorea can be alleviated by reserpine and similar drugs (Carlsson, 1959).

Encountering Disbelief from the British Pioneers

Thus, for the first time, evidence was forthcoming for a role for endogenous agonists, present in brain tissue, in animal behavior. At first serotonin had come into focus, but the subsequent experiments pointed to a role for the catecholamines, and especially dopamine, for the sedative and akinetic actions of reserpine, and the reversal of these actions by L-dopa. We were excited by these findings but were disappointed to meet with considerable resistance to our views by some prominent investigators, especially at a Ciba Symposium on adrenergic mechanisms, held in London in the spring of 1960 (Vane et al., 1960), which was a rather strange experience. At this meeting practically all prominent workers and pioneers in the catecholamine field were present. It was much dominated by the strong group of British pharmacologists, headed by Sir Henry Dale. I was impressed to see how the British pharmacologists, as well as many other former Dale associates, behaved toward Sir Henry, like school children to their teacher, although some of them had indeed reached a mature age. It was also remarkable to find how little disagreement there was among these people, who behaved more or less like a football team. At this meeting I reported on some of our data indicating a role for the catecholamines in motor function and alertness. No doubts were expressed about our observations as such. In fact, Drs. Blaschko and Chrusciel presented observations that confirmed our findings on some essential points.

I have reread the discussions recorded in the Symposium volume, and I am still puzzled by them. To start with, in Sir John Gaddum's summary of the session on central adrenergic mechanisms, he concluded: "The meeting was in a critical mood, and no-one ventured to speculate on the relation between catecholamines and the function of the brain" (Vane et al., 1960, p. 584). My paper, which was titled "On the biochemistry and possible functions of dopamine and noradrenaline in brain," as well as a considerable number of remarks that I made during the discussion sessions, dealt precisely with this issue. Obviously, in Gaddum's mind, I was nobody! Why did he and the other British pharmacologists so completely ignore the evidence that we presented? At first there was some concern about L-dopa being a "poison." This appeared to be based mainly on the observation by Weil-Malherbe that large doses of L-dopa, given together with a monoamine oxidase inhibitor, could be lethal. This discussion ended with a concluding remark by Sir Henry Dale (page 551) that L-dopa is, in fact, a poison, which he found remarkable for an amino acid. Then Paton referred to unpublished data by Edith Bülbring, suggesting the presence of catecholamines in glia

rather than in nerve cells. Responding to a question by Dale, Marthe Vogt concluded (p. 551) that there was absolutely no evidence that the catecholamines in the brain act as synaptic transmitters or serve a general hormonal function. Proposals by me and others that this may be the case were said to depend on the particular pharmacological agents used. A critical survey of all the available evidence led, according to Marthe Vogt, to the conclusion that any of the theories on a relation between catecholamines or serotonin and behavior is "a construction which some day will be amended" (p. 579).

In order to understand the reluctance of some of the most prominent pioneers in chemical transmission to accept that monoamines have a role in brain function it may help to recall that at that time, brain research was dominated by electrophysiology. A vivid debate had been ongoing between Dale and J. C. Eccles about the role of electrical versus chemical transmission in general, and it is possible that Dale had been impressed by the arguments in favor of electrical transmission, at least concerning the brain. From a classical neurophysiological point of view it must have seemed hard to accept, for example, that a loss of nerve function could be alleviated by administering a chemical such as dopamine (given as its precursor, L-dopa). With such a perspective, the alternative interpretation that L-dopa effects were caused by some strange kind of amino acid toxicity may seem less far-fetched.

Visualizing the Monoamines in the Fluorescence Microscope

In any event, this meeting taught me that a scientist's life can sometimes be tough. I suppose that this experience gave me some immunity to criticism and resistance, which I, and presumably most other scientists, have often met with in our professional lives. At this meeting, Hillarp and I decided to further increase our efforts to convince people of our ideas. I had just been appointed professor and chairman of the department of pharmacology at the University of Göteborg. We agreed that Hillarp should join me to work on catecholamines in the new department, provided that he could be freed from his associate professorship in histology in Lund. We applied for the necessary funds from the Swedish Medical Research Council, and our grant was approved. We decided to focus on two problems: to investigate a possible active amine-uptake mechanism by the adrenal medullary granules and its inhibition by reserpine, and to try to develop a histochemical fluorescence method to visualize the catecholamines in tissues. Both projects turned out to be successful. Because detailed accounts of this work have been given elsewhere (Carlsson, 1987; Dahlström and Carlsson, 1986; Carlsson et al., 1962a, 1964; Andén et al., 1964b), they will not be repeated here. Both discoveries had a considerable impact on the scientific community's acceptance of the concept of chemical transmission in the central nervous system (CNS) and on the development of monoaminergic synaptology.

A Paradigm Shift: Chemical Transmission in the Brain and Emerging Synaptology

During the early part of the 1960s, a large number of observations were made in Sweden by Hillarp, me, and our respective collaborators, based on the combination of histochemical, biochemical, and functional studies, and by using a number of pharmacological tools. These observations doubtless contributed greatly to convincing the scientific community of the role of biogenic amines as neurotransmitters and, in more general terms, on chemical transmission as an important physiological principle in the brain. That we can speak of a true paradigm shift during the early 1960s is evident from a comparison between the proceedings of the Ciba meeting on adrenogic mechanisms in London, and an international symposium held in Stockholm, in February 1965, titled "Mechanisms of Release of Biogenic Amines" (von Euler et al., 1966). In his introductory remarks to this symposium, Uvnäs stated that, "these amines play an important role as chemical mediators in the peripheral and central system." None of the distinguished participants in this symposium expressed any doubts on this point.

While the skepticism about the role of chemical transmission in the brain had thus faded, it was followed by an intense debate on the function of various synaptic structures and mechanisms. A major issue dealt with the role of synaptic vesicles in the transmission mechanism. In the mid-1960s opinions still differed on the subcellular distribution of the monoaminergic transmitters. In the fluorescence microscope the accumulation of monoamines in the so-called varicosities of nerve terminals was obvious. This corresponded to the distribution of synaptic vesicles, as observed with the electron microscope. In fact, Hökfelt in 1968 was able to demonstrate the localization of central as well as peripheral monoamines to synaptic vesicles using the electron microscope. However, there was controversy about the nature and size of the extravesicular (or extragranular) neurotransmitter pool. This is evident from the recorded discussions from the Stockholm symposium on biogenic amines. For example, on p. 471, Drs. Julius Axelrod and Ulf von Euler maintained that a considerable part of the transmitter was located outside the granules, mainly in a bound form. This fraction was proposed to be more important than the granular fraction, because it was believed to be more readily available for release. Indeed, the granules were facetiously referred to as garbage cans. Our group had arrived at a different model of the synapse, based on combined biochemical, histochemical, and pharmacological data (Carlsson, 1966). We were convinced that the granules were essential in transmission, and that the transmitter had to be taken up by them in order to become available for release by the nerve impulse. In favor of this contention was our finding that reserpine's site of action is the amine uptake mechanism of the granules. The failure of adrenergic transmission as well as the behavioral actions of

reserpine were correlated with the blockade of granular uptake induced by the drug, rather than to the size of the transmitter stores (Lundborg, 1963). Moreover, extragranular noradrenaline (accumulated in adrenergic nerves by pretreatment with reserpine, followed by an inhibitor of monoamine oxidase (MAO) and systemically administered noradrenaline) was unavailable for release by the nerve impulse, as observed histochemically (Malmfors, 1965). We proposed that, under normal conditions, the extragranular fraction of monoaminergic transmitters was very small, owing to the presence of MAO intracellularly, and that the evidence presented to the contrary was an artefact. Subsequent work in numerous laboratories has lent support to these views. At the Stockholm symposium, William Douglas presented evidence suggesting a calcium-triggered fusion between the granule and the cell membrane, which preceded the release. The release is now generally assumed to take place as exocytosis, even though a fractional, rather than complete, extrusion of the granule content seems to be the most likely alternative. For a discussion of this issue, see a recent paper by Folkow and Nilsson (1997), presented as a tribute to the late Jan Häggendal.

An important issue in the early debate on synaptic structures and mechanisms dealt with the site of action of major psychotropic drugs. In their first studies on reserpine, Brodie and his colleagues had proposed that the agent was capable of releasing serotonin onto receptors, which would suggest the cell membrane to be its site of action. However, our observations demonstrated that reserpine acted on the storage mechanism of the synaptic vesicles. As to the tricyclic antidepressants, Brodie et al. suggested that their site of action was the synaptic vesicles. In their original studies, reported in 1960, Axelrod et al. (see Axelrod, 1964) observed that the uptake of circulating catecholamines by adrenergic nerves could be blocked by a variety of drugs, such as reserpine, chlorpromazine, cocaine, and imipramine. These studies obviously did not distinguish between a number of different pharmacological mechanisms. In our own combined biochemical (Carlsson et al., 1962b, see also the independent, simultaneous work of Kirshner, 1962) and histochemical studies (Malmfors, 1965), two different amine-uptake mechanisms could be distinguished: uptake at the level of the cell membrane, sensitive to cocaine and imipramine, for example, and uptake by the storage granules or synaptic vesicles, sensitive to reserpine, for example. These two mechanisms must be distinguished from each other because of the different, functional consequences of their inhibition—enhancement and inhibition, respectively—of monoaminergic neurotransmission.

Disclosure of the Mode of Action of the Major Antipsychotic Agents

In the early 1960s we were puzzled that the major antipsychotic agents, such as chlorpromazine and haloperidol, had a reserpine-like pharmacolog-

ical and clinical profile, yet lacked the monoamine-depleting properties of the latter drug. We found that chlorpromazine and haloperidol accelerated the formation of the dopamine metabolite 3-methoxytyramine and the noradrenaline metabolite normetanephrine, while leaving the neurotransmitter levels unchanged. In support of the specificity, neither promethazine, a sedative phenothiazine lacking antipsychotic and neuroleptic properties, nor the adrenergic blocker phenoxybenzamine caused any change in the turnover of the catecholamines (Carlsson and Lindqvist, 1963). To us it did not seem farfetched, then, to propose that rather than reducing the availability of monoamines, as does reserpine, the major antipsychotic drugs block the receptors that are involved in dopamine and noradrenaline neurotransmission. This would explain their reserpine-like pharmacological profile. To account for the enhanced catecholamine turnover we proposed that neurons can increase their physiological activity in response to a receptor blockade. This, I believe, was the first time that a receptor-mediated feedback control for neuronal activity was proposed. These findings and interpretations have been amply confirmed and extended by numerous workers, using a variety of techniques. In the following year our research group discovered the neuroleptic-induced increase in the concentrations of deaminated dopamine metabolites (Andén et al., 1964a). Later papers by Andén et al. (1970a) from our own laboratory and by Nybäck and Sedvall (1970) emphasized the effect of neuroleptics on dopamine, and the work of Aghajanian and Bunney (1974) described the effect of dopaminergic agonists and antagonists on the firing of dopaminergic neurons. Other important, subsequent discoveries were the dopamine-sensitive adenylate cyclase by Greengard and his colleagues (Kebabian and Greengard, 1971) and the binding of dopamine to specific cell-membrane sites, from which it could be displaced by neuroleptics (Seeman et al., 1976; Creese et al., 1976).

These observations formed the basis for the "dopamine hypothesis of schizophrenia." It should be noted, however, that the paper by Lindqvist and me did not particularly emphasize dopamine, even though the adrenergic blocker was inactive and the effect of haloperidol was more striking on dopamine than on noradrenaline turnover. In fact, we did not exclude the possibility that serotonin receptors could also be involved in the antipsychotic action. Even though our subsequent research favored an important role for the dopamine-receptor blockade in the antipsychotic action, the data could hardly exclude a contributory role of other monoaminergic receptors. Such a possibility has gained increased interest more recently, thanks to research on clozapine and other atypical antipsychotic agents.

Dopamine, the Reward System, and Drug Dependence

That dopamine plays a crucial role in the reward system and in drug dependence is now generally recognized. Our research group became interested

in this problem in the mid-1960s, when we and others found that amphetamine releases dopamine and that its stimulating action can be blocked by an inhibitor of catecholamine synthesis, α-methyltyrosine. Somewhat later, Gunne also found that the stimulant and euphoriant action of amphetamine in humans could be prevented by treatment with α-methyltyrosine. Our further pursuit of this line of research led to the concept that dopamine is also involved in the psychostimulant and dependence-producing action of some other major drugs of abuse, such as the opiates and ethanol. Thus, in ethanol, we found that its stimulating action in animals is accompanied by an increase in dopamine synthesis (Carlsson and Lindqvist, 1973) and can be prevented by α-methyltyrosine, which can also prevent the stimulating and euphoriant action of ethanol in humans (for a review, see Engel and Carlsson, 1977).

Our studies on the role of dopamine and other neurotransmitters in drug dependence were later pursued and extended by Jörgen Engel and his colleagues. Engel is my successor as professor of pharmacology in our department.

The fundamental role of dopamine in the reward system also has important implications for the treatment of various maladies with neuroleptic drugs. Since they are all dopamine-receptor blocking agents, they are likely to impair the reward system, resulting in dysphoria and anhedonia. Such side effects may be at least as serious as the extrapyramidal side effects. In fact, because the site of action of the reward system is probably in the ventral striatum, which appears to be more sensitive to dopamine-receptor blockade than the dorsal striatum, an impairment of the reward system is likely to show up in lower doses of neuroleptics than the extrapyramidal side effects, which mainly reside in the dorsal striatum.

The Discovery of Dopaminergic Autoreceptors and Their Potential Role as Targets for Drugs

We were investigating autoreceptors in 1963, even though we did not understand it at that time. The nature of the feedback mechanism that we had proposed was obscure, apart from its mediation via receptors that respond to the neurotransmitter in question. Some have said that we proposed a feedback loop, but this is not true. It was not until the early 1970s that we were able to examine the problem further. In the meantime, Farnebo and Hamberger, in 1971, had proposed the existence of presynaptic receptors as one possible explanation for their observation that the release of catecholamines from brain slices after field stimulation could be influenced by receptor agonists and antagonists. After we had developed a method to measure the first, rate-limiting step in the synthesis of catecholamines *in vivo* we discovered that the synthesis of dopamine could be inhibited by a dopamine-receptor agonist and stimulated by an antagonist,

even after exclusion of a feedback loop by means of axotomy (Kehr et al., 1972). Thus, we felt convinced that the receptors involved were presynaptic. In order to avoid confusion over the nature of these receptors, which appeared to be located on various parts of the neuron and possessed a special functional significance among the presynaptic receptors, I proposed to call them "autoreceptors" (Carlsson, 1975), a word that later became generally accepted. I also proposed that agents with selective action on autoreceptors may prove useful not only as research tools but also as therapeutic agents. We already knew that low doses of a dopaminergic receptor agonist could have a preferential action on autoreceptors and thus cause a paradoxical behavioral inhibition.

Four years later, our collaboration with skillful organic chemists led to the discovery of 3-PPP. In our original studies this agent appeared to be highly selective for dopaminergic autoreceptors, but a few years later, when we had the opportunity to study the pure enantiomers of 3-PPP, we discovered that they had different pharmacological profiles. The + form turned out to be an agonist rather similar to apomorphine, though with somewhat lower intrinsic activity, whereas the – form was found to have agonistic properties on the dopaminergic autoreceptors, but with moderate intrinsic activity. On postsynaptic dopamine (D_2) receptors the – form behaved essentially as an antagonist, although it seemed devoid of cataleptogenic properties (for a review, see Clark et al., 1985).

Subsequent work revealed that the profile of (–)-3-PPP, now also called preclamol, is shared by many other dopaminergic agents, which all appear to have in common the property of being partial receptor agonists. Several such agents, with varying intrinsic activities and specificity, have been or are now being tested *in vivo,* mainly as antipsychotic agents. In fact, these agents may test two different, though somewhat related, hypotheses: First, that a preferentially or selectively acting dopaminergic autoreceptor agonist may have antipsychotic properties, though with fewer side effects than the classical neuroleptics, and second, that a partial dopamine receptor agonist may possess a suitable intrinsic activity to avoid extrapyramidal side effects, including tardive dyskinesias, and yet be sufficiently antagonistic on postsynaptic receptors to allow for an antipsychotic action.

In 1986, I received a letter from Carol Tamminga of the Maryland Psychiatric Research Center, in which she enquired about the possibility of trying (–)-3-PPP in patients with schizophrenia. She had been informed by her chief, William Carpenter, about a presentation of mine at a meeting in Heidelberg, in which I had reported preclinical data on this agent, indicating antipsychotic properties and lack of extrapyramidal side effects. Dr. Tamminga had a long-standing interest in the possible usefulness of dopaminergic agonists in the treatment of schizophrenia, starting from her discovery that apomorphine, given in single doses, can alleviate psychotic symptoms in patients with schizophrenia (Tamminga et al., 1978). I replied

that I would be delighted to supply her with the drug and the documents she would need to conduct a new-drug investigation and to assist her as much as possible in carrying out such a study. With her letter a most stimulating and fruitful collaboration began, and is still ongoing.

It took some time to obtain the Investigational New Drug application from the Food and Drug Administration. In 1989, the first series of patients started to receive single, escalating intramuscular doses of (−)-3-PPP or of placebo, in a double-blind study. The results were encouraging. Psychotic symptoms tended to be reduced, and the drug appeared to be well tolerated (Tamminga et al., 1992). We subsequently gave patients with schizophrenia escalating, single oral doses of the drug in an effort to obtain the same plasma levels as we had achieved in the parenteral study. Again, the results were promising. The next step was to give repeated doses of the drug or placebo in a double-blind crossover design. We found that 1 week of treatment with (−)-3-PPP caused a significant antipsychotic response, but that a therapeutic effect did not remain after 2 or 3 weeks. Apparently, some kind of tolerance had developed (Lahti et al., 1997). As expected on the basis of the preclinical data, extrapyramidal effects were not detectable. In fact, (−)-3-PPP is anticataleptic in rats and has been shown to possess mild anti-Parkinson action in clinical studies (Pirtosek et al., 1993). In these studies, the partial dopamine receptor agonism became apparent, in that the drug was able to antagonize dopamine-receptor agonists, while at the same time having anti-Parkinson properties.

Further studies are underway to investigate the possibility of developing (−)-3-PPP to a therapeutically useful antipsychotic agent. If these efforts are successful, they will no doubt represent a breakthrough by being antipsychotic without manifesting the serious side effects induced by too-severe dopamine-receptor blockade. These effects are not limited to motor functions but extend to the endocrine system and to severe dysphoria, probably related to interference with the well-established function of dopamine in the reward system.

Another line of autoreceptor research deals with the preferential dopamine autoreceptor antagonists, which have likewise been developed by our research group (see Svensson et al., 1986). A prototype for these agents is (+)-UH 232 (*N,N*-dipropyl-cis-(+)-(1*S*,2*R*)-5-methoxy-1-methyl-2-aminotetralin). In animal experiments this agent presents a fascinating mixture of behaviorally stimulating and depressant properties. In lower dosages it tends to be predominantly stimulating, apparently the result of a preferential antagonistic action on dopaminergic autoreceptors, whereas higher doses tend to be predominantly depressant, especially if the animal's behavioral baseline level is high. This latter action is apparently caused by an antagonistic action on dopaminergic postsynaptic receptors. In rats, self-administered cocaine (+)-UH232 and related agents have been found to reduce the motivation for this drug-seeking behavior (Roberts and Ranaldi,

1995). So far, (+)-UH232 has only been given in single, oral doses to human volunteers and patients with schizophrenia (unpublished data). In my laboratory a number of compounds with possibly more favorable properties, such as OSU 6162, have been prepared and are now being further evaluated. Preliminary observations suggest that they represent a somewhat heterogeneous group of agents, for reasons such as their effects on D3 receptors and other receptor subtypes that are only partly understood.

After working on the concept of autoreceptors for about 25 years, with the development of preferentially acting dopaminergic agonists and antagonists, my colleagues and I are pleased to note that this area of research is now active. However, another 5 to 10 years will presumably be needed to obtain a reasonably clear evaluation of the autoreceptor approach in psychopharmacology.

Discovery of Selective Serotonin Reuptake Inhibitors

Whereas dopamine, like Cinderella, had to dwell in obscurity for a long time until it came into glory, serotonin took another path. Very soon after the discovery was made that serotonin is a normal brain constituent, it started to attract a great deal of interest. Moreover, a link between serotonin and LSD was discovered and brain serotonin was proposed to play a role in keeping us sane (see Gaddum, 1953). This culminated with the discovery of reserpine's serotonin-depleting action. However, when subsequent work disclosed the catecholamine-depleting action of reserpine, noradrenaline and later dopamine came into focus, and serotonin lost its dominant place. But serotonin has made a splendid comeback in a number of different contexts.

The tricyclic antidepressants were first shown to block the reuptake of noradrenaline, and thus this neurotransmitter was proposed to play a major role in the control of mood and drive. Later we discovered, however, that the tricyclic antidepressants also have powerful actions on the reuptake of serotonin and that this applied particularly to some of the most widely used antidepressants (Carlsson et al., 1968; also see Carlsson, 1976, 1982, 1986). Together with the late Dr. Hans Corrodi, a highly talented Swiss chemist, we then developed the first selective 5-HT uptake inhibitor, zimelidine (Berntsson et al., 1972), which turned out to be an active antidepressant agent, as demonstrated in several well-controlled clinical studies (see Carlsson et al., 1981) but was withdrawn because of rare but serious side effects. Subsequently, a number of other selective serotonin uptake inhibitors were developed and were likewise found to be efficacious antidepressants. This, in conjunction with the previous discovery of an antidepressant action of L-tryptophan (Coppen, 1963) and of reduced concentrations of 5-hydroxyindoleacetic acid in the cerebrospinal fluid of patients with depression and those who were suicidal (Träskman et al., 1981), led to a

marked increase in the visibility of serotonin, which is now generally recognized as an important neurotransmitter in the control of mood.

More recently, serotonin also started to attract a great deal of attention in the control of anxiety. Panic disorders appear to respond especially well to serotonin uptake inhibitors. Most remarkably, obsessive–compulsive conditions appear to respond specifically to serotonergic drugs (see Eriksson and Humble, 1990). The ability of these agents to influence personality aberrations, also within the range of normal variation, has attracted considerable interest, as evident from the book *Listening to Prozac* (Kramer, 1993). The introduction of the selective serotonin reuptake inhibitors (SSRIs) obviously represents a major therapeutic advance in psychiatry as well as a milestone in rational drug development.

Controversial Priority Issues

Because the aim of scientific research is to gain new knowledge, the novelty aspect is of paramount importance. An excellent report of data or proposal of a theory is of limited scientific value if the same thing has been put forward before. In order to get real credit for one's work a scientist has to be first. What may be at stake in this context may, of course, be of decisive importance for a scientist's entire career.

This reminds me of an anecdote stemming from Jean Delay's teacher, Nageotte (Deniker, 1983): "If something new appears in medicine one starts by saying: it is not true. Once the fact has been proven one says it is true, but unimportant. Finally, when a fact has been proven and proven important one says in medicine: it is not he who discovered it." In fact, these few sentences point to some most important, highly legitimate questions that have to be raised about a new discovery. Sadly, however, it is not always in the interest of truth that attempts are made to challenge scientific discoveries.

One case deals with the discovery of dopamine in the brain. It should be clear that this discovery has to be credited entirely to our research group, as we disclosed in our paper in *Science* (Carlsson et al., 1958). However, some authors have challenged this, referring to two papers published in *Nature* the year before (Montagu, 1957; Weil-Malherbe and Bone, 1957). It is curious that, to my knowledge, none of these authors have themselves challenged our claims of having discovered dopamine in the brain. To anybody with an elementary knowledge in techniques of biochemical analysis, who has taken the trouble to read these papers carefully, it will be clear that they have not presented any acceptable evidence for the occurrence of dopamine in the brain, nor proposed any particular function for it. Unfortunately, however, even a few specialists in this field have overlooked the obvious shortcomings of these papers. This is the reason why I feel that I have to comment on them.

Both papers used the same highly unspecific and inadequate method, introduced by Dr. Weil-Malherbe, and the results clearly indicate that the method does not measure dopamine. Thus, in Weil-Malherbe's paper with A. D. Bone, dopamine is found in the brainstem in very large amounts, actually higher than the noradrenaline values. As is well known, the dopamine levels in the brainstem are low, lower than the levels of noradrenaline. Similar inadvertancies can be found in Montagu's paper. Those values of dopamine were obtained by subtracting the fluorescence values that were derived from a highly unspecific ethylene diamine condensation method, from those obtained by a conventional fluorimetric method for measuring adrenaline and noradrenaline. Documentation that this subtraction method measures dopamine is entirely lacking and, in contrast to our own specific method, which became a citation classic, it was never widely used and was soon abandoned, even by Weil-Malherbe himself.

Montagu wisely did not claim that she had identified or measured dopamine, but rather a compound "X." She claimed that compound X (which is likely to be a mixture of several compounds) had the same R_f value as dopamine, but she did not give an R_f value for either dopamine or compound X, nor did she specify the paper-chromatographic system she used, nor did she explain how the spots had been developed. No chromatogram was shown. Such poor documentation, or rather absence of documentation, which was not amended in any subsequent publication, is of course entirely unacceptable. Moreover, even if one generously accepts that Montagu has observed dopamine as a spot on paper chromatography, such a merely qualitative demonstration of dopamine in the brain was not surprising, because dopamine was then already generally believed to serve as a precursor of noradrenaline and adrenaline. It is thus only natural that there was no indication in Montagu's paper that she considered the possible presence of dopamine in the brain to be in any way remarkable.

In contrast, in our *Science* paper in 1958 we identified dopamine in the brain beyond doubt and provided correct figures for its levels. Moreover, we provided pharmacological data demonstrating a relationship between variations in dopamine and brain function. Thus we proposed for the first time, and on the basis of good documentation, that dopamine is not merely a precursor of noradrenaline but an agonist in its own right.

Another issue deals with the discovery of the regional distribution of dopamine in the brain. Credit for this discovery is sometimes given entirely to Bertler and Rosengren (1959). It is fair to mention that Bertler and Rosengren were my graduate students and were preparing for their theses under my direction. We had agreed that the study of the distribution of dopamine in the brain should be part of their thesis work. Thus, according to publication policies in Sweden then, it would have been appropriate not to have my name on the first publication on this issue. To restore the balance, however, I made the first announcement of dopamine's abundance in

the basal ganglia at the First International Catecholamine Symposium, in November 1958 (published in *Pharmacological Reviews,* Carlsson, 1959). Here I also summarized, for the first time, the arguments of a role for dopamine in extrapyramidal functions and disorders.

The most bizarre priority issue that I have personally been involved in deals with the development of the first SSRI. The first SSRI to be developed, both at the preclinical and clinical stage, was zimelidine. Much to my amazement, however, I came across a mini-review in *Life Sciences* in August 1995, titled "Prozac (Fluoxetine, Lilly 110140), the First Selective Serotonin Uptake Inhibitor and an Antidepressant Drug Twenty Years Since Its First Publication" (Wong et al., 1995). I wrote to Dr. Wong at Lilly and reminded him that the disclosure of the SSRI properties of zimelidine came more than 2 years before that of fluoxetine. In terms of clinical development and demonstration of antidepressant properties, zimelidine was even more ahead of fluoxetine. In the widely read book *Listening to Prozac,* in which the Lilly Corporation scientists are interviewed, these scientists likewise appear to give themselves the entire credit for the discovery of the SSRIs.

I managed to convince the Lilly scientists that a correction of their mini-review would be appropriate. Such a correction has now appeared in *Life Sciences.* This note clearly states that the first SSRI was zimelidine (Carlsson and Wong, 1997).

Recent and Ongoing Research

To include recent or ongoing research in an autobiography seems somehow inappropriate, because it lacks historical perspective. Still, at least in my case, it sheds some light on my previous research. I will focus on three research projects that are partly interrelated. Some of it has recently been reviewed (Carlsson et al., 1997).

A Working Hypothesis on a Thalamic Filter and Its Feedback Regulation via the Striatal Complexes

About 10 years ago we tried to design a model to explain the paradox that antipsychotic agents, such as dopamine D_2 receptors which without doubt exert powerful actions on the cerebral cortex, act mainly on targets that are sparse in the human cerebral cortex. Based on available pharmacological and neuroanatomical evidence, we postulated that the striatal complexes, comprising the dorsal and ventral striatum and the corresponding dorsal and ventral pallidum, exert a predominantly inhibitory function on the thalamus, leading to a reduced transmission of sensory information to the cerebral cortex as well as a concomitant reduction of arousal. As is generally recognized, arousal is controlled by the ascending reticular formation,

which operates in close linkage with the sensory input. We assumed that dopamine is predominantly inhibitory on striatal neurons, and thus an increased dopaminergic tone should counteract the inhibitory effect of the striatal complexes on the thalamus and, consequently, enhance the relay of sensory information to the cortex and raise the level of arousal. If the transmission through the thalamus becomes excessive, the integrative capacity of the cortex may break down, and confusion or psychosis will ensue. In the striatum, dopamine is counterbalanced by a powerful corticostriatal glutamatergic system, which is derived from all parts of the cerebral cortex (Carlsson, 1988a).

A simple way to test the predictive value of this model would be to induce hypodopaminergia, leading to immobility (catalepsy), and then to inhibit the corticostriatal glutamatergic function. If the model is valid, mobility should then be restored, despite the absence of dopamine. Maria Carlsson and I did this experiment in 1989, and it came out as we predicted. In this experiment we depleted mice of dopamine through the use of reserpine in combination with α-methyltyrosine. The immobility thus induced was dramatically reversed by treatment with an NMDA-receptor antagonist either systemically or locally in the nucleus accumbens (Carlsson and Carlsson, 1989; Svensson and Carlsson, 1992).

We later discovered powerful interactions indicating that not only was dopamine counterbalanced by glutamate in the striatum but so also were noradrenaline and serotonin, whereas acetylcholine operated in concert with glutamate. Apparently the cerebral cortex exerts a powerful control of the subcortical monoaminergic systems via glutamatergic pathways projecting to the striatum (Carlsson and Carlsson, 1989a–c, 1990). Likewise, corticofugal glutamatergic pathways appear to exert a powerful control over the monoaminergic systems by projecting to the monoaminergic cell bodies in the lower brain stem. This control seems to consist of both an accelerator—a glutamatergic pathway projecting directly to the monoaminergic cells—and a brake, consisting of a glutamatergic pathway, followed by a gabaergic interneuron. A similar accelerator/brake system appears to exist in the striatum, that is, postsynaptically in relation to the monoaminergic systems.

One example illustrating the powerful role of glutamate for controlling the responsiveness of monoaminergic systems is provided by some recent observations we made in our laboratory with 5-HT2 receptors. The stimulant action of the 5-HT2 agonist LSD is strongly potentiated by the NMDA antagonist MK-801 in monoamine-depleted mice, and this effect can be blocked by the potent and selective 5-HT2A-receptor antagonist MDL 100,907. In mice with an intact monoaminergic system, the psychostimulant action of MK-801 can be antagonized by MDL 100,907 already in quite low doses that are but slightly inhibitory on normal behavior. Originally, the scientists at Marion Merrell Dow Pharmaceuticals had discovered that

MDL 100,907 can antagonize amphetamine-induced stimulation, while leaving baseline activity essentially unchanged. From the standpoint of psychotogenesis, these observations are interesting, given that all these neurotransmitters have been shown not only to influence psychomotor activity in animals and in man, but also to play a role in psychosis. In fact, the dopamine hypothesis of schizophrenia now appears to yield to a multifactorial concept of a dysfunction induced by a complex imbalance between several neurotransmitter systems.

The animal model psychosis induced by an NMDA antagonist can be tentatively used for testing the ability of antipsychotic drugs to restore the biochemical pattern in the brain, as revealed by multivariate analysis. Thus, the abnormal biochemical pattern of MK-801-treated rats can be partially restored by haloperidol and clozapine, though in different ways. The improvement by haloperidol occurs exclusively along an axis, steered by an influence on dopaminergic indices, whereas clozapine acts along a perpendicular axis, where serotonergic indices are influential. The effect of MDL 100,907 is similar to that of clozapine, suggesting that the latter drug acts largely via inhibition of 5-HT2A antagonism in this model.

Postmortem Studies

In collaboration with C.-G. Gottfries and others we performed two postmortem studies on brains from patients with schizophrenia. Several brain regions were analyzed for monoaminergic indices, that is, the levels of dopamine, noradrenaline, and serotonin, as well as some of their precursors and metabolites. Using conventional univariate statistics we were unable to detect any striking differences between controls and schizophrenics, when the latter, like the former, were treated as a single group. However, when we applied multivariate statistics, the patients with schizophrenia showed an almost complete separation from the controls. The data further indicated that the patients with schizophrenia did not constitute a homogenous group; both the type of schizophrenic disturbance (paranoid vs nonparanoid) and gender influenced the pattern of monoaminergic indices. Some of the deviating patterns showed similarities to those seen in experimental animals treated with NMDA-receptor antagonists.

In our pattern-recognition studies, using multivariate analyses of postmortem as well as animal experimental data, two members of our research group, Lars O. Hansson and Nicholas Waters, made especially important contributions. Both types of studies emphasize the intimate interactions between a variety of neurotransmitter systems, and the experimental data clearly indicate that a primary disturbance in one system may lead to complex changes in the biochemical pattern involving several neurotransmitters. Clearly, we are far from being able to identify any single factor that could account for the multiple biochemical changes occurring in the schizo-

phrenic brain. Most probably schizophrenia, like so many other major disorders, is heterogeneous and not due to one single cause.

Oxidation of Catechols to Quinones

For a long time the so-called autoxidation of catechols, which may after all, according to recently published studies, be catalyzed by enzymes and thus should not be called autoxidation, has been assumed to occur in the brain. One piece of evidence supporting this contention is the occurrence of neuromelanin in catecholaminergic nerve cells. The possible physiological and pathophysiological role of this metabolic pathway is still obscure. To measure the formation of quinones *in vivo* is difficult, because they are highly reactive (and thus cytotoxic) and will remain in free form for but a very short time after their formation. In order to get a handle on this mechanism we have developed techniques for analyzing the major metabolites of these catechols, that is their 5-S-cysteinyl adducts. We have thus been able to demonstrate the occurrence of the 5-S-cysteinyl adducts of dopamine, dopac, and dopa in the brain. We have found that 5-S-cysteinyldopamine is more elevated than dopamine in the brain of patients with Parkinson's disease, analyzed postmortem, which may be an indication of oxidative stress, possibly leading to degeneration of dopaminergic nerve cells (Fornstedt et al., 1989). Surprisingly, we have also found an elevation of 5-S-cysteinyldopamine in the brains of people with schizophrenia (see Carlsson et al., 1997). Multivariate analysis has also proven most helpful in these studies.

These studies were initiated in collaboration with my former student, Evald Rosengren (now professor emeritus of pharmacology at the University of Lund; Rosengren et al. 1985), who played an important role in our early catecholamine studies in the 1950s and who more recently had studied catechol oxidation mechanisms in peripheral tissues. In the further elaboration of these studies, which required considerable analytical skill, Bodil Fornstedt made a most important contribution.

Collaboration with the Pharmaceutical Industry

I have had the opportunity to collaborate with the pharmaceutical industry for about 40 years. My doctoral thesis work evolved from collaboration with a drug company. I have been engaged in research projects jointly with five different drug companies from 1960 onward. This collaboration has had a considerable impact on my research. It has given me and my research team significantly more financial resources than we otherwise would have had. More important, it has increased our awareness that basic biomedical research should ultimately aim at clinically relevant advances.

Of special importance at an initial stage was the collaboration with Hässle, a subsidiary of the Astra Company, of Sweden. Very soon after my

move from Lund to become the chairman of pharmacology at the University of Göteborg I was approached by the head of research at Hässle, Mr. Ivan Östholm. Östholm and the management of Hässle had a generous and sympathetic attitude toward collaboration with academic researchers. According to their philosophy, a collaboration should be based on a genuine mutual research interest. Thus, Hässle showed considerable flexibility in formulating their research projects so as to foster close collaboration with university groups.

At Hässle, the decision had been made to develop a drug for the treatment of heart arrhythmia by reducing the sympathetic tone. This decision was based on advice from a number of university researchers. When I learned about this project in 1961 I suggested that Hässle focus their efforts on developing a beta-adrenergic blocking agent. At that time the work at Eli Lilly Company on dichloroisoproterenol (DSI) was already known. I had learned about it at the First International Catecholamine Symposium in Bethesda, Maryland, in 1958 and in subsequent work, further illustrating the role of beta-adrenergic receptors on heart function. I proposed that Hässle start out from the structure of DCI to develop a clinically useful beta-adrenergic blocking agent.

At that time, a skillful Swiss organic chemist, Dr. Hans Corrodi, had just been employed by Hässle. Corrodi and I started a fruitful and stimulating collaboration, which continued until his untimely death in 1973. Corrodi started synthetic work around the DCI molecule, and one such agent was taken to the clinical testing stage but was found to possess too-high intrinsic activity. Finally, the Hässle chemists made alprenolol, which turned out to be a clinical useful beta-adrenergic blocking agent and was placed on the market.

At the outset we did not know that ICI had started a similar research project and that they were somewhat ahead of us (for details, see Shanks, 1984). But in any event, alprenolol was one of the first beta-blocking agents to be placed on the market and became a milestone in the development and growth of the then very small drug company, Hässle. Later, Hässle developed the beta-1-selective antagonist metoprolol, which became an even greater success on the market. For a long time the beta-blockers belonged to the most important drugs marketed by the Astra group, as a whole. Moreover, a spinoff project on beta-adrenergic agonists, which was started at Hässle but which they could not pursue because of their limited resources, was transferred to the Astra subsidiary, Draco, where it resulted in successful drugs for the treatment of asthma. Thus, the company was able to build up the financial strength they needed to subsequently develop several other very successful drugs, such as omeprazol.

From a scientific point of view, the most important outcome of my collaboration with Hässle and Astra was the development of the first SSRI, zimelidine. In 1995, Dr. Östholm published an account of the successful and

dramatic development that took place during his time as head of research at Hässle.

Medicinal Chemistry

Another important result of my collaboration with Hässle was that we were able to work directly with medicinal chemists, some of whom actually became members of our research group in the department of pharmacology, whereas others were located at the School of Pharmacy of the University of Uppsala. The latter group was initially headed by Dr. L.J.G. Nilsson, who managed to recruit a large group of graduate students, several of whom were later able to defend their Ph.D. theses within the framework of our collaboration.

In my opinion, a close collaboration between pharmacologists and medicinal chemists in an academic setting leads to a most fruitful cross-fertilization and should thus be more widely implemented.

The collaboration with Astra during the 1970s and 1980s was a scientific success. For example, during that time the first dopamine autoreceptor-preferring agonists and antagonists, as well as the first selective 5HT1A receptor agonist 8-hydroxy-DPAT, still a gold standard, were developed. However, the spirit of the early collaboration, when Dr. Östholm was head of research at Hässle, had faded. The successful growth of Astra had led to the recruitment of a competent scientific staff, which, of course, was an important and useful development. But at the same time, the "NIH syndrome" (NIH = Not Invented Here) became prominent. Thus, the ideas generated from our collaboration with Astra were not given high priority, and Astra decided not to invest into further development of any agents synthesized within the scope of our collaboration.

In 1987, we started a fruitful collaboration with the Upjohn Company, and the collaboration with Astra/Hässle was then terminated. Thanks to Upjohn's generous financial support we were able to increase both the pharmacological and chemical moieties of our staff. This collaboration lasted for 7 years and was a scientific success. For example, it was during this time that we were able to develop our concept of the thalamic filter mechanism and the interaction between neurotransmitters in neural circuitries. From the point of view of drug development it is still too early to have a final judgment, in view of some still-ongoing projects generated by our collaboration. In my opinion, however, the collaboration suffered clearly from the NIH syndrome.

After the termination of our collaboration with Upjohn in 1994 we were no longer able to keep our medicinal chemistry and pharmacology groups together in one and the same project. However, both groups are still actively involved in research, thanks to joint projects with three other drug companies. Among these, the one with Hoechst Marion Roussell (formerly Marion

Merrell Dow) has been ongoing for the longest time. Our most stimulating collaboration was to increase our understanding of the involvement of serotonin, and especially the 5-HT2A receptors, in our circuitry models. This collaboration has been most successful. Among other things, it has disclosed an intimate relationship between the serotonergic and glutamatergic systems.

Collaborators

During the past half-century of active research I have had the privilege to work with hundreds of collaborators. The two most critical phases in my professional life were the sabbatical in Brodie's lab and the first 3 years following my return to Lund. I have already pointed out how much I owe to Steve Brodie and his colleague, Park Shore, who generously introduced me to modern techniques in biochemical pharmacology and to the fascinating field of neuropsychopharmacology. Sadly, Steve is no longer with us, but I still enjoy a longstanding friendship with Park, and his wife, Helen.

Following my return to Sweden I faced the challenge of setting up a modern lab of biochemical pharmacology. I realized that I needed a lot of help to be able to do this. When I was still in Brodie's lab I wrote to Nils-Åke Hillarp with a proposal to collaborate with him. Fortunately, he agreed. The first thing I did after returning to Sweden in January 1956 was to order an Aminco-Bowman spectrophotofluorimeter. I had no money for this expensive equipment, but I considered it absolutely essential to get it as quickly as possible. I applied to the Swedish Medical Research Council for the necessary funds. My application was referred to Professor Ulf von Euler. He did not consider this instrument necessary for measuring catecholamines. He had himself published a method to determine adrenaline and noradrenaline, using a filter fluorimeter, which, in his opinion, was adequate. Fortunately, I had mentioned in my application that I also intended to measure serotonin. Because serotonin could not be measured in his instrument, he supported my application, and I received the grant.

When I returned to Sweden a number of highly qualified and enthusiastic people were waiting for me at my home department. They had been working with me on calcium metabolism and were quite willing to join me in the new research area. My first laboratory assistant was Margit Lindqvist. She introduced me to laboratory techniques, starting in 1944, with the subcutaneous injection of drugs into guinea pigs. She was an enormously talented laboratory assistant, who, during the many years of our collaboration acquired various skills, especially in biochemical analysis. Her competence soon reached a level clearly above that of a laboratory assistant and made her a highly valued research associate. With her I wrote numerous papers, including the citation classic about the mode of action of major neuroleptics (Carlsson and Lindqvist, 1963). Sadly, she died prematurely, in 1978.

Tor Magnusson, another collaborator, started to work with me in 1949. He is a chemical engineer, is unusually talented, and has broad knowledge, extending from biochemical analysis to surgical techniques and statistics. He became assistant professor in pharmacological techniques. Although he has formally retired, he still comes to our department almost every day and is still of great help. Like Margit Lindqvist, he has coauthored many seminal papers in my bibliography. For example, he is a coauthor of the two seminal papers on L-dopa and dopamine, published by Carlsson et al. in *Nature,* in 1957, and in *Science,* in 1958. Tor has volunteered in a number of self-experiments with drugs. In 1957 we gave him an intravenous infusion of L-dopa. We expected to see some dramatic mental actions, but the only effect we could see was emesis.

Bertil Waldeck is also a chemical engineer. He started to work with me in 1956. In 1958, he and I published a paper on the fluorimetric measurement of dopamine (Carlsson and Waldeck, 1958). This paper also became a citation classic. He also coauthored our paper on dopamine in *Science,* in 1958. Like Margit Lindqvist and Tor Magnusson, Bertil Waldeck joined me when I moved from Lund to Göteborg, in 1959. I have published numerous papers with Waldeck. He successfully defended his Ph.D. thesis in 1975. Somewhat later, he was offered and accepted a prestigious position at the Astra subsidiary, Draco.

When I returned to Sweden in 1956, two graduate students who had worked with me on calcium metabolism joined me: Evald Rosengren and Åke Bertler. They liked to work together and nicely supplemented each other. Rosengren had a restlessly searching mind, while Bertler was the systematic organizer. Both of them contributed greatly to our research in various ways. They were instrumental in working out our method for analysis of adrenaline and noradrenaline. This became another citation classic (Bertler, Carlsson, and Rosengren, 1958). They later became professors of pharmacology and clinical pharmacology, respectively.

In 1960 the department of pharmacology moved into a brand new building, and we had generous funds for equipment. Later in the same year, Nils-Åke Hillarp and his skillful research assistant, Georg Thieme, joined us. (For a discussion of some of Thieme's most important contributions, see Dahlström and Carlsson, 1986.) We could thus set up our methods and resume our research in the new department without much delay. The early 1960s were characterized by lots of activity, through which we contributed to a paradigm shift in brain research. After Hillarp's move to the Karolinska Institute in 1962 to take over the chair of histology, he recruited a large number of young, enthusiastic students, and a fruitful collaboration began between his new group and our equally enthusiastic group, which likewise expanded with many new students. At about the same time Hans Corrodi, a skillful medicinal chemist, started to collaborate, first with us and later with both groups. Corrodi's contributions in several areas became quite important to our research.

Sadly, many of the people who were actively engaged in this important development have passed away, in most cases, prematurely: Nils-Åke Hillarp, Hans Corrodi, Margit Lindqvist, Bengt Werdinius, Nils-Erik Andén, Björn-Erik Roos, Jan Häggendal, and more recently, Georg Thieme. Unfortunately, Hillarp and Corrodi did not live long enough to witness the spectacular outcome of their research efforts.

I have had the pleasure of seeing about 40 of my graduate students defending their Ph.D. theses successfully, and of working with an equally large number of foreign postdoctoral fellows, who have also contributed much to our success. Among the latter was our first foreign fellow, Lewis S. Seiden, who is now professor of pharmacology at the University of Chicago. The most remarkable thing about Lew's stay with us was that he was able to teach us just about as much as we could teach him. Lew had had very good training in animal behavior, and introduced, for example, the technique of conditioned avoidance. We were then able to demonstrate, for the first time, the ability of L-dopa to restore the conditioned avoidance response in reserpine-treated animals (Seiden and Carlsson, 1963). As a result of Lew's contribution a number of people have since defended their Ph.D. theses based on behavioral experiments, including my successor as professor of pharmacology, Jörgen Engel (for review, see Engel and Carlsson, 1977).

Collaboration with scientists in other departments was also important for our group. They have belonged to many different disciplines. For example, in animal behavior, we had a stimulating collaboration with Knut Larsson and his colleagues. With them, we demonstrated the remarkable ability of 5-HT1A agonists, such as 8-hydroxy-DPAT, to stimulate sexual behavior in the male rat (Ahlenius et al., 1981). In psychiatry, we performed postmortem studies on brains from patients with schizophrenia and dementia with C.-G. Gottfries (see Carlsson, 1981), and drug trials with Jan Wålinder and others on α-methyltyrosine–neuroleptic interactions in patients with schizophrenia (Wålinder et al., 1976) and on tryptophan–clomipramine interactions in patients with depression. We also have a longstanding collaboration with C.A. Tamminga and her colleagues at the Maryland Psychiatric Research Center, in Baltimore, studying the action of (−)-3PPP in patients with schizophrenia (Tamminga et al., 1992; Lahti et al., 1997).

With neurologists A. Svanborg, G. Steg, and their colleagues, we performed the first clinical study in Sweden with L-dopa in patients with Parkinson's disease (Andén et al., 1970b), and with G. Stern, at the Middlesex Hospital in London, we studied the action of (−)-3PPP in patients with Parkinson's disease (Pirtosek et al., 1993).

The first of these two studies was initiated after I had attended a meeting in Canada, in 1967, where George Cotzias presented his first dramatic results with oral L-dopa in the treatment of Parkinson's disease. This was

the first time that I met George. We became friends and had many stimulating discussions. My colleague Tor Magnusson spent an exciting sabbatical with George's group in the mid-1970s. George's untimely death in 1977 was a great loss to his many friends, as well as to science. In this context I must also mention the late Walther Birkmayer, whose friendship I appreciated a lot. Both Walther and George had intensely searching minds, were highly creative, and contributed enormously to the advances of clinical neuroscience. I miss them both very much.

We also collaborated with the neuropathologist A. Brun, in postmortem studies of Parkinson's disease (Fornstedt et al., 1989), and with C. Kjellström (Fornstedt et al., to be published).

Attending Scientific Meetings

Meetings of various kinds are, of course, an essential component of scientific activity. In my own experience they have turned out to be of utmost importance, not only because of the scheduled programs but also because they provide valuable opportunities for informal discussions with colleagues and to learn about the latest "scientific gossip." Personal contacts can probably never be entirely replaced by even the most sophisticated advances in communication techniques. Many of our ideas as well as opportunities for fruitful collaboration have been generated at scientific meetings. The proceedings that are sometimes published after scientific meetings are often of great value because they provide convenient access to accounts on significant advances, and—especially if the discussions are recorded—they can be invaluable historical documents by displaying the state of the art at a given point in time. Finally, but not least, meetings are a source of immense pleasure because they provide the opportunity to maintain friendships with many colleagues.

There is a rather special series of meetings that I have enjoyed attending for about 20 years. They were initially sponsored by Mr. and Mrs. Denghausen, who provided annual donations to Nathan Kline to enable him to assemble up to a dozen clinical and preclinical neuroscientists to spend a week on a Caribbean island, together with their wives. The purpose of these meetings is to create a relaxed atmosphere where the researchers have the opportunity to discuss neuropsychiatric issues in depth. The format is that each scientist presents some data of his own in an informal way with access only to a blackboard. The emphasis is on a brainstorming interaction between all the participants, who represent a broad area of knowledge. Thus, the speaker is interrupted throughout his presentation with questions and comments. The scheduled meetings take place only in the morning. The rest of the day gives the opportunity for even more informal scientific discussions. For a long time, Nate Kline was the central figure at these meetings. Nate was one of the most important pioneers of biological psychiatry

and psychopharmacology, as is amply documented by numerous interviews of prominent people in the field made by David Healy (1996) in *The Psychopharmacologists.* Nate is often described as a flamboyant person, but when I met him he was in a later stage of his life, still with a lot of charisma but rather like a wise King Solomon. After Nate passed away in 1983, his function as organizer of these meetings was taken over by Robert Cancro, who managed to keep a similar format and atmosphere as before. I have found these meetings most enjoyable, and I am convinced that they have affected all the participants, not least by the generation of new ideas and by initiating new lines of research.

Reflections on Some Current Trends in Drug Research

The last few decades have seen a dramatic evolution of techniques that are useful in drug research, extending from the molecular level all the way to the highest levels of integration. Unfortunately, the spectacular advances in molecular biology have led to an overoptimism on future possibilities in drug discovery. In the past, this discovery process has nearly always depended on observations at higher levels of integration, and in fact, not seldom, on unexpected clinical findings. Insofar as the molecular mechanism of action is concerned, it has generally become disclosed after the discovery of a new therapeutic principle. Actually, cases are known where the mode of action has remained obscure for decades and even still remain unknown, as is the case with lithium.

Today, the belief is often expressed that from now on, drug discovery will take a new path, starting out with the genome and the identification and cloning of proteins involved in pathogenetic mechanisms. However, the question of how to identify those proteins that are useful as drug targets, remains unanswered.

Managers of drug companies have become reluctant to develop drug candidates with interesting and promising new pharmacological profiles until the precise molecular mechanism has been disclosed. Such an attitude may not only lead to missed opportunities, but may also cause a longstanding loss of competence in their scientific staffs, owing to a too-heavy weight placed on molecular biology at the expense of expertise at higher levels of integration.

Paradoxically, the ever-increasing sensitivity of techniques leads to a new problem: as the sensitivity approaches the background noise of nature, there is a risk that the detection and identification of a new molecule will initiate resource-demanding work for years, which will finally lead to the conclusion that the molecule in question is just the result of a failure of the precision of biology. The aspect of redundancy or superfluousness calls for a lot more awareness than was previously the case, when detection tech-

niques were rather insensitive and the risk of touching the background noise was minimal.

Thus, it can be argued, for example, that a number of the numerous, admittedly highly active neuropeptides that have been found in the brain are not necessarily functionally important. They may, for example, be redundant vestiges from a time before the evolution of neurons from round cells, in which they played an important role as hormones, but with the advent of long processes to make nerve cells they may have become less useful, given that they had to be elaborated around the cell nucleus before being transported to their site of function, the nerve terminal (for further discussion, see Carlsson, 1988b). Similar views have been expressed by Bowers (1990), who emphasized the marked species variation in the occurrence and distribution of neuropeptides in the brain should arouse the suspicion of superfluousness.

My Family

A successful career always depends at least to some extent on luck. I was fortunate to grow up in an academic environment and to be encouraged and supported in many ways by my parents.

My wife, Ulla-Lisa, and I have been married since 1945. We had attended the same school and thus had already known each other for many years. My wife is a physician but practiced medicine for only a short time. We have five children altogether; our first child was born in 1947. Like my mother, Ulla-Lisa has given priority to raising our children and keeping our home in good shape. However, as the children grew up and left our home she has spent an increasing amount of time assisting me in my research in many respects, for example, looking after my correspondence, keeping all my papers in good order and reading and criticizing my manuscripts. Needless to say, the priorities my wife chose have been favorable for my scientific career. Without her loyalty, assistance, and support, in numerous ways I would not have been able to accomplish by far as much as has now been possible.

I also owe a lot to our five children, not least to our two daughters. The older one, Lena, is a science writer, and together with her I have had the most stimulating experience of writing a book titled *Messengers of the Brain.* It was intended for educated laymen, students of psychology, and others. Unfortunately, the Swedish version, which appeared in 1988, is now out of print. A Japanese version has appeared, thanks to the initiative of my friend, Professor H. Narabayashi, who actually did the translation from English together with a colleague.

Our younger daughter, Maria, is assistant professor of pharmacology in our department. With her I have done a lot of stimulating and successful

research on the interactions between different neurotransmitters in circuitries connecting the cerebral cortex with various subcortical structures. Some of this work has been mentioned in this autobiography.

My three sons have chosen different careers. Bo is an ophthalmologist, and works at the University Hospital. Hans is an economist who specializes in game theory. He is employed as assistant professor at the University of Lund, where I received my professional and scientific training. Magnus, the youngest of our children, has a Ph.D. in computer science.

Clearly, the assembled knowledge of our children is quite broad and has been very useful to the whole family. In addition, we have seven grandchildren. To be able to follow their growth and development has been, and still is, a great privilege and source of pleasure.

Concluding Reflections

Ideally, a scientific discovery may be thought of as an instantaneous, "eureka" kind of happening. There is no doubt that such events do occur. One example is the demonstration of humoral transmission in the frog heart by Otto Loewi. More frequently, however, a discovery is a process that evolves from a series of observations by different investigators over a varying length of time. A fascinating example is the discovery of the planets' rotation around the sun. This may seem a far-fetched example in the present context, but I find it remarkably illuminating and instructive, not least owing to the clever and penetrating way in which this particular discovery process has been narrated and analyzed by Arthur Koestler (1959) in *The Sleepwalkers*. It started with Copernicus' postulate in the 16th century (actually an iteration of Aristarchos' contention, 1800 years before), and became well-established by Kepler in the beginning of the 17th century, thanks to his mathematical analysis of the extensive and careful astronomical observations by Tycho Brahe for two decades at the end of the 16th century. However, an understanding of the underlying mechanisms was not reached until the end of the 17th century through Newton's further analysis of Kepler's "laws," which led to the concept of gravity. Even though the discovery process is generally more rapid today, this example may still be looked upon as a role model by demonstrating the complexly interweaved contributions of different personalities using different approaches and technologies.

A comprehensive and fully adequate account of the dramatic development in which my colleagues and I have had the opportunity of taking part will have to await an outstanding narrator like Arthur Koestler. A scientist who has been actively engaged in such a process can, at best, be expected to give a reasonably fair account of his own contributions and to bring them into the context of the work of others. If at all possible, he would probably prefer to bring his account in conformity with the eureka model of dis-

covery. One hopes that he would be able to do this without omitting or deemphasizing contributions by others. It will have to be left to my readers' judgment as to what degree I am successful in this respect in this autobiography, and then not least when I try to summarize below the most salient scientific contributions by me and my co-workers.

Not far from the eureka model of discovery would be our identification of dopamine as a normal brain constituent, coupled with the recognition that dopamine plays an important role as an agonist in its own right not only in normal brain function but also in the pathophysiology of mental and motor disorders and in the mode of action of some important drugs.

To the same category would also belong our development of the first SSRI, zimelidine.

In a broader context, we have played an active part in a paradigm shift in brain research, through the recognition that chemical, rather than electrical, transmission is a major mechanism by means of which nerve cells communicate with one another in the brain. This paradigm shift has, of course, had a strong impact on basic brain research, but as exemplified by our own work, it has also opened up possibilities to unravel new pathophysiological mechanisms and to discover novel targets for therapeutically useful drugs.

I am very grateful for the ample recognition that has been bestowed upon me in the form of prestigious prizes, honorary degrees, and memberships. However, what I find most gratifying is alleviating the suffering of millions of people who are afflicted by various mental and neurological disorders, which the pursuit of our research has led to.

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