Leo Lisen

Leslie L. Iversen

Born:

Exeter, England
October 31, 1937

Education:

Cambridge University, B.A. (Biochemistry) (1961)
Cambridge University, Ph.D. (Pharmacology) (1964)

Appointments:

Postdoctoral Fellow, National Institutes of Health (1964–1965)
Postdoctoral Fellow, Harvard Medical School (1965–1966)
Research Fellow, Trinity College, Cambridge (1966–1967)
Locke Research Fellow, Cambridge University (1967–1970)
Director MRC Neurochemical Pharmacology Unit, Cambridge, (1970–1983)
Director Neuroscience Research Centre, Merck Sharp & Dohme Ltd, Harlow, UK (1983–1995)
Vice-President Neuroscience, Merck Research Labs (1986–1995)
Visiting Professor of Pharmacology, Oxford University (1995–)
Director, Wolfson Centre for Age Related Diseases, King's College, London (1999–2004)

Honors and awards:

Gaddum Lecturer, British Pharmacological Society (1971)
F. O. Schmitt Lectureship, MIT, USA (1974)
Associate of Neuroscience Research Program, MIT, USA (1975–1984)
Fellow of the Royal Society, London (1980–)
Honorary Member, American Academy of Arts and Sciences (1981–)
Rennebohm Lecturer, University of Wisconsin, USA (1984)
Ferrier Lecturer, Royal Society, London (1984)
Foreign Associate Member, National Academy of Sciences USA (1986)
Honoured Professor, Beijing Medical University, China (1988)
Hans Kosterlitz Memorial Lecturer, British Physiological Soc (2000)
Wellcome Gold Medal in Pharmacology, Brit. Pharm. Soc (2003)
Lifetime Achievement Award, Brit. Assoc. Psychopharmacology (2006)

Leslie Iversen has been at the forefront of research on neurotransmitters and neuropeptides and understanding the mode of action of CNS drugs. In his early work on catecholamines he was among the first to describe the detailed properties and pharmacological specificity of the noradrenaline transporter (NAT) in sympathetic nerves and brain, and he helped to strengthen the concept of antipsychotic drugs as dopamine receptor antagonists. In his work on GABA he participated in the first demonstration of the release of GABA on activation of an inhibitory synapse, and was the first to describe GABA uptake into inhibitory nerve endings in mammalian brain. In the field of neuropeptide research his efforts were eventually rewarded whilst working at Merck Research Laboratories by the development of the substance P receptor antagonist aprepitant as a novel treatment for nausea and vomiting associated with cancer chemotherapy. He has been keen to explain the complex scientific issues associated with the use of psychoactive drugs to a general audience, and has written books about marijuana and amphetamines.

Leslie L. Iversen

I was born in the West Country of England, in the beautiful cathedral city of Exeter, in October 1937. My parents came to England from Denmark in the 1920s, so I was almost a first-generation immigrant. My father was the 10th child in a poor farming family, and he was sent to England to be educated and to work for the Danish farmers' cooperative movement—which had established the Danish Bacon Company to help sell Danish agricultural produce in England. He eventually became manager of the company branch in Exeter—responsible for distributing Danish produce to the many small grocers throughout the West Country.

By the standards of the 1930s, our family was reasonably well-off. We lived in a large house with enough land to grow our own vegetables and fruit, and to keep pigs, chickens, and a cow. These proved very valuable assets when the World War II brought severe shortages of food with strict rationing. I was also doubly fortunate in escaping the 5 years of Nazi occupation that the rest of our family suffered in Denmark. Although neither of my parents had been to the university, our home had plenty of books, and education was much prized. I was fortunate to succeed in gaining a place at the local grammar school, Hele's School, at the age of 11 and received a first-rate education there. It soon became clear that science was what fascinated me—and I developed a strong interest in biology and the natural world.

My elder half-brother Niels, who was studying botany at Exeter University, inspired me to become interested in plants—and I soon amassed a large collection of pressed wild plants—and learned the precise Latin names of most of them. This stood me in good stead later when I applied for a scholarship at Cambridge University. I applied to read botany, and during the interview at Cambridge I was shown a long bench on which local plants and wild flowers had been laid out. To the surprise of the interviewer I was able to walk along the bench identifying virtually every specimen with its correct Latin name! This surely helped in gaining me the scholarship and led to me to many happy years as a student and scientist in Cambridge. In retrospect this was a very lucky break. My parents as recent immigrants were quite unfamiliar with educational system in England—and without good advice from my schoolteachers I would never have thought of attempting a place at one of Britain's top universities.

But before enjoying the privileges of a Cambridge education I had first to serve for 2 years in Her Majesty's Royal Navy—military service was obligatory in those days.

I was trained to operate the coding machines used for secure communication at sea and sent to the island of Malta for the remaining 18 months of my service. I was attached to a submarine depot ship that never went to sea—but was able to get some sea voyages on destroyers—and enjoyed the Mediterranean recreations of dinghy sailing and scuba diving. My time in the Navy was good for me; as a shy child I had to learn how to live in close quarters with others and to fend for myself.

Student Life in Cambridge

In October 1958 I entered the new world of Cambridge, where I was a member of Trinity College. Here I studied natural sciences—initially physiology, chemistry, and botany. Trinity College had many famous physiologists, the Nobel Laureates Edgar Adrian, Alan Hodgkin, and Andrew Huxley, together with visual physiologist Horace Barlow and neurologist Patrick Merton. I remember vividly one of my first tutorials with Andrew Huxley in 1958, 5 years before he was awarded the Nobel Prize for Physiology and Medicine. Tutorials were and are one of the very special features of a Cambridge or Oxford education. In addition to the University lecture courses, students spend an hour each week in their College with an expert in each of the subjects they are studying—sometimes alone, more often in groups of two or three.

Immediately after 2 years of military service it was struggle to get back to the world of learning. Huxley launched into a discussion of how action potentials were transmitted along nerve fibers and soon got into an analysis of this in terms of "cable theory" that involved some fairly complicated mathematics. My partner (who had also recently ended military service) and I compared notes later and found that we had not understood most of this. Next week at the tutorial I plucked up courage to tell Huxley that we were having difficulty following him, particularly the calculus involved. He was amazed that anyone at Trinity could have difficulty in understanding calculus and said, "In that case, I hope that you are not contemplating a career in research." Fortunately I did not take his advice seriously!

Although I went to Cambridge with a scholarship to study botany, the classical manner in which the subject was taught in Cambridge in those days soon put me off—it emphasized taxonomy and classification, which was no longer exciting to me. At the end of my first year I abandoned botany in favor of the far more glamorous biochemistry—which was entering one of its most flourishing periods in Cambridge—this was only a few years after Crick and Watson described the double helix. Biochemistry became my sole focus for the final year, in a class of 40 students, and it was very well taught.

Meanwhile I had met and fallen in love with Susan Kibble, another grammar school student, also studying natural sciences. We met in the practical

laboratory when studying physiology—and despite this prosaic beginning we have lived happily together ever since. We married at the end of our undergraduate years in 1961. Sue developed a very successful research career in experimental psychology, and later became Head of the Department of Experimental Psychology in Oxford and subsequently a Pro-Vice Chancellor of the University.

Sue and I almost automatically assumed that we would stay in Cambridge for postgraduate studies if at all possible—although making satisfactory arrangements for Ph.D. study that would suit both of us was not easy; but again we were lucky. Sue joined the Department of Experimental Psychology, to be supervised by Larry Weiskrantz, an expert in the study of higher brain functions in primates. She worked on memory mechanisms in monkeys. I was also committed to studying the brain—having been strongly influenced by another member of the Huxley family on reading Aldous Huxley's books *The Doors of Perception* and *Heaven and Hell*, which described his experiences after taking the psychedelic drugs mescaline and later LSD. Although never tempted to try these myself, I found these books absolutely fascinating. The mystery, which Huxley described so beautifully, was how could minute amounts of these chemicals so totally alter your perception, your consciousness, and your view of the world, even to the extent of believing that you have had a visionary experience? I was looking for someone to teach me about brain biochemistry, but there was no one in the Cambridge Biochemistry Department who was doing anything like this. Fortunately, in the nick of time Gordon Whitby, a former member of the Department of Biochemistry in Cambridge returned to Cambridge after working in Julius Axelrod's laboratory at the National Institutes of Health. He offered to supervise my Ph.D. on the catecholamine research that he had been involved in there.

Gordon had worked with Julie Axelrod at a very critical time. They had acquired tritium-labeled epinephrine and norepinephrine of high specific radioactivity, so for the first time it was possible to administer doses to animals that were in the normal physiological range. Julie had discovered a novel enzyme in catecholamine metabolism, catechol-O-methyl transferase and was particularly interested to see how much of an administered dose was disposed of by that route. Much to their surprise, although a significant proportion of the radiolabelled catecholamine did end up as O-methylated metabolites, a substantial proportion of the injected dose persisted in tissues unchanged (Whitby et al., 1961). Further experiments by Hertting and Axelrod (1961) showed that what was happening was an uptake of radiolabelled norepinephrine by sympathetic nerve endings, from which the amine could subsequently be released again by nerve stimulation. This revealed an entirely novel mechanism for inactivating neurotransmitters after their release by means of a reuptake mechanism. This was the key discovery for which Julie shared the Nobel Prize in Physiology and Medicine in 1970.

Thus, by having Gordon Whitby as my supervisor I was one of the first people outside the Axelrod lab to get involved at a very early stage in what proved to be an exciting branch of neurochemistry and neuropharmacology, and to use the techniques that he had just learned in one of the world's top laboratories.

I started out in 1961 by repeating some of the whole animal disposition studies in mice, comparing H^3-epinephrine with H^3-norepinephrine. We found that a higher proportion of labeled norepinephrine was retained unchanged (54%) than for labeled epinephrine (34%), suggesting that the tissue uptake process preferred norepinephrine as a substrate. We also found that as the injected dose of either catecholamine was increased less was retained unchanged, suggesting that the uptake process was saturable. These results were sufficient to gain me my first peer-reviewed paper (Iversen and Whitby, 1962). After that I switched to using the Langendorff isolated perfused rat heart preparation, which remained viable in vitro for several hours. H^3-norepinephrine was rapidly accumulated from the perfusate by the sympathetic nerve endings in the heart—and this allowed control of the exact substrate concentration and time of exposure, and the study of potential uptake inhibitors. I was able to make detailed measurements of the kinetics of norepinephrine uptake; to show that it was stereospecific for the (-)enantiomer; to see how exogenous catecholamine equilibrated with the endogenous amine stores; and to investigate numerous inhibitors and to find out precisely how potent they were (Iversen, 1963). This latter exercise was facilitated by a change of supervisor which occurred at the end of my first year when Gordon Whitby left to take a Chair in Edinburgh, and I came under the wing of Arnold Burgen, the newly appointed Head of the Department of Pharmacology in Cambridge. Arnold was able to get free samples of most of the drugs we needed to test, and he taught me about the many different catecholamine analogs that exist among the sympathomimetic amines. This allowed us to explore the structure-activity relations of the norepinephrine uptake process in some detail (Burgen and Iversen, 1965). My most original finding was the unexpected discovery of a second uptake process in the heart, of low affinity and high capacity, that emerged at high substrate concentrations, and which I called "$Uptake_2$" (Iversen, 1965). $Uptake_2$ is not located on sympathetic nerves but is present in several peripheral tissues and in the brain. It is not dependent on Na^+ or Cl^-, has a low affinity for substrates and a high capacity. It is sensitive to inhibition by O-methylated catecholamine metabolites and by steroids. The $Uptake_2$ transporter has been cloned in animals, where it is termed "organic cation transporter 30" and in man where it is called "extraneuronal monoamine transporter." This uptake system may represent a second line of defense that inactivates monoamines that have escaped neuronal uptake, and thus prevents uncontrolled spread of the signal.

Arnold Burgen was a wonderfully knowledgeable and supportive mentor, with an encyclopedic knowledge of science and the arts. At this time he

was building the Department of Pharmacology in Cambridge—independent for the first time from Physiology. In time the Department became one of the strongest in Britain. My work moved ahead well, and data and publications accumulated fast. The drawback of the isolated heart work was that each data point involved the sacrifice of a rat; to complete the studies in my Ph.D. thesis several thousand were needed. Nowadays one could do all this in a few tissue culture dishes, and one would work with the human transporter protein, but rats were inexpensive in those days, and the modern techniques of molecular pharmacology were not yet available. Research funds were difficult to obtain in postwar austerity Britain. I had access to one of the only liquid scintillation counters in Cambridge to measure the radioactivity in my samples, but we could not afford to buy the many special glass vials needed to feed samples into this machine. Consequently many hours were spent carefully washing these for reuse!

I was able to submit a modified form of my Ph.D. thesis to Trinity College and was successful in gaining the award of a College Research Fellowship. Subsequently this dissertation was worked up to a monograph *The Uptake and Storage of Noradrenaline in Sympathetic Nerves*, published by Cambridge University Press in 1967, which gained some popularity among scientists working in the burgeoning catecholamine field.

Postdoctoral Work in the Axelrod Laboratory

At the end of our Ph.D. studies Sue and I again almost automatically assumed that we would be going to the United States to continue our research training. The "BTA" (Been To America) qualification was almost a sine qua non for young British scientists in the 1960s.

But arranging Fellowship support and finding suitable laboratories and supervisors in the same town was not so easy; however, we were fortunate once more. Sue gained a NATO Fellowship; and I was awarded a Harkness Fellowship. I was accepted to work in Julie Axelrod's laboratory (having been introduced by Gordon Whitby), and Sue worked with a world leader in experimental psychology, Mort Mishkin (who knew Larry Weiskrantz well); both laboratories were at the National Institutes of Health. We traveled to the United States in September 1964 aboard the Queen Elizabeth.

Working in the Axelrod lab was a mind-blowing experience. The National Institutes of Health (NIH) was in period of expansion and unlike the austerity I had encountered in Cambridge, resources seemed almost unlimited. There was no question of washing the scintillation counter vials there!

Julie Axelrod was something of a "late starter." He gained his Ph.D. late in life, having worked for many years as a laboratory technician for the famous pharmacologist Bernard Brodie. Julie did not have his own research group until he was in his forties. But he soon made up for lost time, and his research was enormously productive for almost another 50 years. He trained

many young scientists from all over the world, many of whom went on to successful careers in neuroscience, but I was among the first generation of foreign visitors and postdocs in his lab. It was a great time. So many things remained to be discovered in the field of catecholamine research, following the availability of the radiolabelled amines and the discovery of the tissue reuptake mechanism. Jacques Glowinski, a French visitor, and I worked closely together, capitalizing on work that he had already started with Julie in the previous year. The project was based on the idea that one could study catecholamine metabolism and drug effects on the brain by labeling the catecholamine-containing neurons with radioactive amines. But the amines could not pass the blood–brain barrier, so they had to be injected directly into the brain. Jacques had devised a simple technique for injecting radiolabelled catecholamines into the ventricular system of rat brain and had already confirmed that tricyclic antidepressant drugs inhibited norepinephrine uptake in the brain as had been found previously in the periphery by Georg Hertting (Glowinski and Axelrod, 1964). This was a key new insight into how these drugs worked. Jacques and I did hundred of experiments together, and we were able to throw new light on the differing rates of turnover of catecholamines in various brain regions, their subcellular distribution, and the actions of various classes of central nervous system (CNS) drugs. Thousands of scintillation vials were stacked up outside the lab door each day, and we worked from morning to night. We published several papers from this hectic period of activity (e.g., Glowinski and Iversen, 1966), and we remain close friends. He went back to France and he developed a highly successful neuropharmacology laboratory at the Collège de France in Paris, where he brought modern neuropharmacological approaches and trained a whole generation of French neuroscientists

Julie gave us great encouragement, on the one hand he had more research ideas than we could possibly handle, but he also gave us an extraordinary degree of freedom. He was always interested in what we were doing. He had no office but had a small desk in a laboratory in which he would daily carry out his own experiments. The desk was immediately adjacent to the only balance in the lab, so everyone would have to use this at least once a day—and Julie could find out what they were up to! Julie also had a masterful technique for writing papers. We would all sit down at his desk and write the paper from start to finish—with his clear corrections and lucid explanations. The three of us would move our wheeled chairs together from one end of the room to the other—and the end result would be typed and ready for revision (there were no word processors in those days, so revisions had to be patiently retyped). We had no electronic calculators either, let alone computers, so data were analyzed by slide rule or by what we considered quite advanced mechanical calculator machines—which resembled large cash registers. The one piece of equipment that was really modern was the scintillation counter, and we would hang around watching the data come off this machine—often

setting it to count each sample for only a short period of time, so that we could see if the experiment had worked. Julie was also an enthusiast for this "look-and-see" approach and would join us to watch the flashing red lights on the front of the machine.

The NIH was an enormously stimulating place to be doing research during this period. Part of the reason for this was that the best output from U.S. medical schools had decided quite reasonably that a couple of years of military service doing research at the NIH would be preferable to the alternative in the jungles of Vietnam. There was a rapid turnover of such extraordinarily bright people. The 1960s was an immensely optimistic period for biological psychiatry. We had the naïve belief that we would be able to understand the biochemical basis of mental illnesses and to treat them far more effectively. The 1960s saw the introduction in a very short space of time of the first really effective drugs to treat schizophrenia, depression, and anxiety. I suppose we all felt that progress like this would continue—and there would be more and more rational ways of approaching the development of drugs to treat psychiatric conditions. We didn't realize that the discoveries of the 1960s were to represent the only major advances in drug treatment for the rest of the century. What happened later was far less spectacular.

During my stay at the NIH many other long-lasting friendships and contacts were made. Sol Snyder was beginning his research career in Julie's lab, not working on catecholamines but on another of Julie's favorite topics, the pineal gland and on histamine. But Sol and I became close friends and have remained so—I have followed his subsequent research in great detail and with much admiration. He is a person of extraordinary intellect and originality who knows when to jump into a field and when to move on, which is equally important. He says that he owes a great deal of that way of doing research to his mentor Julie Axelrod—who was a fountain of creativity and originality. Julie would say, "Don't read the literature because it will only confuse you. You should just get on and do your own thing." That has been very much Sol's way—and he has been very successful not only in contributing to numerous topics in neuroscience, but also in training a whole group of people, many of whom have gone on to important senior positions in U.S. medical research.

There were other famous neuropharmacologists at the NIH while I was there, but we never got to visit people like Erminio Costa, Sidney Spector, or Sidney Udenfriend who worked in Bernard Brodie's laboratory, even though they were in the same building as us. The Axelrod lab was not on speaking terms with the Brodie lab—perhaps because Brodie resented the fact that his former pupil Julie Axelrod had become so spectacularly successful. I don't know the details, but we only ever saw these people at seminars. Costa would have stand-up arguments with Jacques Glowinski at conferences about their different interpretation of measurements of CNS catecholamine metabolism. Both Jacques and Mimo sometimes let their Latin

temperaments get the better of them—which made for entertaining spectator sport! But I got to know Mimo Costa quite well later and admired him as an intelligent, inventive, and ingenious person who contributed much to modern neurochemistry and pharmacology. In his 1970s he lost his job with the Fidia Research Laboratory in Georgetown, Washington, D.C., because the company went bankrupt. But he got himself a new job and a new career in Chicago. You have to admire someone who can keep going like that, wanting to research and having good ideas.

Postdoctoral Work in Steve Kuffler's Department at Harvard

After the hectic period in Julie's lab it was a relief to take a break before moving on to a second postdoc at Harvard. My Fellowship from the Harkness Foundation was intended to foster Anglo-American relations, and as part of this the Fellows were required to travel for several weeks each year to get to know the United States. I was provided with a large Chevrolet and told to head West. Sue and I spent a memorable 6 weeks during the summer of 1965 crossing the country from Washington, D.C., to the West Coast and back—and visiting a variety of academic labs en route—a fantastic experience. We Europeans had no idea just how big a country the United States was until we had driven 700 miles in one day along a dead straight road in Kansas!

In September 1965 we arrived in Boston. Again Sue and I had been fortunate to arrange excellent positions for a second period of postdoctoral research. Sue joined the group of Peter Dews at Harvard and learned new skills in behavioral pharmacology, and I went to the newly formed Department of Neurobiology at Harvard Medical School. This was headed by the brilliant neuroscientist Steve Kuffler—to whom my mentor Arnold Burgen had introduced me. I was supervised by Ed Kravitz, a biochemist who had joined Steve Kuffler's group from the NIH, where he had been a contemporary of Roy Vagelos—who later became head of Merck & Co., Inc., where I was subsequently to work. I was to be Ed's first postdoc, and we got on very well together—he taught me a great deal.

To be in Steve Kuffler's lab for a year was a great privilege and a joy. At Harvard I met a group of quite different scientists. They were much more interested in neurobiology, physiology, and cell biology and less biochemistry or pharmacology oriented than the Axelrod group. They also favored the use of invertebrate organisms with their simpler nervous systems—so I worked on lobsters instead of rats. I joined the "GABA project" which had already been under way for some years by a team that included Steve Kuffler, David Potter, and Ed Kravitz. We worked on the inhibitory motor nerves of the lobster. Unlike mammals, where inhibition goes on only in the CNS, lobster muscles receive a dual innervation by inhibitory and excitatory motor nerves. A meticulous comparison of the neurophysiological actions of

γ-aminobutyric acid (GABA) on lobster muscle with the inhibitory synaptic potentials elicited by stimulating inhibitor motor nerves had convinced Steve that GABA was most likely the neurotransmitter released at such synapses. But proof of this was lacking. By careful dissection of inhibitory versus excitatory nerves and sensitive biochemical assays the team had established that GABA was indeed present at high concentrations in the inhibitory fibers, but not at all in the excitatory ones. Ed and I set out, with the collaboration of a Japanese visitor Masanori Otsuka, and occasional help from a graduate student Zach Hall, to demonstrate that GABA was selectively released when inhibitory nerves were stimulated. Ed devised an ingenious preparation of the large crusher claw of the lobster in which most of the shell was removed to leave a single large muscle exposed together with its inhibitory and excitatory nerves. The preparation was constantly superfused with sea water, and the efflux collected at timed interval. I helped to devise a method for isolating the tiny amounts of GABA that were released and assaying them—not easy as we were trying to isolate amounts of GABA in the subnanomole range from 40 to 50 milliliters of seawater! Masanori would set up the stimulating electrodes to separately stimulate inhibitory or excitatory nerves and would check that they were working correctly by recording synaptic potentials in muscle fibers after impaling these with a microelectrode. After the many technical difficulties had finally been overcome—and with only a few weeks of my stay remaining—we were able to carry out some successful experiments, showing the selective release of GABA when inhibitory but not excitatory nerves were stimulated, and showing furthermore that the amounts released were dependent on the stimulation frequency and required the presence of calcium. We were thus able to provide what we felt was the final piece of evidence that GABA was the inhibitory motor neurotransmitter. Ed Kravitz and Zach Hall had to finish the experiments after Masanori and I had left to return home—but by that time we all knew that it was in the bag! We published a paper describing our results in *Proceedings of the National Academy of Sciences USA* (Otsuka et a1., 1966), and we awaited the acclaim that we all felt to be our due—after all this was only the third neurotransmitter whose identity had been proved! But initially far from acclaim our results were met with skepticism and derision. Ed gave a paper at the U.S. Federation Meetings in the spring of 1966 and was met by hostile questioning from an audience not yet ready to admit that GABA had any function in the nervous system other than as a metabolite. At a meeting of the Physiological Society in England in the autumn of 1966 I experienced a similarly skeptical reaction, and I was only rescued from the hostile questioning by the intervention of the Chairman of the session, Bernard Katz (who was later to share the 1976 Nobel Prize with Julie Axelrod). He reminded the audience that it was customary for members to be more courteous to a young member who was giving his first paper to the Society! Acclaim or no acclaim we were all very proud to have been involved in the final stages of

Steve Kuffler's "GABA Project"—and in due course GABA became to be recognized as one of the most widely used inhibitory neurotransmitters in invertebrates and vertebrates.

Steve Kuffler was an extraordinary genius and a man of great charm and modesty. He had the knack of choosing the right people and finding the right sort of preparation to solve particular problems in neurobiology. While I was there he was working on electrophysiological recordings from the large glial cells found in the optic nerve of the mud puppy. This work showed that far from being nonfunctional, glial cells exhibited electrical potential changes as the surrounding nerve fibers were activated. At the same time in another part of the lab Hubel and Wiesel were carrying out their ground-breaking work on the visual cortex, showing that there were individual neurons that recognized the direction and orientation of visual stimuli, work that had originated from Kuffler's earlier research on ON and OFF fields in the retina. This was a great introduction for me to the wider world of neuroscience, in one of the first academic departments anywhere in the world devoted solely to this field.

Return to Cambridge

I returned to the Department of Pharmacology in Cambridge—where Arnold Burgen continued to offer me every support. I was personally supported by my Trinity College Fellowship and later by a named research fellowship from the Royal Society, the Locke Fellowship. This meant that I was not a member of the teaching faculty and could spend all my time on research, apart from some College tutorial work in the evenings at Trinity. Initially I shared a laboratory with a lecturer in the department, Brian Callingham who was extraordinarily tolerant of the increasing number of graduate students and postdoctoral visitors that I continued to squeeze in to the limited space. My first graduate students, Bevyn Jarrott from Australia and Patrick Salt joined, and were followed soon by another Australian graduate student Ian Hendry and my first postdocs, Norman Uretsky from Chicago, Mike Simmonds from London, and Ira Black, who had just completed a period in Julie Axelrod's lab.

During the next 4 years research ranged widely as I gradually developed my own research group. Research topics included the inhibition of $Uptake_2$ by steroids (P. Salt); distinctions between monoamine oxidase A and B (B. Jarrott); effects of ambient temperature on catecholamine turnover in brain (M. Simmonds); nerve growth factor (I. Hendry); and synaptic plasticity (I. Black). I was also able to maintain an interest in GABA by collaborating with another faculty member, Mike Neal. We were the first to show the presence of a high affinity saturable uptake of GABA by rat brain slice preparations in vitro (Iversen and Neal, 1968). Forty years on, we now know that there are no fewer than four different high affinity GABA transporters in brain.

In similar experiments with Graham Johnston, a visitor from David Curtis' lab in Australia, we showed that a high affinity uptake of glycine could also be demonstrated in spinal cord in vitro (Johnston and Iversen, 1971). My interest in GABA continued with collaboration with James Mitchell, a senior faculty member, who had devised a cortical cup technique that allowed the collection of samples from the cat visual cortex, while applying various stimuli. Using the sensitive GABA assay technique that I had developed for the lobster studies, we were able to show that there was an increase in GABA release from mammalian cortex associated with inhibitory activity.

Having demonstrated that a high affinity uptake of GABA was present in mammalian central nervous system (CNS) the question remained of how to show whether or not this was localized on GABAergic nerve endings as a reuptake mechanism, equivalent to the norepinephrine uptake system in sympathetic nerves. One way would be to use radiolabelled GABA and then to attempt to localize this in tissue sections by autoradiography. But at the light microscope level this would not have sufficient spatial resolution to give an unequivocal answer about the cellular location of the uptake sites. This could only be done at the electron microscope level. So I ambitiously sought to obtain funds to purchase an electron microscope for the Department and to hire an experienced technical assistant. With help from Arnold Burgen this was successfully accomplished in 1969, and I set out to teach myself how to use the microscope and how to go about getting ready to do some autoradiography. I would never have achieved this without a lot of help from my friend Floyd Bloom, who was an expert in this methodology. Floyd had not worked at the NIH campus in Maryland, where Julie's lab was, but he was in another NIH-supported research group at St. Elizabeth's Hospital in downtown Washington, D.C. He had developed a very successful research career combining expertise in neurophysiology and neuroanatomy to studies of neurotransmitters, and I had got to know him and visited his lab several times. We became good friends, and remain so. Floyd offered detailed advice about what was needed to set up light and electron microscopic autoradiography and even offered to come over himself to help me get started. He came to Cambridge in the summer of 1970, and although he stayed for only just over 6 weeks we accomplished an amazing amount, largely because of careful planning beforehand. With the electron microscope method we were able to study in detail the cellular location of H^3-GABA that had been accumulated by slices of rat cerebral cortex. Floyd taught me how to apply quantitative morphometric methods to this analysis, and although the preservation of tissue structure in such small tissue slices was poor, we were able to conclude that the majority of the H^3-GABA had accumulated in synaptic nerve endings, and furthermore showed that only a subpopulation of nerve terminals was labeled. We were able to publish our results quite rapidly (Bloom and Iversen, 1971)—and this was just as well because Tomas Hökfelt in Sweden was also publishing similar studies of the autoradiographic

localization of H^3-GABA uptake sites. Tomas and I are contemporaries and have had a friendly competition on a number of topics over the years.

The autoradiographic studies with H^3-GABA were later extended to examine the localization of H^3-glycine that was again found to be localized to nerve terminals. In homogenates of spinal cord it was possible to show that each amino acid labeled a separate population of synaptic terminals, amounting to approximately 25% of the total in each case. But autoradiographic studies of H^3-GABA uptake in retina done with Mike Neal produced a surprising result. Instead of labeling a population of inhibitory interneurons as we had expected, the radiolabelled GABA was prominently accumulated by a particular population of large retinal glial cells, the Müller Cells (Neal and Iversen, 1972). A study of H^3-GABA uptake in slices of rat cerebellum conducted with a graduate student Fred Schon also showed a prominent glial localization (Schon and Iversen, 1972). In retrospect this is no longer surprising, as we know that GABA transporters are located on neuronal and glial sites in mammalian CNS, but at the time we were puzzled. The failure to observe glial uptake sites for GABA in our previous experiments using small brain slices or homogenates was probably due to the poor preservation of glial cells in such preparations.

In the catecholamine arena Norman Uretsky and I were among the first to show that the selective neurotoxin 6-hydroxydopamine worked on adrenergic neurons in CNS in the same way that Hans Thoenen had demonstrated for sympathetic nerves in the periphery (Uretsky and Iversen, 1970). When administered into the brain this chemically reactive catecholamine analog is selectively taken up into catecholamine neurons (noradrenergic and dopaminergic) and subsequently kills them. 6-Hydroxydopamine has since become widely used as a tool for studying the functions of CNS adrenergic neurons by using local microinjections of the toxin to create selective lesions of particular pathways. Such methods were adopted by Sue and the students in her laboratory and yielded many important advances in understanding the role of the various dopaminergic and noradrenergic circuits involved in the behavioral responses to drugs, particularly the amphetamines. There was a frequent interchange of students and postdocs between our laboratories. Sue and I also worked together to write a much-needed student textbook *Behavioral Pharmacology*, published by Oxford University Press in 1981.

Particularly exciting for me was the work that was done in collaboration with Ira Black and Ian Hendry and a graduate student Angus Mackay on the role of nerve growth factor, and the way in which nerve activity affected the expression of key enzymes in adrenergic neurons. We found that the level of the biosynthetic enzyme tyrosine hydroxylase in sympathetic ganglion cells or in the adrenal medulla was elevated by sustained increases in the activity of presynaptic fibers, and decreased if these fibers were lesioned (Black et al., 1971). These were among the first models available for studying how neuronal

activity affects gene expression. Ian Hendry showed that the effects of increased nerve activity could be mimicked by administration of nerve growth factor (NGF)—and went on to propose that NGF might act as a retrograde signal picked up by sympathetic nerve endings and transported back to the cell bodies (Hendry and Iversen, 1973). When Ian completed his Ph.D. and left to join Hans Thoenen's lab in Switzerland we continued to collaborate for a while, and I was able to provide the first direct autoradiographic evidence for the retrograde transport of radiolabelled NGF that he had posulated (Hendry et al., 1974). The concept of NGF as a retrograde cell signaling mechanisms is by now widely accepted.

MRC Neurochemical Pharmacology Unit (1970–1983)

In 1970 my research career received another boost. During the previous year I had applied to the Medical Research Council (MRC) (the main government funding agency for biomedical research in Britain) for the Directorship of the MRC Neurochemistry Unit at Carshalton in Surrey, a vacancy created by the retirement of its founding Director Derek Richter. I was short-listed for this post but in the end was not appointed. However, as a consolation prize the MRC offered something even better—my own small Unit in Cambridge! So the MRC Neurochemical Pharmacology Unit was formed, and I spent the next 12 years very happily as its Director. In those days the MRC gave Unit Directors a very free hand in determining their research programs, and although the resources available to the MRC were not as great as those of the NIH we did not complain about any lack of equipment or staff positions. The Unit's core budget was entirely funded by MRC, so I no longer had to write grant applications. The Director had to submit a written report for review every 3 years, and the Unit had a site visit once every 6 years—this was not a very onerous regime! Although we were always short of space, the Unit—colloquially known as "Nick Pooh"—was very productive and attracted a wonderfully talented cohort of students, postdocs, and overseas visitors. At that time it was relatively easy for Americans to obtain Fellowship support for a period of research training overseas, and we benefited greatly from this. "Nick Pooh" was always a very warm and friendly lab—we were never more than about 30 people, and often had parties (usually hosted by Sue at home) or picnics together.

As the Unit became established several research projects developed. John Kelly had joined the Unit from Kres Krnjevik's laboratory at McGill University. John brought the latest neurophysiological techniques to the Unit, including intracellular single cell patch-clamp recordings; multibarreled iontophoretic microelectrodes; and computer analysis of data. The Unit purchased the latest PDP8 lab computer, its flashing red lights and apparent miles of cabling always impressed visitors! John developed his own group of staff and visitors, focused mainly on amino acid neurotransmitter pharmacology.

My own interests stayed initially with the catecholamines, but later became increasingly focused on the neuropeptides.

In the catecholamine field I was particularly struck by a lecture that Sol Snyder gave at a Summer School in Boulder, Colorado, sponsored by the Neuroscience Research Program (NRP). This was a so-called invisible university of the brain based at MIT, founded by the charismatic polymath Frank Schmitt. I was fortunate to be among the small group of Associates of the NRP for almost 10 years (1975–1984) and attended its meetings in Boston three to four times a year—it gave me an invaluable continuing contact with leaders of neuroscience in the United States, and I benefited greatly from my membership. In 1972, prior to becoming an Associate, I was invited to lecture at the Summer School. Sol Snyder gave a lecture on the "dopamine hypothesis" of schizophrenia, putting together the gathering evidence for what was then a very new concept. I had not appreciated how strong this evidence was, and I became convinced that this was a field that the Unit in Cambridge should get involved in. Fortunately at that time an outstanding new graduate student Richard Miller joined me, straight from a Biochemistry degree in Bristol University. A recently published paper by John Kebabian and Paul Greengard had described a dopamine-sensitive adenylate cyclase in rat pituitary gland, which seemed to offer for the first time a biochemical test tube model for dopamine receptors. Richard soon found that a similar dopamine-sensitive adenylate cyclase could be demonstrated in the dopamine-rich basal ganglia of rat brain, and he rapidly established this as a model system for studying drug actions on brain dopamine receptors. In particular we were excited to be able to test a key tenet of the "dopamine hypothesis," namely that the drugs used to treat schizophrenia all acted as dopamine receptor antagonists (Miller et al., 1974). At first our results seemed to support this hypothesis. Among the phenothiazines and thioxanthenes there was a close correspondence between the antagonist affinities of the drugs against the adenylate cyclase and their known behavioral or clinical potencies. But anomalies soon emerged—whole classes of potent antipsychotic drugs—the butryophenones and substituted benzamides were virtually inactive as antagonists in the adenylate cyclase model. Meanwhile Kebabian and Greengard were coming to the same conclusions, having also studied a dopamine-stimulated adenylate cyclase in rat brain (Clement-Cormier et al., 1974). It was not until Phil Seeman and Sol Snyder independently discovered a second dopamine receptor in brain by measuring the binding of a radiolabelled tracer that the true target of the antipsychotic drugs was found—now called the dopamine D_2 receptor (Creese et al., 1976; Seeman et al.,1975). What we had been studying is now known as the dopamine D_1 receptor, and molecular cloning studies later revealed a further three dopamine receptors exist in mammalian brain. But of course we did not know any of this at the time.

Another way of testing the "dopamine hypothesis" of schizophrenia was to see if abnormalities could be detected in the dopamine systems in the

brains of schizophrenic patients postmortem. In the Unit we had started to collect postmortem human brain tissue because of the enthusiasm of an U.S. visitor, Ted Bird, who had the idea of looking for neurochemical abnormalities in the brains of patients dying with Huntington's disease. Although I was initially skeptical of the value of biochemical measurements in postmortem human tissue, Ted went ahead anyway, and it soon became apparent that a number of neurotransmitters and associated biochemical markers were remarkably stable in postmortem human brain—so that valid measurements could be made. In Huntington's disease Ted showed that were gross deficiencies in the inhibitory transmitter GABA in basal ganglia, which we thought might be associated with the uncontrolled movements that such patients suffer (Bird and Iversen, 1974). It was an obvious next step for us to start collecting postmortem brain tissue from patients dying with a diagnosis of schizophrenia, and Ted Bird and Angus Mackay, who planned a career in psychiatry, soon got this started. What proved more difficult, however, was the interpretation of the biochemical data. Although like others we did find elevated levels of brain dopamine, and increased densities of dopamine receptor binding sites in schizophrenic brain it was not clear if these were really associated with the illness, or merely the result of chronic treatment with dopamine-blocking antipsychotic drugs, which were known to elicit such changes in the brains of experimental animals. In the small number of patients in our collection who had not been treated with antipsychotic drugs no abnormalities in dopamine or dopamine receptors were seen, but the sample was very small (Mackay et al., 1980). We concluded that this approach would not yield any unequivocal answers, although others disagreed. Other labs have continued to search for dopamine excess in schizophrenia in recent years, using ever more sophisticated brain imaging tools to examine dopamine systems in the living brain. The latest imaging findings do suggest that dopamine hyperactivity does occur in the brains of patients who are in the florid stages of psychosis.

Later, in the 1980s, the work on human postmortem brain was extended to Alzheimer's disease. This project was led by Martin Rossor, a trainee in Neurology who was taking time out to do research. We carried out an extensive series of studies on neurotransmitters and neuropeptides, confirming in detail the cholinergic lesion and observing differences in the pattern of cholinergic damage in young versus old Alzheimer's disease patients (Rossor et al., 1981). During a brief visit to Floyd Bloom's lab at the Salk Institute I was able to confirm that in addition to the cholinergic damage Alzheimer's disease there is a profound loss of noradrenergic cells from locus coeruleus (Iversen et al., 1983) A useful off-shoot of our activities on human postmortem brain was that we were able to establish the MRC Brain Tissue Bank as a resource in Cambridge and supplied samples of frozen tissue for biochemical analysis to researchers in many different laboratories around the world. This was one of the first "brain banks" to be established in the United

Kingdom, and it still continues to operate today—although the restrictions and regulations surrounding work on human tissues are now far more onerous than they were 30 years ago.

In the 1970s I became fascinated by the rapidly growing field of neuropeptide research, which had been boosted by the discovery of the first of the endogenous opioid peptides, the enkephalins by John Hughes and Hans Kosterlitz in Aberdeen. Hans Kosterlitz was a remarkable example, like Julie Axelrod, of someone whose best research was done after he reached the normal retirement age! He had to retire from his post as Head of the Department of Pharmacology at the University of Aberdeen but was able to continue his research on opiate pharmacology there through support from the National Institute on Drug Abuse in the United States. After the discovery of the opiate receptor by Sol Snyder and Candice Pert it became obvious that naturally occurring ligands for these receptors must exist in brain, and the search began in several different laboratories. I attended a meeting of the Neuroscience Research Program devoted entirely to this topic in May 1974, and there was considerable sparring between the rival camps—notably Sol Snyder, Lars Terenius, and John Hughes, all of whom were close to discovering the enkephalins. John Hughes came to Cambridge shortly after to give a seminar, and I invited Howard Morris, an expert in the mass spectrometry of peptides and proteins. At the end of the seminar Morris challenged John by saying that if he could have a few milligrams of the peptide that John has isolated, the structure could be worked out quickly. John did not initially take up this challenge, although some time later he did, and Morris helped to solve the conundrum that Hughes had struggled with—he had isolated not one peptide but two closely related substances, Leu- and Met-enkephalin.

My entry to this field came with another neuropeptide, substance P (SP). Although discovered in 1936 by Ulf von Euler and John Gaddum, the structure of this undecapeptide was only revealed for the first time by Susan Leeman in 1970, but the peptide was not commercially available for some time thereafter. Shortly after the establishment of the MRC Unit, however, I was fortunate to receive a generous gift of 25 mg of the synthetic peptide from Ralph Hirschman a peptide chemist working at Merck Research Laboratories.

Research Laboratories in the United States (someone I would come to know very well when I later joined this company). Although this was a small amount of peptide, it was more than enough to sustain our SP research program for many years to come. We were able to use some the peptide to prepare antibodies that were used to develop sensitive immunoassays or for immunohistochemical mapping studies. Claudio Cuello, an Argentinean visitor who was very well trained in neuroanatomy, prepared a complete map of the SP-containing neurons in rat brain and spinal cord (Cuello and Kanazawa, 1978)—competing directly again with Tomas Hökfelt and his team at the Karolinska Institute in Sweden.

Tom Jessell, a new graduate student, used a radioimmunoassay to demonstrate the calcium-dependent release of SP from superfused brain slices in vitro on depolarization. Although there were many SP-containing neuronal pathways within the brain, we were particularly interested in the presence of SP in a class of primary sensory neurons, where it was thought to be involved in the transmission of pain information into CNS. My former colleague from Harvard Masanori Otsuka had carried out a meticulous series of neurophysiological studies suggesting the possible role of SP in these nerves as a sensory neurotransmitter. Tom Jessell was able to establish an in vitro preparation of rat brainstem slices in which SP release from primary sensory nerve endings could be demonstrated. Most importantly he went on to show that morphine could suppress the stimulus-evoked release of SP—suggesting a novel way in which opiate analgesics might act as inhibitory modulators at the first sensory relay carrying pain information into CNS (Jessell and Iversen, 1977).

Another graduate student, Chi Ming Lee from Hong Kong, studied the pharmacological actions of peptides related to SP on a variety of in vitro smooth muscle preparation and provided evidence for the existence of multiple receptors—one category preferring SP itself, another preferred the related naturally occurring peptides eledoisin or kassinin (Lee et al., 1982). This work was carried forward further by Steve Watson later. We also provided evidence for the existence of a second SP-related peptide in mammalian CNS, which we called "neuropeptide K." These findings proved to be the forerunner of our present understanding that there are three naturally occurring peptides in the SP family: SP and neurokinins A and B, and they are recognized by three related receptors: NK1, NK2, and NK3. We were also interested in understanding how SP was enzymically degraded, with the idea that inhibitors of such enzymes might provide a way of pharmacologically enhancing SP actions in vivo. Together with Bengt Sandberg, a Swedish chemist visiting the lab, and Michael Hanley a postdoc we made some progress in purifying a SP-degrading enzyme and devised and synthesized metabolically stable synthetic analogs of SP (Sandberg et al., 1981). But because of their broad specificity peptidases have not so far proved useful drug discovery targets for this or other neuropeptides.

My interest in SP continued after I joined the pharmaceutical industry, but meanwhile a summer visit to Floyd Bloom's laboratory at the Salk Institute in California and a collaboration with Wylie Vale (a former colleague of Roger Guillemin) allowed the demonstration for the first time of the calcium-dependent, stimulus-evoked release of enkephalins (Iversen et al., 1978b) and somatostatin (Iversen et al., 1978a) from mammalian brain slices in vitro. During a subsequent summer visit to Salk, I showed that in the posterior pituitary, as in primary sensory nerves, opiates acted presynaptically to suppress the stimulus-evoked release of vasopressin. In Cambridge, Piers Emson, a staff member of NCPU, carried out extensive studies of the neuropeptide

vasoactive intestinal polypeptide (VIP) and neurotensin in rat brain, and studied these also in human postmortem brain.

Not all aspects of my plans for NCPU succeeded. My biggest disappointment was the failure to establish a clinical research presence in Cambridge. Angus Mackay, now a fully qualified psychiatrist and a talented scientist, rejoined the Unit, and we had plans to start a small clinical research effort in schizophrenia. But despite every encouragement from the newly appointed Professor of Psychiatry Martin Roth and positive support from MRC this proved impossible. Angus eventually left to become a very successful director of one of the largest psychiatric hospitals in Scotland. The problem was that British psychiatry during the 1970s and 1980s was very much oriented to the fashionable concepts of group therapy and counseling—and if not antagonistic toward biological research, psychiatrists were largely indifferent to it. The local psychiatric hospital in Cambridge was no exception. Even the new Professor of Psychiatry found it difficult to establish a clinical research presence there, and we had no chance.

Being Director of NCPU (1970–1983) was one of the most satisfying jobs I ever had. Election to the Fellowship of the Royal Society of London toward the end of this period came as an unexpected surprise and privilege and helped to round out this phase of my career. The MRC gave me every support and freedom, and we attracted a group of very talented people to work in the lab—many of whom have gone on to highly successful research careers and to senior academic positions. It is hard to imagine a better environment in which to do productive research—but being a restless person I decided to move on.

Merck Research Laboratories (1983–1995)

In 1981 I was visited in Cambridge by two senior research directors from the U.S. pharmaceutical company Merck, Clem Stone and Paul Anderson. They told me of an ambitious plan that the company had to establish a large new research laboratory in England, which would become the focus of Merck's drug discovery research in the neuroscience field. Merck had been through a very successful period and wanted its research to become more global in coverage, to reflect the international status of the company; during the next decade new laboratories would be opened in France, Italy, and Japan in addition to the one in England. Another factor in England was that because of the National Health Service the U.K. government was the sole purchaser of Merck's prescription medicines. As such the government could control the prices that Merck was allowed to charge. If the company established research or manufacturing facilities in Britain, however, they could gain some concessions in such price negotiations. Merck did both—establishing the Neuroscience Research Centre in Harlow, Essex, and a large new manufacturing plant in Newcastle.

What Clem Stone and Paul Anderson wanted to know was whether I would be willing to act as a consultant to Merck and offer advice on this big new project. They were unfamiliar with the neuroscience research scene in Britain or the rest of Europe. In particular they wanted advice on who they might appoint as the Director of the new laboratory. I found the project ambitious and exciting, although at first the idea that I might personally become the Director of this new venture hardly crossed my mind.

At that time the MRC, which had hitherto not encouraged its research staff to have much to do with industry had announced new rules that permitted their scientific staff to act as consultants to industry. Thinking that this would allow me to work as a consultant to Merck I asked MRC Head Office to confirm that this was permissible. To my dismay the answer was no; consultancies would only be permitted if the company in question was British—thus ruling out formal approval for me to work for Merck. I found this patently absurd because the new Merck research laboratory would offer a considerable boost to research in Britain. So I decided to ignore the MRC ruling and went ahead informally as Merck's consultant anyway. As I did so I got to know and respect the Merck people involved, and as I learned more about the details of their plans I became more and more enthusiastic about what the project had to offer. Eventually in 1982 I accepted Merck's offer to become the Director of the Neuroscience Research Centre and joined the company in temporary lab facilities at their commercial headquarters in Hoddesdon, Herts, in October 1983—after a rather uncomfortable year in Cambridge trying to ensure a soft landing for NCPU—which eventually happened with the appointment of the very talented Eric Barnard as my successor.

Some of my former academic colleagues were shocked to see me move into the world of commerce, or "trade" as some snidely called it, but most expressed admiration, and my move was soon followed by other academics who left their ivory towers to join industry—as other companies followed Merck's lead and established neuroscience research laboratories in the United Kingdom. John Hughes went to direct the Parke Davis laboratory in Cambridge, Humphrey Rang to the Novartis Institute at University College, London, and Richard Green to Astra Zeneca.

The appointment at Merck was an opportunity of a lifetime. I had the freedom to recruit an entirely new scientific team (the existing members of Merck's small CNS group in the United States declined the offer to move to England), to plan a whole new program of drug discovery research, and to be involved in the development of a wonderful modern research centre on a green-field site. The site was in 30 acres of parkland near Hoddesdon, which had formerly been the grounds of a country house, known as Terlings Park. My first priority was to recruit some senior staff members. Sue was to join the lab as Director of Behavioral Pharmacology, and initially we appointed Geoff Woodruff, an academic pharmacologist from the University of Southampton

as overall Head of Pharmacology. Biochemistry was under the direction of Ian Ragan, another ex-Southampton academic; and with help from Merck chemists we appointed Ray Baker, also from Southampton, to be head of the Medicinal Chemistry group; Bill Raab who had overseen the development of the laboratory stayed on as a very professional administrator. We were to be completely self-sufficient, with our own large chemistry group equipped with all the analytical equipment and computer modeling facilities that they needed. Fortunately for us, research and development (R&D) efforts other pharmaceutical companies in Britain were not in a particularly expansionist mode at the time, so we were able to recruit numbers of very well qualified scientists. The Neuroscience Research Centre built up over the years to total of more than 300 people working on-site.

We quickly established a number of major research projects. One of the first aimed to discover a muscarinic agonist drug to treat the cholinergic deficiency in Alzheimer's disease. Despite heroic efforts this proved a very difficult objective. Although our chemists synthesized some novel and highly potent agonists (Freeman et al., 1990) we did not have the molecular pharmacology tools in 1983 to study the selectivity of drugs on human muscarinic receptors, and finding compounds that were selective for the target—the M1 receptor—that were safe to use eventually proved too difficult. It was not a goal that anyone else was able to achieve either. Despite decades of research by many major pharmaceutical companies the muscarinic agonist approach has still not reached fruition.

Another way of enhancing cholinergic synaptic function is to use inhibitors of the acetylcholine inactivating enzyme acetylcholinesterase, and this led eventually to the compounds now available for the symptomatic treatment of Alzheimer's dementia. In the late 1980s we adopted this approach by licensing an analog of physostigmine from the Italian company Mediolanum. Physostigmine had already been show to have beneficial actions in treating the cognitive deficits in Alzheimer's patients—but it suffered from a very short half-life in humans and was not a practical therapy. The simple analog heptylphysostigmine was far longer lasting, at least in animals (and we subsequently found in humans). In animal behavioral studies it showed considerable promise in reversing cholinergic deficits, and we quickly took this compound forward into development at Merck's facilities in the United States. The compound seemed to be safe and well tolerated in human volunteer studies, and it was possible to achieve a significant degree of inhibition of the cholinesterase (as measured in red cells). But when the compound entered Phase II clinical trial in Alzheimer's patients, there were a couple of instances of white cell abnormalities in patients, and Merck considered these to be sufficiently serious to abandon any further work with the compound. Mediolanum continued the clinical development of heptylphysostigmine for a few more years, but they too eventually had to give up. This was very sad, as Merck could have been one of the first to offer an acetylcholinesterase inhibitor for

the treatment of Alzheimer's disease—compounds from other companies have since become the front-line medicines for this indication. I soon learned that no matter how smart you think you are, only about one development compound in every 10 ever makes it successfully through all stages of development to the marketplace. This was true for the Neuroscience Research Centre just as it was elsewhere in pharmaceutical R&D.

We developed a strong interest in excitatory amino acid pharmacology early on. The Merck CNS group in the United States a few years earlier had discovered that the compound MK-801(dizocilpine) possessed powerful anticonvulsant activity in animal models and had considered developing it as an antiepileptic. I was asked to see whether we could work out its mechanism of action, which was unknown. The approach we adopted was to prepare radiolabelled MK-801 and to see if we could identify specific binding sites for it in rat brain membranes. Eric Wong succeeded in doing this and tested a range of neurotransmitters, peptides, and drugs on these binding sites to see if they corresponded to any known receptor in brain. Almost nothing competed with MK-801 for binding, except for a few psychotomimetic drugs—notably ketamine and phencyclidine. This was not much help because no one knew how these compounds worked. But just before then the neuropharmacologist David Lodge had reported that ketamine and phencyclidine acted in vivo as antagonists at the glutamate receptor subtype known as the N-methyl-D-aspartate (NMDA) receptor. This gave us the clue that we needed, and John Kemp and colleagues in the neurophysiology lab were soon able to show that MK-801 was a potent noncompetitive antagonist at the NMDA receptor (Wong et al., 1986). This was an important discovery; MK-801 was already known to be an orally acting long-lasting compound, so if we could identify a clinical use for it the compound could rapidly become a development candidate.

One obvious idea was to see if MK-801 could protect neurons against excitotoxic damage and death that resulted from exposure to an excess of L-glutamate. As a corollary, could MK-801 protect neurons against damage in animal models of stroke—because cerebral ischemia was thought to cause damage in part because it released an uncontrolled flood of L-glutamate from excitatory nerve endings? We soon obtained positive results in a variety of animal models that were run in-house. Positive results were also obtained in what was then regarded as the "gold standard" rat model of stroke, which involved the surgical occlusion of the middle cerebral artery in brain—one which is commonly affected in human stroke cases. Such studies required great surgical skill and were beyond our competence, but we were fortunate in collaborating with Jim McCulloch in Glasgow, who was an expert in this field. He showed that MK-801 treatment was able to reduce the cerebral infract size by as much as two thirds, and there appeared to be at least some time window available in which the drug remained effective even when given after the ischemic insult. We were keen to see MK-801 advanced to a

"proof of concept" clinical trial in stroke, but there many hurdles to overcome. Clinical trials in human volunteers showed that small doses of the drug appeared to be safe and well tolerated, but at slightly higher doses it had adverse effects on blood pressure, and subjects reported subjective feelings of "dissociation"; feeling, for example, that their limbs were no longer part of the rest of their body. Although these were not frank hallucinations the worry remained that the drug might prove to be psychotomimetic—as ketamine and phencyclidine were known to be. A further complication arose in 1989 when James Olney, a respected figure in glutamate pharmacology and father of the concept of glutamate as an "excitotoxin," published a paper describing what appeared to be brain damage in rats treated with moderate doses of MK-801. Neurons in circumscribed regions of cerebral cortex developed large vacuoles and looked sick (Olney et al., 1989). We immediately attempted to repeat these findings, and although we did observe numerous vacuolated neurons after treatment with MK-801, these changes were almost completely reversible with time. Olney's findings were taken very seriously, and in the United States the regulatory agency Food and Drug Administration (FDA) convened a special meeting to discuss the development of MK-801 and other NMDA antagonists in light of these data. I was summoned as a witness—my only experience of being questioned by an FDA panel. Although we argued that the neuronal vacuolation was essentially a reversible phenomenon, Dr. Paul Leber, Head of the Neuropharmacology Division of FDA, and well known as a hard-liner, continued to refer to the "brain lesion" caused by the drug. This culminated in a series of exacting requirements by FDA for further animal studies, including experiments in primates, before MK-801 could be allowed to enter clinical development. Given these demands, and the worries about whether the drug might prove to be psychotomimetic, Merck senior management decided to abandon further development of the drug in 1990. Although we were disappointed at the time, in retrospect this was not such a bad decision. Other companies fulfilled the FDA requirements and brought NMDA antagonists into clinical trials but found them to be potent psychotomimetic agents; none of these compounds survived to adequate "proof of concept" trials in stroke, and subsequent trials of many other pharmacological approaches to the treatment of stroke have all ended in failure. Despite showing promise in animal models a number of compounds failed to show significant clinical benefits. It seems that stroke is a far more variable condition, with varying outcomes, that cannot be simulated in any of the animal models. Stroke provides a salutary lesson about the reliability of animal models of complex illness: although animal models are an indispensable part of pharmaceutical R&D, they do not always provide reliable predictors of clinical outcome.

But we did not give up the idea that the excitotoxic actions of glutamate acting at NMDA receptors might play a key role in the secondary damage caused by stroke or other cerebral ischemic insults. In 1987, Philippe Ascher

and colleagues in Paris discovered that glycine could markedly facilitate NMDA responses. Glycine achieved this effect by binding to a distinct site within the NMDA receptor complex that allosterically regulates receptor function. This effect of glycine is so great that virtually no response can be elicited in the absence of glycine, suggesting that it acts with L-glutamate as a coagonist. It soon became clear that two existing NMDA antagonists, kynurenic acid and the aminopyrrolidone HA-966, acted by blocking the effects of glycine (Singh et al., 1990). We used these compounds as the basis of a substantial medicinal chemistry program aimed at discovering potent glycine-site directed NMDA antagonists as alternatives to MK-801. Our chemists synthesized several very potent compounds of this type, and in vivo these compounds proved to be neuroprotective in the same models used to test MK-801—and as a bonus they did not cause cortical neuron vacuolation (Leeson and Iversen, 1994). But the compounds were very insoluble in water, and they bound strongly to plasma proteins that limited their utility. We were not able to find a suitable development compound, and the project was abandoned. Other companies persisted with the approach, however, and Glaxo Smith Kline (GSK) took the glycine-site directed NMDA antagonist gavestinel into advanced (Phase III) clinical trials for the acute treatment of stroke—but gavestinel failed to provide significant clinical benefit, and it too had to be abandoned.

By the late 1980s the Neuroscience Research Centre had entered the new era of molecular pharmacology, with a molecular biology group ably headed by Dr. Paul Whiting. We decided to embark on a long-term project to analyze the subunit composition of the NMDA receptor in different CNS regions, in the hope that subtype-selective drugs might in future offer more selective pharmaceutical weapons. This was a formidable undertaking, as the NMDA receptor was known to contain a mixture of different subunits, comprising NR1 (with various different splicing isoforms) together with one or more of the NR2 subunits, A, B, C, or D. By cloning and expressing these various subunits and preparing antisera, it was possible to use immunochemistry to gain insight into the composition of native NMDA receptors, and we were able to show that some contained more than one of the NR2 subunit categories. Clearly this was going to be a long task, and I was not at the laboratory long enough to see it come to fruition. An advantage of working for a strong science-led company such as Merck in those days was the willingness to tackle major long-term basic research questions such as this.

Another of the projects initiated at the Neuroscience Research Centre was one related to the inhibitory amino acid GABA. We started collaboration very early on with a Danish research group who were then working in the company Ferrosan. Their head Jorgen Buus-Lassen, and the chemist Frank Watjen became close colleagues, and we learned a great deal from their experience and knowledge of pharmaceutical R&D—which was at first unknown territory to me and to most of my colleagues in the Merck lab, who

had largely been recruited from academia. The objective of our collaboration with Ferrosan was to discover drugs that acted as partial agonists at the benzodiazepine modulatory site in the GABA-A receptor. Conventional benzodiazepine tranquilizers, such as diazepam ("Valium") were full agonists at the site and suffered from disadvantages such as sedation, ataxia, and dependence liability. Preliminary data from "BZ partial agonists" suggested that they might retain the desired anticonvulsant and antianxiety effects while lacking these disadvantages. Frank Watjen undertook an imaginative medicinal chemistry program, synthesizing oxadiazole derivatives of the imididobenzodiazepine antagonist drug flumazenil. The compounds were assessed in the behavioral pharmacology lab at Terlings Park, headed by my wife Sue. Some of these compounds showed considerable promise as potent anticonvulsants and were active in animal models of anxiety, with greatly reduced sedative or ataxic properties (Tricklebank et al., 1990). Long-term tests showed that the lead compounds also had reduced dependence liability. One of our lead compounds entered formal development in Merck in the United States, but it failed early on in toxicology. By then both sides of the collaboration were running out of chemistry space in which to work—we found ourselves isolated on small islands of patent-free chemical territory surrounded by an ocean of very broad patents, written by the Swiss company Roche, who were also pursuing the idea of benzodiazepine partial agonists. It was my first experience of the monopoly power that patents can confer. In fact the concept of benzodiazepine partial agonists has never been shown to work in humans—several compounds with this profile did enter clinical trials, but it was found that the animal models were not accurately predictive—in particular most of these compounds continued to exhibit unacceptable levels of sedation.

We continued to believe that drugs that modulated GABA-A receptor function could prove attractive as psychoactive agents. Our approach switched to targeting different subtypes of the GABA-A receptor. From the molecular pharmacology studies of Eric Barnard (who succeeded me at the MRC Unit in Cambridge) it was known that the GABA-A receptor was composed of several different protein subunits. There were four families: 6 α-subunits; 3 β-subunits; 3 γ-subunits; and one δ-subunit. At least one α, one β, and one γ-subunit were needed to form a functional receptor complex, but no one knew which combinations actually existed most commonly, or whether these differed from one brain region to another. Keith Wafford, Paul Whiting, and Ruth McKernan set out on the heroic task to answer these questions. By preparing antibodies to the different subunits and using immunoadsorption methods they painstakingly discovered which receptor subunit combinations were commonly found in mammalian brain. Although in theory there were thousands of possible subunit permutations, in fact fewer than 20 such combinations accounted for most of the GABA-A receptors in brain. At the time I left Merck this work was still ongoing, but it later

matured and led to the discovery of novel drugs that targeted specific receptor subtypes—and some of these showed early promise as anxiolytics, cognitive enhancers, or antialcohol agents.

But my own personal research interest was increasingly focused on research on the neuropeptides, which allowed me to continue the fascination with the subject that I had acquired while in Cambridge. At the Neuroscience Research Centre we developed two major projects—one based on the concept that cholecystokinin antagonists might prove valuable as a novel class of antipanic/antianxiety drugs, the other based on the concept of substance P antagonists as potential novel analgesics.

The cholecystokinin project was inherited from earlier work in the Merck labs in the United States. By the traditional approach of screening natural products Merck scientists had discovered the naturally occurring benzodiazepine compound asperlicin—which proved to be a selective antagonist of the CCK-1 receptors found in the gut. Merck chemists went on to synthesize simplified compounds based on the asperlicin structure, and one of these, devazepide, was a thousand times or potent than the natural product—retaining a high degree of selectivity of the CCK-1 receptor subtype. Merck chemists undertook further structural modifications to obtain the first "brain selective" compound L-365,260, which had selectivity for the CCK-2 receptor subtype most commonly found in brain. At the time these were breakthroughs in the field of neuropeptide pharmacology because outside the opiate field almost no nonpeptide drugs were known that acted with potency and selectivity at neuropeptide receptors.

We started to explore the CNS pharmacology of these compounds in animals. We were attracted by the findings published at that time of the effects of C-terminal fragments of CCK in human volunteers. The Canadians Bradwejn and De Montigny in Montreal reported that the intravenous injection of microgram amounts of such peptides reliably caused a psychic panic reaction in the volunteers, which was mercifully short lived, but clearly dose-dependent. When such intravenous challenges were administered to patients who suffered endogenous panic attacks they reported that the chemically induced panics were identical to those which they experienced spontaneously. Although there were no reliable animal models of panic, we were able to show that L-365,260 possessed some anxiolytic effects in animal models of anxiety. The compound entered development as a potential new antipanic agent—and initial clinical trials data were encouraging. It was possible to show that pretreatment with an oral dose of L-365,260 could completely protect human volunteers from the panic attack normally elicited by intravenous challenge with a CCK fragment (Bradwejn et al., 1994). Furthermore, the effect of L-365,260 was dose-related, so it was possible to determine just how much was needed for the antipanic effect. But unfortunately when the clinical trials of this compound were extended to a 6-week, placebo controlled trial in patients with endogenous panic attacks the results

were entirely negative—there was no reduction either in the frequency of spontaneous panic attacks, or the level of anxiety patients experience between attacks (Kramer et al., 1995). We seem to have fallen for the logical non sequitur: "CCK Causes Panic, Therefore Panic is Caused by CCK."

Although we had invested a considerable effort in discovering second-generation back-up compounds for L-365,260, Merck senior management decided to stop further development of the CCK antagonist program. A number of other major companies had CCK antagonist programs, but these rapidly faded from sight, and no other CCK antagonist has so far reached the market as an antipanic/anxiolytic agent.

Apart from the antipanic idea, we had considered other possible applications for CCK antagonists—particularly in the field of pain control. The CCK system in spinal cord and brainstem appears to represent a parallel but distinct neuronal system to the system of neurons containing enkephalins and other endorphins, and the CCK system seems to act as an "antiopioid" control mechanism. In some chronic pain conditions an imbalance between the CCK and opioid control systems may develop, so that CCK overrides the pain-relieving actions of the endogenous opioids. We were able to show in animal models that CCK antagonists could enhance the pain-relieving actions of morphine and related opiate analgesics (Dourish et al., 1988) and we wanted to see if this might extend to the clinic. But I was unable to pursue this idea until after I left Merck in 1995—when I was able to negotiate a license to acquire the rights to all of the Merck CCK antagonists—and to purse the idea of their potential utility as adjunct of opiates—for more details see below.

The largest neuropeptide project at the Neuroscience Research Centre was the Substance P (SP) program that was an extension of my earlier interest in this peptide while in Cambridge. We set ourselves the task of discovering potent SP receptor antagonists that could be used to test the idea that such compounds might prove to act as novel centrally acting nonopioid analgesics. This was not easy, as no nonpeptide drugs were known that acted on SP receptors. Brian Williams, a peptide chemist in our lab, set out to design more rigid molecules by synthesizing cyclic peptide derivatives. He discovered a series of such peptides that acted as moderately potent antagonists (McKnight et al., 1991)—but these were still peptides, with all the disadvantages that these possess—including lack of oral availability, failure to penetrate into the CNS, and susceptibility to metabolism. An effort was made to identify a nonpeptide antagonist lead through natural product screening, which had proved so successful for CCK. Using Merck Research Laboratories Spanish natural products screening laboratory, parallel assays using I^{125}-SP and I^{125} eledoisin binding to rat brain membranes (NK-1 and NK-3 respectively) were established. During a 2-year period more than 50,000 fermentation broths were screened in each of these assays, but no positive leads were identified. The breakthrough eventually came in 1991, when

chemists at the Pfizer company published the structure of the first subnanomolar potency nonpeptide SP antagonist, CP-96,345. It was remarkable how quickly after this other companies were able to discover their own SP antagonist leads, usually by computer searches of their chemical collections, using the pharmacophore defined by the Pfizer compound. Merck launched a substantial medicinal chemistry program initially at Terlings Park but later accompanied by an equally large chemistry effort in the U.S. laboratories at Rahway. Ed Scolnick, who was head of Merck's research, was a passionate believer in the SP project—and occasionally he liked to generate some in-house competition by setting up rival teams with the same objectives!

Both chemistry teams generated some remarkably potent compounds, with picomolar affinity for the NK-1 SP receptor subtype—which by then had been selected as the key target. Although pain remained a key clinical target, we used other animal models to quickly sort out orally active potent compounds—among these models the antiemetic actions of the SP antagonists in the ferret and blockade of SP-induced extravasation in guinea pig skin proved particularly useful, and there were several compounds whose potencies were measured in micrograms per kilo in these assays. The biological aspects of this work were complicated by the finding that lead compounds from various chemical classes proved to have much lower affinities for the NK-1 receptors in rats and mice than for human or other mammals. This meant that standard rodent models could not be used, and new tests had to be devised in such species as ferrets, gerbils, and guinea pigs. By the time I left Merck we had begun to deliver development compounds into the Merck system—and within a few years the first disappointing results had been generated in clinical trials of these compounds against various human pain conditions—they were not sufficiently effective to justify any further development for this indication. For a while Merck became excited by the possibility that the SP antagonists might act as novel antidepressants, but the positive clinical data obtained in an early trials could not be repeated in a Phase III trial.

At the end of the day it was the antiemetic properties of the SP antagonists that translated reliably into the clinic. The SP antagonist aprepitant was launched as Emend® for the treatment of nausea and vomiting associated with cancer chemotherapy, an increasing problem with the new powerful cytotoxic drugs such as taxol or cisplatin. Aprepitant is usually added to a 5-HT_3 receptor antagonist, and the combination provides better overall protection; the SP antagonist seems particularly valuable in protecting against the delayed phases of emesis experienced several days after the initial chemotherapy (Gralla et al., 2005). Although emesis was not in our original plan, it is very gratifying to see the first genuine medical use for a SP-based medicine—particularly for someone like me who has worked on SP off and on for more than 30 years!

We were more successful in another project aimed at pain relief compounds—in this case for the treatment of migraine headache. In 1987

Glaxo scientists discovered a radical new approach to the treatment of migraine in the form of the drug sumitriptan, a serotonin agonist that for the first time was able to stop a migraine headache even after the attack had already begun. Migraine is a very common and distressing condition, and sumitriptan was immediately recognized as an important breakthrough. Along with several other companies we decided to see if we could discover a second-generation version of sumitriptan with some advantages over the original compound. A weakness of sumitriptan is its poor oral bioavailability; the first version of the drug to be marketed was a subcutaneous self-injectable form. Patients on the whole do not like injecting themselves, and the product was also extremely high priced. We launched a medicinal chemistry project to see if we could discover compound with better oral absorption properties, and thanks to some excellent chemistry we were able to develop rizatriptan, which had a far more rapid oral absorption, and as it proved in the clinic, a faster onset of headache relief. Merck combined these properties with a freeze-dried "wafer" formulation that dissolved instantly in the mouth so that patients found the product easy to take (Goldstein et al., 1998). Rizatriptan was launched on the market soon after I left Merck, and under the trade name Maxalt® it has competed successfully with the several other "triptans" now available. Although rizatriptan was undisguisedly a "me too" project, like many other such products in the pharmaceutical world it did offer some real advantages, and from a morale point of view it was good for the Neuroscience Research Centre to see that we really could discover and launch a new medicine! During my 12 years as Director we saw only two products coming near to registration—rizatriptan and aprepitant—and we had seen a number of development candidates fail at various stages in the development process.

My 12 years working for Merck Research Laboratories were hectic but rewarding. I learned a great deal about research in an industry that is highly competitive and demanding. I was fortunate to work for Merck—one of the leading research-based companies in the pharmaceutical world—led at that time by Roy Vagelos, originally an NIH scientist. Roy brought his work and ideas on cholesterol metabolism with him to Merck and successfully pioneered the first "statins" to control excess cholesterolemia—drugs that have had an impact on mortality from cardiovascular disease at least as great as that of the earlier antihypertensive medicines. During my period at the company Merck and Vagelos were riding high—with double-digit increases in income and profits every year and the accolade of *Fortune* magazine's annual survey as "America's Most Admired Company" for three straight years (1987–1989). With the remit to build a completely new research laboratory, and great freedom to choose which projects to work on, I had a unique opportunity and enjoyed taking it. Of course there were pressures to deliver results—I found it curious that basic research scientists at Merck were asked to state their annual objectives in very specific terms—to discover a new drug by a particular point in the year was hardly something one could

guarantee to deliver! But management by objectives and reward by achievements were the principles by which U.S. companies operated—even though both ideas were at first unfamiliar to the academic mind. I soon realized that my job necessitated a good deal of transatlantic travel, if only on the principle that it was a good idea to be in the room when your program and budget were being discussed! Fortunately I had many excellent colleagues in Merck, who patiently helped to teach me all the things that I needed to know about the complexities of pharmaceutical R&D—my first boss Clement Stone and my later boss Bennett Shapiro were particular strengths—although Bennett like me came straight from an academic job as Chair of Biochemistry in Seattle overnight to be in charge of all preclinical research at Merck! It is sad to see Merck now suffering from the withdrawal of one of its leading new products, the anti-inflammatory agent Vioxx. In the subsequent cost-cutting exercise that was needed it was decided that the Neuroscience Research Centre should be closed down, and Merck withdrew from most of its research activities in the CNS arena, choosing instead to focus on the company's traditional strengths in vaccines and in the cardiovascular field.

Life After Merck

In 1993 Sue was offered the chance to apply for the Chair of Experimental Psychology at Oxford University—which had previously been held by her former mentor Larry Weiskrantz. This was one of the premier departments in the country, and one that Sue had always admired. She applied and was offered the job; this was a big decision but the opportunity was too good to miss and she accepted. Sue entered Oxford University where there was only a handful of other female Heads of Department at the time, compared to several hundred men, although this gender imbalance has improved a little in the past decade! Under her leadership the Department continued to flourish as one the leading centers for experimental physiological psychology, with a considerable emphasis on studies of animal behavior. Sue later moved from her post as Head of Department to join the Vice-Chancellor's office as a Pro-Vice Chancellor, in charge of planning and resource allocation—two concepts that were difficult to explain to most academics!

I stayed on at the Neuroscience Research Centre for a couple of years after we moved our home to a village near Oxford—but I found it increasingly stressful to commute to work each day on the busy motorways around London—with a journey time that could vary from one to several hours. Also becoming somewhat restless after having done the job for more than 12 years, I opted to take early retirement and left Merck in March 1995.

Fortunately I discovered that "life after Merck" was possible, and even enjoyable. I was able to obtain a license from Merck for all of the CCK antagonist compounds that we had worked on, and developed a start-up company,

Panos Therapeutics Ltd., to continue the development of some of these drugs. I was fortunate in finding a business partner, Michael Clark, with considerable knowledge of the pharmaceutical business, and we formed a collaborative partnership with a small British pharmaceutical company, ML Laboratories. Their scientists planned and undertook several clinical trials aimed at seeing whether the addition of a CCK antagonist to strong opiate analgesics might improve pain relief. The culmination of the studies was in the form of two parallel "proof of concept" Phase II clinical trials which compared the CCK-1 antagonist devazepide with the CCK-2 antagonist L-365, 260. The results were clear, whereas devazepide offered significant improvements in pain relief, L-365,260 did not. This probably reflects the fact that the CCK-1 receptor predominates in human spinal cord and brainstem—the most likely sites for the CCK/opiate interaction. Unfortunately after a boardroom takeover, ML Laboratories was no longer interested in pursuing further research on our compounds—and we parted company from them. Subsequently we were also able to get release from any further obligations to Merck. I continue to hope that Panos Therapeutics will be able to continue developing devazepide as an adjunct to opiates because the preliminary clinical data were promising.

In Oxford I was fortunate to be offered an honorary appointment as a Visiting Professor in the Department of Pharmacology, by the head of department, David Smith. This entailed a small amount of student lectures and tutorials in return for an office in the department; a place to park a car in the center of Oxford (a considerable perk!); and the ability to use the title of professor in the University of Oxford. This privilege has continued to this day. In addition I acquired several other academic jobs over subsequent years. From 1996–1999 I acted as a part-time consultant to the MRC Cyclotron Unit at the Hammersmith Hospital campus in west London. This was the country's leading brain imaging research centre, specializing in positron emission tomography—but the MRC were keen to see it develop more collaborative relationships with external groups, particularly those in industry. I learned a great deal about the fascinating field of positron emission tomography (PET) imaging—which is becoming increasingly important to pharmacology as a means of visualizing receptors in the intact human brain through the binding of selective radiotracers and assessing drug interactions with such receptors. Subsequently this laboratory was partly "privatized" and now earns a considerable segment of its income through contracts with industry. Another challenging job was at King's College, London where I was a part-time professor (1999–2004) helping to develop a new research laboratory, The Wolfson Centre for Age Related Diseases. This was sponsored by a grant from the Wolfson Foundation, which allowed the building of a modern new research wing on the Guy's Hospital campus of the medical school. Although this was an exciting new venture, I also learned just how starved of resources our major British

universities had become. I was keen to attract a "high flier" in the Alzheimer's disease research field from overseas to take over from me as Director—but I found that what little King's had to offer in any "package" could not compete with what was available in the United States or Europe to attractive candidates. We eventually made a very satisfactory internal appointment, and the Centre has flourished with an excellent combination of basic and clinical research.

Some of my most interesting jobs since leaving Merck have been at the interface between science and business, where I feel that my experience of both worlds may have something particular to offer. I have acted as a member of the Scientific Advisory Board for a Danish venture capital fund, BankInvest, for the past 10 years, and found this an intriguing job—trying to assess the scientific merit and the commercial reality of new start-up companies in the human health field—and assessing the performance of the existing portfolio companies. In the United States, where Sue and I have continued summer visits to San Diego, California, on a regular basis, I have acted as an informal consultant to the local fund Forward Ventures, from whom I also learned a great deal about the biotechnology boom there. Also in San Diego I serve as Chairman of the Board of Directors for Acadia Pharmaceuticals Inc., a local company developing products for CNS indications. I have known the scientific founder of Acadia, Mark Brann, since he was a summer student in my lab in Cambridge more than 20 years ago—and have followed Acadia's development from the beginning. The company is now at an exciting stage of growth—having moved several products into advanced stages of clinical development. I attend Board meetings every quarter and spend some weeks in the company each summer.

Back at home I developed an interest in the pharmacology of cannabis and other illicit psychoactive drugs. I was coopted by the UK House of Lords Science and Technology Committee to act as their scientific advisor for their inquiry into cannabis (1998). I knew virtually nothing about the subject but soon learned and found the process of summoning witnesses for questioning by the Select Committee in the grand surrounding of the House of Lords an intriguing new experience. Our report, which advocated more research on the medical uses of cannabis, and deflated some of the more aggressive claims about the harmfulness of the drug, was greeted with instant dismissal by the government of the day—but it may have had some delayed impact. The U.K. government permitted a small company, GW Pharmaceuticals, to establish a cannabis growing facility and to undertake clinical trials of cannabis-based medicines. Their herbal cannabis extract "Sativex" has recently been approved in Canada and awaits probable European registration in the next few years. Meanwhile, a liberal-minded British Home Secretary, David Blunkett, recommended that cannabis be downgraded from Class B to Class C (which carries reduced criminal penalties), and this was duly done in 2001. Since then various politicians have sought to reinstate

cannabis to Class B—which eventually happened in 2008. My own view is that the harmfulness of all psychoactive drugs (including the legal ones, alcohol and nicotine) needs to be reassessed using scientifically objective evidence. If this were done I believe that cannabis would rate at about the same level of harm as alcohol—and it does not deserve the criminal penalties incurred for its use on both sides of the Atlantic. Although the misuse of psychoactive drugs is a major social problem in the Western world, our current "war on drugs" has failed to stem the increased use of such drugs, and it may be time for a radical reappraisal of policies. In many ways the criminalization of psychoactive drug use may have done more harm than good, both to individuals and to society. I have become a member of the U.K. government's Advisory Council on the Misuse of Drugs whose job it is to advise into which classes various illicit drugs should be placed, so I am right in the firing line now! My newly acquired expertise in the cannabis field was distilled into a monograph *The Science of Marijuana* published by Oxford University Press in 2001, intending to bring what is known about the scientific and medical aspects of cannabis to a nontechnical readership. The scientific field has since moved on rapidly, particularly with the discovery of the naturally occurring endocannabinoids, and a second edition of my book was completed in 2007. This gave me a taste for scientific writing, and I followed the cannabis book with a short volume in the Oxford University Press series of "Very Short Introductions," *A Very Short Introduction to Drugs*, published in 2001 covered the medical and recreational uses of drugs. It was a considerable challenge to condense everything one knew about pharmacology into 40,000 words! This small book proved to be a success and has been translated into several languages. I also wrote a popular science monograph on the amphetamines, titled *Speed, Ecstasy, Ritalin: the Science of Amphetamines*, which was published also by Oxford University Press in 2006. I greatly enjoyed these writing jobs and intend to continue. The next challenge is to complete a student text with Sue and my friends Floyd Bloom and Bob Roth as coauthors, titled *Introduction to Neuropsychopharmacology*—combining basic neuropharmacology with information on how psychoactive drugs are used medically and recreationally. Stemming from a conference held in 2007 in Sweden to celebrate "50 Years of Dopamine," I will also coedit the *Handbook of Dopamine* to record the advances in research on this most productive of all monoamines.

In Conclusion

I consider myself very fortunate in having often been in the right places at the right times that allowed me to achieve some degree of success. I had the good fortune to enter research on a "hot" area of neuroscience at a very early stage in its development. Although I have never had the innate creativity or originality of a Julie Axelrod or a Sol Snyder, being in the right

places enabled me to take advantage of opportunities as they arose. Research on the catecholamines and other neurotransmitters has since grown beyond all recognition. The past 50 years have seen amazing advances in the techniques now available for their study—including the ability to visualize the function of these chemicals in the living intact human brain through imaging techniques. In the same period the treatment of psychiatric illnesses has been transformed by drugs that act in one way or another on the brain monoamine systems. Although the pace of such medical advances has slowed, we look to the genetic revolution to bring us the next generation of such drugs, including the ability to treat hitherto intractable conditions such as Alzheimer's disease. For the first time we may gain a real understanding of the fundamental molecular basis of psychiatric illness.

Apart from the privilege of having taken part in some small way in the explosive growth of neuroscience in the past few decades I have also been blessed by association with the many talented colleagues who came to work in Cambridge or in Terlings Park as students, visitors, postdocs, or staff. Many have gone on to their own productive research careers and it is a wonderful pleasure to see their creativity and success.

Selected Bibliography

Bird ED, Iversen LL. Huntington's Chorea—post-mortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in the basal ganglia. *Brain* 1974;97:457–472.

Black IB, Hendry IA, Iversen LL. Differences in the regulation of tyrosine hydroxylase and dopa decarboxylase in sympathetic ganglia and adrenals. *Nature New Biol*. 1971;231:27–29.

Bloom FE, Iversen LL. Localizing ^{3}H-GABA in nerve terminals of rat cerebral cortex by electron microscopic autoradiography. *Nature* 1971;229:628–630.

Bradwejn J, Koszycki D, Couetoux du Tertre A, van Megen H, Den boer J, Westenberg H. The panicogenic effects of cholecystokinin-tetrapeptide are antagonized by L-365,260, a central cholecystokinin receptor antagonist, in patients with panic disorder. *Arch Gen Psychiatry* 1994;51:486–493.

Burgen ASV, Iversen LL. The inhibition of noradrenaline uptake by sympathomimetic amines. *Br J Pharmacol* 1965;25:34–43.

Clement-Cormier YC, Kebabian JW, Petzold GL, Greengard P. Dopamine-sensitive adenylate cyclase in mammalian brain: a possible site of action of antipsychotic drugs. *Proc Natl Acad Sci USA* 1974;71:1113–1117.

Creese I, Burt, DR, Snyder SH. Dopamine receptors and average clinical doses. *Science* 1976;194:546.

Cuello AC, Kanazawa I. The distribution of substance P immunoreactive fibers in the rat central nervous system. *J Comp Neurol* 1978;178:129–156.

Dourish CT, Clark ML, Iversen SD. Enhancement of morphine analgesia and prevention of morphine tolerance in the rat by the cholecystokinin antagonist L-364,718. *Eur J Pharmac* 1988;147:469–472.

Freedman SB, Harley EA, Patel S, Newberry NR, Gilbert MJ, Mcknight AT, Maguire J, Mudunkotuwa NT, Baker R, Street L, Macleod A, Saunders J, Iversen LL. A novel series of non quaternary oxadiazoles acting as full agonists at muscarinic receptors. *Brit J Pharmac* 1990;101:575–580.

Glowinski J, Axelrod, J. Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. *Nature* 1964;204:1318–1319.

Glowinski J, Iversen LL. Regional studies of catecholamines in the rat brain I: the disposition of H^3-norepinephrine, H^3-dopamine and H^3-DOPA in various regions of the brain. *J Neurochem* 1966;13:655–669.

Goldstein J, Ryan R, Jiang K, Getson A, Norman B, Block GA, Lines C. Crossover comparison of rizatriptan 5 mg and 10 mg versus sumatriptan 25 mg and 50 mg in migraine. Rizatriptan protocol 046 Study Group. *Headache* 1998;38: 737–747.

Gralla RJ, de Wit R, Herrstedt J, Carides AD, Ianus J, Guoguang-ma J, Evans JK, Horgan KJ. Antiemetic efficacy of the neurokinin-1 antagonist, aprepitant, plus a 5HT3 antagonist and a corticosteroid in patients receiving anthracyclines or cyclophosphamide in addition to high-dose cisplatin: analysis of com bined data from two phase III randomized clinical trials. *Cancer* 2005;104: 864–868.

Hendry IA, Iversen LL. Reduction in the concentration of nerve growth factor in mice after sialectomy and castration. *Nature* 1973;243:500–504.

Hendry IA, Stockel K, Thoenen H, Iversen LL. The retrograde axonal transport of nerve growth factor. *Brain Res* 1974;68:103–121.

Hertting G, Axelrod J. The fate of tritiated noradrenaline at the sympathetic nerve endings. *Nature* 1961;192:172–173.

Iversen LL. The uptake of noradrenaline by the isolated perfused rat heart. *Br J Pharmacol* 1963;21:523–537.

Iversen LL. The uptake of catecholamines at high perfusion concentrations in the isolated rat heart: a novel catecholamine uptake process. *Br J Pharmacol* 1965; 25:18–33.

Iversen LL, Iversen SD, Bloom FE, Douglas C, Brown M, Vale W. Calcium-dependent release of somatostatin and neurotensin from rat brain *in vitro*. *Nature* 1978a;273:161–163.

Iversen LL, Iversen SD, Bloom FE, Vargo T, Guillemin R. Release of enkephalin from rat globus pallidus *in vitro*. *Nature* 1978b; 271:679–681.

Iversen LL, Neal MJ. The uptake of ^{3}H-GABA by slices of rat cerebral cortex. *J Neurochem* 1968;15:1141–114.

Iversen LL, Rossor MN, Reynolds GP, Hills R, Roth M, Mountjoy CQ, Foote SL, Morrison JH, Bloom FE. Loss of pigmented dopamine-beta-hydroxylase positive cells from locus coeruleus in senile dementia of Alzheimer type *Neurosci Lett* 1983;39:95–100.

Iversen LL, Whitby LG. The retention of injected catecholamines in the mouse. *Br J Pharmacol* 1962;19:355–364.

Jessell TM, Iversen LL. Opiate analgesics inhibit substance P release from rat trigeminal nucleus. *Nature* 1977;268:549–551.

Johnston GAR, Iversen LL. Glycine uptake in rat CNS slices and homogenates: evidence for different uptake systems in spinal cord and cerebral cortex. *J Neurochem* 1971;18:1951-1961.

Kramer MS, Cutler NR, Ballenger JC, Patterson WM, Mendels J, Chenault A, Shrivastava R, Matzura-Wolfe D, Lines C, Reines S. A placebo-controlled trial of L-365,260, a CCKB antagonist, in panic disorder. *Biol Psychiatry* 1995;37: 462–466.

Lee CM, Iversen LL, Hanley MR, Sandberg BEB. The possible existence of multiple receptors for substance P. *N S Arch Pharmac* 1982;318:281–287.

Leeson PD, Iversen LL. The glycine site on the NMDA receptor: structure-activity relationships and therapeutic potential. *J Med Chem* 1994;37:4053–4067.

Mackay AV, Bird ED, Spokes EG, Rossor M, Iversen LL, Creese I, Snyder SH. Dopamine receptors and schizophrenia: drug effect or illness? *Lancet* 1980;2: 915–916.

Mcknight AT, Maguire JJ, Elliott NJ, Fletcher AE, Foster AC, Tridgett R, Williams BJ, Longmore J, Iversen LL. Pharmacological specificity of novel synthetic cyclic peptides as antagonists at tachykinin receptors. *Br J Pharmac* 1991;104: 355–360.

Miller RJ, Horn AS, Iversen LL. The action of neuroleptic drugs on dopamine-stimulated adenosine cyclic 3,' 5'-monophosphate production in rat neostriatum and limbic forebrain. *Mol Pharmac* 1974;10:749–766.

Neal MJ, Iversen LL. Autoradiographic localization of ^{3}H-GABA in rat retina. *Nature New Biol* 1972;235:217–218.

Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 1989;244:1360–1362.

Otsuka M, Iversen LL, Hall ZW, Kravitz EA. Release of gamma-aminobutyric acid from inhibitory nerves of lobster. *Proc Nat Acad Sci USA* 1966;56:1110–1115.

Rossor MN, Iversen LL, Johnson AJ, Mountjoy CQ, Roth M. Cholinergic deficit in frontal cerebral cortex in Alzheimer's disease is age dependent. *Lancet* 1981; 2:1422.

Sandberg BEB, Lee CM, Hanley MR, Iversen LL. Synthesis and biological properties of enzyme-resistant substance P analogues. *Eur J Biochem* 1981;114: 329–337.

Schon F, Iversen LL. Selective accumulation of ^{3}H-GABA by stellate cells in rat cerebellar cortex *in vivo*. *Brain Res* 1972;42:503–507.

Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proc Nat Acad Sci USA* 1975;72: 4376–4380.

Singh L, Donald AE, Foster AC, Hutson PH, Iversen LL, Iversen SD et al. The enantiomers of HA-966 (3-amino-1-hydroxypyrrolid-2-one) exhibit distinct CNS effects: (+)-HA-966 is a selective glycine/NMDA receptor antagonist but (-)-HA-966 is a potent gamma butyrolactone-like sedative. *Proc Nat Acad Sci USA* 1990;87:347–351.

Tricklebank MD, Honore T, Iversen SD, et al. The pharmacological properties of the imidobenzodiazepine FG-8205 a novel partial agonist at the benzodiazepine receptor. *Br J Pharmacol* 1990;101:753–761.

Uretsky NJ, Iversen LL. Effects of 6-hydroxydopamine on catecholamine containing neurones in the rat brain. *J Neurochem* 1970;17:269–278.

Whitby LG, Axelrod J, Weil-Malherbe H. The fate of H ^{3}-norepinephrine in animals. *J Pharmacol Exp Ther* 1961;132:193–201.

Wong EHF, Kemp JA, Priestley T, Knight AR, Woodruff GN, Iversen LL. The anticonvulsant MK-801 is a potent N-methyl-d-aspartate antagonist. *Proc Nat Acad Sci USA* 1986;83:7104–7108.