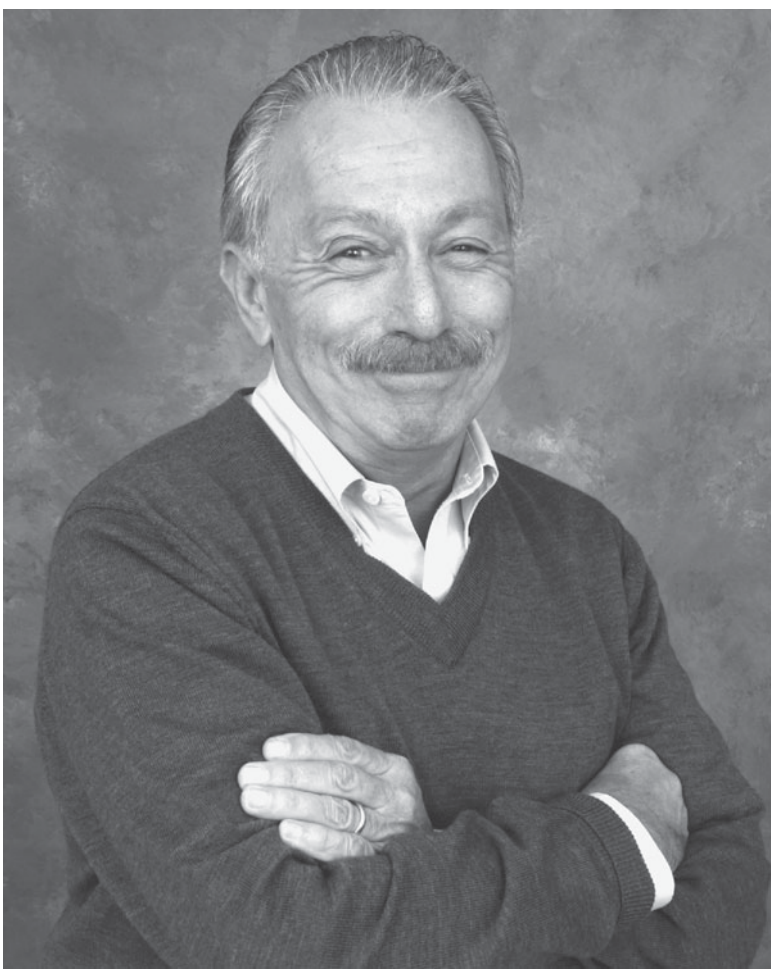
The History of Neuroscience in Autobiography
Volume 7

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-19-539613-8

Floyd E. Bloom

pp. 0–56

https://doi.org/10.1093/acprof:oso/9780195396133.003.0001



Floyd E. Bloom

Born:

Minneapolis, Minnesota
October 8, 1936

Education:

Southern Methodist University, A.B., cum laude (1956)
Washington University, School of Medicine, M.D., cum laude (1960)

Appointments:

Intern and First Year Assistant Resident, Ward Medical Service, Barnes Hospital, St. Louis (1960–1962)
Research Associate, NIMH at St. Elizabeths Hospital (1962–1964)
Yale University, USPHS Special Postdoctoral Fellow in Anatomy (1964–1966); Assistant Professor Pharmacology, Anatomy, and Psychiatry (1966–1967); Associate Professor (1968)
Chief, Laboratory of Neuropharmacology, Division of Special Mental Health Research Programs, NIMH (1968–1975); Acting Director Division of Special Mental Health Research Programs (1973–1975)
Director, Arthur V. Davis Center for Behavioral Neurobiology, The Salk Institute (1975–1983)
The Scripps Research Institute (1983–present) Director Division of Preclinical Neuroscience and Endocrinology (1983–1989); Chairman Department of Neuropharmacology (1989–2005); Professor Emeritus (2005–present)

Honors and Awards (Selected):

President, Society for Neuroscience (1976–1977); American College of Neuropsychopharmacology (1988–1989); Research Society for Alcoholism (1991–1993)
A. Cressy Morrison Award (1971)
Arthur S. Flemming Award (1972)
National Academy of Sciences (l977)
Institute of Medicine (1982); Council (1986–1989)
Doctor of Science, hon. caus., Southern Methodist University (1983)
Doctor of Science, hon. caus., Hahnemann University, Philadelphia (1985)
Doctor of Science, hon. caus., University of Rochester, New York (1985)
Distinguished Fellow, American Psychiatric Association (1986)
Foreign Member, Royal Swedish Academy of Sciences (1989)
American Philosophical Society (1989)
Doctor of Science, hon. caus., Mt. Sinai School of Medicine, New York, NY (1996)
Honorary Doctor of Science, Thomas Jefferson University, Philadelphia (1997)
Doctor of Science, hon. caus., Washington University (1998)
Rhoda and Bernard Sarnat International Prize in Mental Health, Institute of Medicine (2005)

Floyd Bloom began his biomedical research career with investigations of the conduction properties of single isolated axons, and he transitioned to single neuron pharmacology in the early applications of microiontophoresis. Bloom was among the first to study neurotransmitter systems at the anatomical, physiological, and pharmacological levels beginning with the noradrenergic innervation of cerebellum, hippocampus, and cerebral cortex. He was one of the first neurobiologists to utilize modern molecular biological techniques to identify, functionally characterize, and map brain specific genes. Recognizing the value of computers in neuroscience, he pioneered their application to neuroanatomic investigations and the development of neuroanatomic databases. His work has found considerable applicability to many enigmatic disorders of the nervous system, such as the addictive states, the dementias, and the major psychoses. From 1995 to 2000, he was Editor-in-Chief of Science.

Floyd E. Bloom

Introduction

The reason I agreed to write this autobiographical review of my scientific career was to be able to recognize publicly the many mentors and colleagues who helped me succeed at so many of the endeavors I chose to pursue. I hope to identify the key events and the stand-out individuals and recall what I can about the critical decision points along the way. I consider myself a physician-scientist, who followed some minor deviations into molecular and cellular neuroscience in the middle of my hands-on period of bench work. For the last decade or two, I have worked less with my hands and more as a lab leader and statesman for my areas of neuroscience. I shall endeavor to avoid what Sigmund Freud referred to as the mendacity of most autobiographical works, while enjoying the brief retrospective of summarizing my career.

Background and Schooling

My earliest memory as a child was listening to Franklin Delano Roosevelt on the radio addressing Congress with the declaration of war on Japan the day after their attack on Pearl Harbor. I had turned 5 years old just a couple of months earlier, but the look on my parents' faces told me this was an extremely important event. Three days later, we declared war on Germany and Italy, and my parents told me this was World War II. The home we lived in was not ours, but rather the home of Andrew and Catherine Johnson, a plumber and his wife who had been willing to take boarders into their home in suburban Minneapolis. Catherine was my surrogate mom, while both my parents worked in two small pharmacies a few blocks away.

My dad was the first member of his family to complete a college education, and his three brothers and two sisters did likewise, which was quite an accomplishment for their father who supported the family working as a freight handler for the railroad. Two of my dad's brothers followed his lead to become pharmacists, and the third became a dentist. My mom, who had been born in Russia and immigrated to America at the age of 9, came from an even poorer family and had to go work before she finished high school. When they married, they considered themselves too poor to start a family and waited 7 years before I was born. Their patterns of hard work, long hours, and scrupulous honesty in business matters were my gold standards of behavior. My dad had wanted to go to medical school and, whether he had

the grades to make it there he never really said, but he viewed pharmacy as a close alternative and thought highly of the medical profession his whole career.

As I entered elementary school, I can dimly recall selling War Savings Stamps, marching with my classmates in parades to raise money for War Bonds, and using rationing stamps for grocery items. Within a year, my dad's dentist brother enlisted in the Navy and was assigned to the First Marine Division. On weekends my dad would take me to see the war newsreels to try to spot Uncle Harvey doing dental work in Guadalcanal after the beach head there had been established. The only real war hardship I recall was from gasoline rationing, which curtailed our regular Sunday automobile trips with my dad's parents to a point where there was barely enough time to hear the whole Jack Benny show and a part of Fred Allen on the car radio before we were back home.

After World War II ended, my dad sold his two stores, and we took some very long car trips through the Dakotas and Montana. When we returned to Minneapolis, my dad decided to join his next younger pharmacist brother Stanley in Dallas; Uncle Stanley had moved there in the final days of the war and from his perspective Dallas could use another good drug store. The youngest pharmacist brother, Jerry, came along to work in my dad's store. In 1946, we moved to a new house in a new city. I was devastated to leave all my friends behind and face a whole new class of students that I didn't know at all. Dallas in the summer was extremely hot. My mom's brother-in-law, Uncle Abe, who also lived in Dallas ran what I think now was a war surplus store that sold fixtures and furniture to small businesses. That first summer, I worked for him assembling metal stools with screws that got so hot in the Texas sun that I couldn't pick them up.

When I started school that fall at Stonewall Jackson Elementary, it quickly became apparent to my teachers that everything they were about to instill in me in the fifth grade in Dallas, I had already learned in the fourth grade in Minneapolis. As a result, I was advanced a half year, into a much smaller group of students who either because of their birthdays or prior failures were set back from the annual classes. I stayed a half-year out of synch with my age peers for the rest of my public education, graduating high school in the winter of 1953.

I cannot pass over the 6 years of junior high (Alex Spence Junior High) and high school (Woodrow Wilson High School) because those years shaped both my mind and my body. In junior high, my pubertal growth spurt came early among my male classmates and for the eighth grade, I was suddenly a big fellow. I tried out for and made the football team, playing left guard on defense, although not very well. When we started into ninth grade in high school, all my classmates had had their growth spurts, and it was clear that I would no longer be competitive in football. However, as that first spring rolled around, and students were trying out for the baseball team, Coach

Helms, who taught business accounting, asked me to become the freshman team student manager (also known pejoratively as a "water boy"), an assignment I readily accepted because it was clear I had little promise as a player.

Becoming student manager was probably the best move I could ever have made. When, after a month of practice, we still had all the baseballs, towels, and bats, Coach Helms began to think I could also do the job for the junior varsity, and then asked me back to do that for the varsity team the next year. I ended up with three letters in baseball, which also gave me entry to the manager position for our school's football team, where I ended up with two more letters before graduation. That senior year was really very exciting because our football team won the Dallas city Championship, and then went two more rounds to the state semifinals. I made a lot of good friends among the athletes and got to know the cheerleaders pretty well too. I never lost a jersey.

For my senior English class, I decided to do a report based on a survey of the student managers at about 18 big-time colleges, writing them a series of questions to pose problems I had encountered as a manager for our high school team. Surprisingly, at least to me, more than a dozen replies came in and I recall that my English teacher and Coach Riley, the head coach of the football team, were very impressed. I finished second in my class, although I thought my grades in algebra, chemistry, and physics should have been weighted more heavily than the home economics and accounting classes that the valedictorian took.

My high school did not have career counseling, but they did provide some guidance in the form of aptitude tests. My test scores were interpreted to mean that I should pursue subjects like public relations, advertising, or journalism and avoid hard science and mathematics. Before passing that valuable information on to my parents, I first did some research and found that the closest School of Journalism that was highly regarded was the University of Missouri. I had an admissions application mailed to me and when it arrived I informed the folks. My dad's reaction was that the idea was interesting and, as soon as I finished medical school, I could pursue any career I wanted to. Having worked as a helper in my dad's pharmacy throughout my teenage years, I knew a lot of doctors that he served and admired many of them. So we went on to plan B.

Coach Riley was said to have been a member of the 1935 Rose Bowl team from Southern Methodist University, and he suggested not only that I apply there, but that he would back me to become a student manager for their football team. In those days, applying to SMU meant going over and paying my starting tuition—no SATs, no interviews, no essays, just money. Once I was accepted for admission to the winter term in 1954, I decided to wait until the fall to see how I did with my premed classes before talking to anyone about being a collegiate sports manager. It's good that I waited,

because the first class I took to complete my medical school application requirements was Physics, and the only course I could get into was Physics for Engineers. While I had done well in algebra and geometry in high school, calculus had not been offered. Unfortunately for me, the Physics for Engineers course relied heavily on calculus-based formulas, and I was very lucky to get through the course with a C, giving myself quite a grade point average handicap as I edged toward medical school.

Fortunately, one of the courses I did really well in was German, and after I got my first A, I decided to double up on German courses and ended up with a major in German Literature. That, plus good grades in all my chemistry and biology courses and the rest of my curriculum, helped me get my grade point average up to 3.6. In fact I was so proficient in German that I renewed my contact with athletics and became a tutor to the members of the varsity basketball team in 1955—the first year that SMU made it to the NCAA final four. One of my students was the All-American Center, Jim Krebs. By going to school every summer, and taking evening courses at the downtown branch of SMU (Dallas College), I was able to take the Medical Course Aptitude Tests in order to apply to medical school in the fall of 1955 for admission in the fall of 1956, completing my B.A. degree by August 1956, 2½ years after entering.

The main gatekeeper for all premed students at SMU was our Organic Chemistry Professor, Harold Jeskey. Next to Coach Riley, he was the most important mentor of my young career. He used to lecture in a long brown chemist's lab coat and always wore a bright red four-in-hand tie except on the days when he gave exams when the tie was black (see Fig. 1.1). His lectures were more than organic chemistry—every reaction he described included some of the history of the chemist who created it, and the philosophy of the applications to which the reaction had already been put, always delivered with sly humor and always without any notes at all.

Because I did well in the first half of his course, Dr. Jeskey wrote very positive letters of support for my medical school applications and in the spring of 1956 I was accepted to Washington University in St. Louis. Washington University even then was a highly ranked medical school, and with my SMU classmate Alan Eberstein, we were only the third and fourth SMU students ever to be accepted there. Dr. Jeskey remained a loyal supporter of my career and, when I returned to Dallas on holidays, I made it a point to visit with him as did all his "boys" as he liked to call us. In 1967, the Red Tie Society of former Jeskey students started an endowed scholarship in his name, and that effort grew into the Jeskey Chair in Chemistry and a 98-seat Jeskey Lecture Hall in 2001. Although he retired from teaching in 1987, Dr. Jeskey continued to tutor freshman medical students in biochemistry at the University of Texas Southwestern Medical Center until his death in 2006 at the age of 94. Interestingly, in his final years he and my former Coach Riley lived in the same facility for senior citizens. His red tie is the

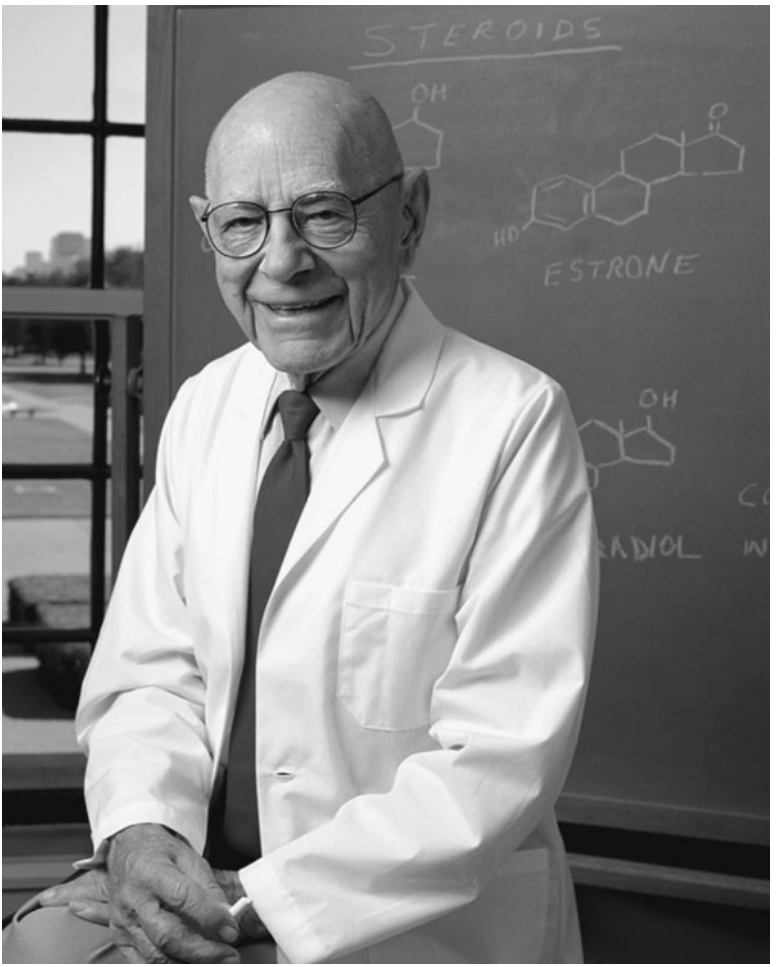


Fig. 1.1 Professor Harold A. Jeskey, R. S. Lazenby Professor of Chemistry at Southern Methodist University, 1912–2006, as photographed in 2005. Photo courtesy of Southern Methodist University.

reason that when ever I have an important talk to give, I feel insecure unless my bow tie contains a lot of red. I'll mention the reason for the bow ties and the mustache later.

My Years in St. Louis (1956–1962)

In the fall of 1956, married to my high school sweetheart, I packed my clothes, books, and a new microscope into a trailer and moved to St. Louis to begin medical school. The experience of learning about the biology of human health and disease at the level of intensity to which I was exposed was

exhilarating, and the quality of the faculty was astounding. The first person I encountered on the day I walked up to store my microscope was a fragile older lady struggling to open the sliding safety door of the elevator—I later learned that she was Dr. Gertie Cori, a Nobelist, with her husband Carl. He later lectured us in their Cori cycle of energy movement from muscle to liver and back to muscle. An hour later, I met a second faculty member, Professor Sam Clark, who chatted with me amiably for a while and then encouraged me to get interested in advancing knowledge by pursuing the big questions with the best chance of getting clarifying answers—a lesson that has remained uppermost in my career pursuit of research.

However, in 1956, neuroscience as a field did not yet exist. We studied neuroanatomy in one course (for which Rita Levi-Montalcini came over from the undergraduate campus to describe her nerve growth factor), neurophysiology in another, and eventually neuropharmacology (led by Oliver Lowry, whose paper on the assay for protein is the most cited publication ever) in yet another. We were exposed to neurology (led by James O'Leary and Bill Landau) and psychiatry (led by Eli Robins, Sam Guze, George Winokur, and George Murphy) in two separate clinical clerkships. Although none of us students realized it at the time, the psychiatry group at Washington University was probably the most interesting because, under Robins leadership, their practice of psychiatry began to approach mental illness as medicine approached any other physical disease, using hard diagnostic and epidemiological criteria and the underlying preclinical science. Their work eventually led to the *Diagnostic and Statistical Manual of Mental Disorders*, used today throughout the world. On top of that, Robins also lectured us on the chemistry of neurotransmitters as freshmen in the neuroanatomy course.

However, my point of departure from all this excellence almost came in the neurophysiology section of the physiology course. The lectures in this course came after our daily lunch break, and the postprandial diversion of blood from brain to gut was not conducive to close scrutiny of the details being presented. To top off that physiological diversion, the detailed description of the recently reported Hodgkin-Huxley equations explaining how ion flow could result in the nerve action potential was totally developed in calculus, my once and continuing nemesis. Again, I passed, but only barely. After the exam, the lecturer for this section of the course, Professor Gordon Schoepfle, invited me into his laboratory for the summer to repeat the experiments of Hodgkin and Huxley so I could better understand the importance of these principles. Dr. Schoepfle was the last postdoctoral fellow of Nobelist Joseph Erlanger, who had described the properties of the compound action potential with the first laboratory oscilloscope. When I went into the Schoepfle lab that summer, there on his bench top was the axon wet chamber that Erlanger and his Nobel partner Herbert Gasser had used for their recordings. I was awestruck.

Schoepfle had developed his own method of studying ion flow in axons, the single air gap isolated node of Ranvier prepared from a microdissection

of the frog sciatic nerve. He had hand-built his apparatus out of Plexiglas and a jeweler's lathe to perform this analysis. After we went through those experiments watching action potential properties undergo dynamic shifts with changes in the ionic content of the physiological saline solutions, we went on to study Schoepfle's main interest, the energy requirements of these ion movements. That summer's work earned me co-authorship on a publication in the *American Journal of Physiology* and an invitation to return the next summer, which led to two further publications. As a senior, I was invited to be an Assistant Instructor in the Pharmacology course and to help prepare animals for the laboratory experiments. This gave me the chance to sit at lunch as Dr. Lowry listened to the faculty present progress reports on their work; while listening, he would compute the statistics in his head and tell them how many more animals they needed to make those differences meaningful. I was also able to do some independent work with local anesthetics from which I was able to assemble a research thesis between Physiology and Pharmacology that earned me a Cum Laude when I graduated.

Even now, some 50 years after graduating, I am blessed to recall many highlights from those 4 years of massive learning. In the Microbiology and Immunology course, led by Arthur Kornberg, we synthesized DNA and never realized how cutting edge this enzymatic reaction was. The next year, Kornberg took most of the Department with him to Stanford University's new Medical School, including his postdoctoral fellow, Paul Berg. A year later Kornberg was awarded the Nobel Prize for his DNA studies, and in 1980 Paul Berg achieved the same recognition in Chemistry for his pioneering work in recombinant DNA. In our class, we drew each others' blood and found out that more than half the class had already been exposed to the poliomyelitis virus before we took our first doses of the Salk vaccine. That part of the course was taught by Mel Cohn whom I encountered again two decades later when I joined the faculty at The Salk Institute.

Although medical school was probably as hard mentally as anything I had ever tried to do, my classmates were always ready to find the humorous side of student life. Early in our matriculation, we were asked to elect class officers but, since we had only just met each other, very few people knew more than 3 or 4 of the 85 members of the class—all men except for 5 women. One of those nominated for class vice president was Sam Farley; he didn't win, but both in biochemistry and histology, his name became well known because after the exams the professors would ask the class to please urge "Mr. Farley" to come in for a conference (he never even seemed to come to class) so some tutoring could be offered to help with his failing grades. His exam books were often found with no answers at all. At the end of the year, many of us were surprised to learn that in fact Sam Farley didn't exist at all, but was a hoax. Nevertheless, he stayed with us in spirit throughout the 4 years, and in our junior year when we were challenged to create an entertainment for the senior class and the faculty, our class did a parody of

My Fair Lady that we called *My Fair Farley*, in which the Professor of Medicine wagered he could take anyone off the streets and make a passable Washington University medical student out of him. Those lyrics were a riot. When we graduated in 1960, Dean Edward Dempsey awarded Sam Farley his medical degree "sine laude," and the class cheered. Recently, at the 50-year reunion of our graduating class, we voted unanimously to recommend to the Chancellor that Sam Farley be appointed a University Professor Demeritus.

The high point of the senior year was our clerkship on the Ward Medical Service, where we worked in teams of two pairs of students as subinterns on a very busy, very intense more-or-less public ward in Barnes Hospital. I found that if I wore a bow tie, I could draw the blood samples on my patients without blocking my field of view the way a long tie would when I leaned down, and I have stayed with that style of cravat ever since. Barnes Hospital was the elite medical service for the entire Midwest, and doctors whose patients' illnesses could not be diagnosed or treated by them would routinely send their patients here. Since I aspired to an internship in internal medicine, I opted to take this clerkship early in my senior year so that I could ask my professors for letters of recommendation when applying in the late fall and winter for internships and residencies.

In my team of four were Paula Clayton, who went on to a distinguished career in academic psychiatry, later serving as President of the Psychiatric Research Society (1977–1978), the American Psychopathological Association (1981), and the Society of Biological Psychiatry (1986–1987); Mark Abramowicz, who trained in pediatrics at Boston Children's Hospital and went on to become the Editor-in-Chief of the very highly regarded Medical Letter on Drugs and Therapeutics, and their several handbooks that prep physicians for the board exams and continuing medical education; and Louis Miller, elected to membership in the National Academy of Sciences for his work in malaria and defining the molecular receptor by which the parasite invades red blood cells, and who is currently the chief of the Laboratory of Parasitic Diseases at the National Institute of Allergy and Infectious Diseases.

With such comrades I also had to do well and I must have, for early in 1960, after completing my tour of interviews on the East Coast for possible internship posts at the University of Rochester, Yale, and Duke, Dr. Carl Moore, the Bixby Professor of Medicine, called me into his office on the eve of turning in our choices for preferred hospitals. He puffed on his pipe and stared at me in silence with a slight smile on his face, and he said that he hoped I had enjoyed my clerkship in medicine and that I was serious about going on to be trained in internal medicine. When I assured him I was, he said that they would like to include me in their choice of interns, and if I were also to rate Barnes as my number 1 choice, I would be assured of being selected. I was bowled over. Never had I imagined that I would be

offered such an opportunity. I celebrated for the rest of the spring by taking my wife to Nassau and lying on the beach for 6 weeks to rest up for the next 2 years.

The internship year on the Ward Medical Service contrasted with the Private Medical Service, because all the attending physicians on the Ward Service were full-time academic faculty, and they were very serious and rigorous about teaching the house staff how to diagnose, treat, and otherwise manage whatever patients were admitted to our service. We were on call every other night for the entire year except for our 2 weeks of vacation, and for the 3 months when we worked in the outpatient clinics. My service routinely covered 18–20 patients, and it was not a rare day when 5 or more new patients were admitted. Learning how to handle all the various tests and evaluations in a fluid manner to keep hospitalizations to the minimum was an intense experience. I was very fortunate to be supervised in my initial weeks by a very wise but mild-mannered resident, Dr. Richard Aach, who would guide me mentally through the various diagnostic steps in the workup of each patient, and in such a way that I would be led to the best next step and think of it as my own insight. He also subtly guided me into setting up the testing in a logical manner so that every evening at our rounds we could determine what had been learned to confirm or alter our management of the patient.

Truly, that year was an exhausting but exhilarating experience, one which I am so pleased to have undertaken, and without which I may never have understood what I was capable of doing under the pressures of life and death. My most memorable case was a 16 year-old girl who had been seen in the dermatology clinic for a wart on the sole of her foot and had been given a month's supply of Bismuth tablets. When it was time to come back for her first checkup, she realized she had not taken her pills as she was supposed to have and took all the rest of them at once. Her kidneys turned off and, when she was admitted to my ward, she was in early renal failure. Artificial kidney machines were not yet available, and we treated her with round-the-clock intraperitoneal dialysis, infusing liters of sterile saline into her abdominal cavity, then after 2 hours lowering the bottles to drain out the fluid, now containing the urea, creatinine, and other catabolites that the kidneys should have filtered into the urine. After about a week of these treatments, her kidneys started to function again, and she walked out of the hospital healthy, but with that wart still on her foot. My intern partner on this vigil was William A. Peck from the University of Rochester, who went on to become the Dean of the Washington University School of Medicine.

In the spring of 1962, we lost one of our second-year residents who had been called into military duty because of the Berlin Crisis, early in President Kennedy's term of office, and the Chief Resident J. Russell Little assigned me to take on his responsibilities. The Doctors Draft laws then in effect meant that a physician could be drafted into military service at any time up

to the age of 45. This meant that, if one hoped to be able to complete an internship and residency uninterrupted by military service, additional effort needed to be expended. In my case, because of my Uncle Harvey, the Naval dentist, I had during college enlisted in the "Ensign 1999" program, which meant I would be commissioned an Ensign in the Naval Medical Corps when admitted to medical school and that I would get longevity credit going all the way back to my graduation from high school. While this seemed like an excellent step before I got into medical school, by the time I was a third-year student, the Navy began urging me to decide which Naval Hospital I wanted for my postgraduate education. By that time, although still inexperienced in the ways of academic medical training, I realized that my better opportunities were in academic hospitals, and not military hospitals. Thanks to Morris Odoroff, husband of my dad's oldest sister (and the statistician for the first research studies showing the link between cigarette smoking and lung cancer), I was able to transfer my commission from the Navy to the U.S. Public Health Service at a moment when the Navy thought they had all the doctors they needed.

The spring of 1961 saw me off to the National Institutes of Health (NIH) to compete for a Research Associate post, the kind of external achievement that Dr. Moore and the Department of Medicine regarded as one of their criteria for deciding which of the five first-year residents would be invited back for one of the three second-year residency slots and a chance to become Chief Resident in Medicine in the third year of postinternship training. Going to NIH was initially going to be just a matter of going through the steps, because Dr. Schoepfle had arranged for me to work as a Research Associate with one his well-known contemporaries, Dr. Abraham Shanes. Shanes had just published a *Pharmacological Reviews* paper on the mechanisms of action of local anesthetics, the topic of my medical school thesis. When I arrived for my interviews, my pockets stuffed with photos of my research data, I was immediately bothered by the fact that Dr. Shanes was not on the list of NIH investigators I was scheduled to see.

When I got a brief break, I called Shanes, introduced myself, and asked whether he understood why I had not been scheduled to interview with him given that he and Schoepfle had a tacit agreement to take me. He paused and then said, "Oh, I've been meaning to call you. I'm leaving the NIH in a couple of months." It turned out he had been diagnosed with cancer and wanted to earn a better salary for a year or two, not knowing what his future might be.

Of course, now I was dumbfounded as to what to do. Dr. Robert Berliner, who was then the head of the NIH Intramural Program and in charge of the Research Associate selection process, saw my distress and suggested I consider taking a taxi (more than $40 in those days) to St. Elizabeths Hospital in southwest Washington, DC, where the National Institute of Mental Health (NIMH) had established "some sort of neuropharmacological entity."

When I got there, I had the good fortune to be interviewed by Joel Elkes, the Director of the Clinical Neuropharmacology Research Center at St. Elizabeths. Elkes had been an early analyst of myelin, using X-ray diffraction, and so he was quite interested in my studies of single frog axons. After our chat, he took me to meet Gian-Carlo (Nino) Salmoiraghi, the head of the Section on Neurophysiology, an Italian M.D., who after the war and after service treating tuberculosis patients in the Red Cross, had done a Ph.D. in Neurophysiology at McGill University before coming to Washington. After he and I chatted pleasantly and favorably, I returned to St. Louis in a somewhat better frame of mind, and I was even more relieved to get a letter a few days later inviting me to accept a Research Associate slot with him for 2 years, from 1962 to 1964. Both Elkes and Salmoiraghi have been mentors to me ever since, and I was able to complete my 2 years of Internal Medicine training at Barnes, knowing that after NIH I could be in the competition for a second-year residency slot. That spring, I audited a calculus course on the undergraduate campus and finally began to understand what higher mathematics was all about.

St. Elizabeths Hospital (1962–1964)

When I first met Nino Salmoiraghi, his experimental focus had been to characterize with intracellular electrode recordings the neurons in the cat medulla that fired with inspiration and expiration and, having identified them, to give intra-arterial injections of drugs that would enhance or antagonize acetylcholine, then the only chemical considered for a role as a central neurotransmitter. It was tedious work of a kind I had never done, having spent my whole brief research life pithing frogs and taking out their sciatic nerves.

When I reported for duty in July 1962, Salmoiraghi was developing his own version of single-cell brain neuropharmacology, using an assembly of five fused microcapillary tubes, four grouped around a central tube, then drawn in the molten state to a common tip. Then, manually and under microscopic visualization, the tip was tapped on the end to fracture the sealed ends. When lucky, a new tip was created with five open channels. After opening the tip, the barrels were filled with solutions of chemicals to be tested, and then centrifuged at high speed to drive the solutions down into the tips of the pipets. With this device, measuring less than 5 micra at the tip, the assembly could be driven into the brain, the center barrel being used as a conventional extracellular recording electrode. Three of the other four barrels contained solutions of candidate natural substances to be tested as "putative" neurotransmitters, or solutions of drugs that would block the receptors that had been characterized for these putative agents. Since most such natural substances and their related drugs were either cations or

anions in solution, the drugs could be ejected from the tip in an almost volumeless delivery by passing the proper polarity of current into the drug barrel. Salmoiraghi's design employed the fourth barrel as a neutralizing current so that whatever polarity was used to eject the drugs would result in a zero net charge difference at the tip that was recording from the neuron being tested.

It seemed like a great system, a developmental effort that only the NIH's Intramural Research Program could undertake with its instrument shop infrastructure and relatively limitless resources. Similar systems of microiontophoresis had been developed in Australia, Canada, and the United Kingdom without the use of the neutralizing control barrel, setting up grounds for differing results and scientific competition.

In the atmosphere of the NIMH Intramural Program, the biggest buzz had been the Catecholamine Hypothesis of Depression, promulgated by the Director of the Intramural Program, Seymour Kety, and one of his senior Fellows, Joseph Schildkraut. Their hypothesis in its simplest form was based on one of the founding principles of what today we call "biological psychiatry," namely that drugs that affected human and experimental animal emotion in similar ways did so because of their similar neurochemical effects. The leading example in the early 1960s was the Indian antihypertensive drug reserpine. When given to animals, their hypokinetic and hypersedated demeanor was coupled with loss of both brain serotonin and norepinephrine. When depressed patients were examined, they showed loss of catecholamine catabolites in both their urine and in their cerebrospinal fluid. At the time I was a House Officer at Barnes, the *Journal of the American Medical Association* had published several studies from Europe indicating that patients treated for their hypertension with reserpine were showing increased frequency of suicide attempts.

When depressed animals and depressed patients were given monoamine oxidase inhibitors to slow catabolism of the amine, both groups showed improved emotional status and increased physical activity. A third piece of confirming evidence was that when the reserpine-treated subjects were given amphetamine or L-dihydroxyphenylalanine (L-DOPA), the precursor of norepinephrine, activity and levels of emotion were elevated, but there was no recovery when given 5-hydroxytryptophan, the precursor of serotonin. The hypothesis was that depression was the result of hypofunctioning brain norepinephrine circuits, while mania—the emotional opposite of depression—was the result of too much activity in norepinephrine circuits.

The only problem was that the evidence required to establish that norepinephrine was a neurotransmitter in the brain as it was in the sympathetic autonomic nervous system did not exist, and it was unclear from the neurochemical assays on grossly dissected brain regions where in the brain such synapses might be. So my first assignment was to use the microiontophoresis

method to probe the hypothalamus, then considered to be the main central relay site for regulation of the autonomic nervous system, and characterize the actions of norepinephrine there.

The species of choice for single-cell recordings at that time was the cat, as cats could tolerate prolonged neurosurgical procedures to expose the regions of the brain or spinal cord that one sought to examine. Cats could also tolerate prolonged hypothermia, and that allowed the slowing of brain metabolism and the maintenance of good brain activity. Most of the John Eccles work on spinal physiology was done in cats that were very hypothermic. However, in the cat, the use of the five-barrel microelectrode assembly presented a major problem for studies on the hypothalamus—while narrow at the common tip and perhaps a centimeter or more above the common tip, the glass assembly quickly widened. To reach the hypothalamus from above was virtually impossible and would have created fatal major wounds in the overlying cortex and thalamus.

I therefore set about exposing the base of the cat brain through the roof of the mouth and pharynx. Several cats later, with the basic procedure working, I was able to collect data on maybe 50 neurons in the cat hypothalamus, divided into three anteroposterior levels, in which roughly one-third of the neurons showed their spontaneous discharge rates to be depressed when norepinephrine was applied, another one-third of neurons fired faster, and the final third did not respond at all. These data were uninterpretable, and we never published them except as an abstract for the Federation of American Societies for Experimental Biology, then known as FASEB, that met annually in Atlantic City to bring biochemists, physiologists, and pharmacologists together.

Although disappointed that my hard work in self-taught neurosurgery was for naught, two events occurred that helped rescue my productivity. A German physiologist, Rudolph Von Baumgarten, who was an expert in the physiology of the rabbit olfactory bulb—a much more easily accomplished dissection—came for my second summer. Soon we had healthier, more active animals to study, and a visible pathway—the lateral olfactory tract (LOT). Now we could stimulate, and thereby identify, our recording targets as mitral cells when the neurons we were recording from were antidromically activated by stimulation of the LOT. Here the responses were much more consistent, with norepinephrine uniformly depressing spontaneous activity and prolonging the depression that followed the antidromic stimulation. Even though we had no way to identify that norepinephrine-containing fibers innervated the mitral cells, we were able to put together consistent enough data to publish two reports on the system.

The second major event that brightened my early experiences with single-cell neuropharmacology was the decision by Erminio Costa, the Deputy Chief of the Bernard Brodie lab in the National Heart Institute, to come to St. Elizabeths several times a month and work with us, first on the

pharmacology of norepinephrine in the rabbit olfactory bulb, and later on the early investigations of dopamine in the cat caudate nucleus. With his many contacts in the pharmaceutical industry, Costa was able to give us head starts on the pharmacological dissection of the receptor subtypes for the norepinephrine, dopamine, and acetylcholine responses. He taught me more pharmacology than I ever knew and mentored me throughout my career.

To connect back to the Catecholamine Hypothesis of Depression, we also investigated rabbits during the first 4 hours after treating them with large doses of reserpine, the idea being that if norepinephrine fibers were activated when we stimulated the LOT, those effects should be greatly diminished when the reserpine depleted the nerves of their norepinephrine content. The problem that arose in these experiments, as might be expected given the antihypertensive effects of reserpine, was that the anesthetized rabbits would go into shock about 2–3 hours into the reserpine treatment period. Tired of losing whole days of work, I devised a means to harvest the blood from the just expired rabbit, anticoagulate it, and then use that blood to keep the next rabbit alive long enough to test for the loss of the norepinephrine effect, and that we did see.

While Costa was of great help in those rabbit olfactory bulb experiments, his interest then was in assessing what dopamine did. Although there had been an initial assumption that dopamine in the brain was present only as a precursor to norepinephrine, Costa pointed out that in the caudate nucleus of the cat, rat, and rabbit, there was a very high level of dopamine but virtually no norepinephrine. So we proceeded to study the effects of dopamine in the anesthetized cat caudate. We included acetylcholine in one of the iontophoresis barrels as well because the caudate was rich in the acetylcholine metabolizing enzyme, acetylcholinesterase, and by presumption acetylcholine was a strong candidate transmitter there. But nothing of value is ever easy.

To our chagrin, putting electrodes into the cat's caudate detected very few spontaneously active neurons. Interpreting that neuronal quietude as potentially the result of the general anesthesia, we switched from ether to chloralose to barbiturates, all with the same result. As a last gasp, we implemented an unanesthetized preparation by using electro-cautery through the inferior colliculi to isolate the forebrain, including the caudate and overlying cortex, from the brain stem, where the intact autonomic and respiratory systems could maintain the animal once the starting anesthetic wore off. Sure enough, when we attempted to record in these "cerveau isolé" preparations, there was much better spontaneous activity in the caudate.

These neurons were often excited by acetylcholine and depressed by dopamine (and by norepinephrine, but we assumed the two catecholamines were similar enough that the same receptors could recognize both). One short burst of dopamine could extend for many minutes the excitatory effects of acetylcholine. The paper we wrote emphasized that when we gave

the decerebrate cats general anesthetics, the acetylcholine effect would go from excitatory to inhibitory. Of greater interest in retrospect is that implementing the decerebration almost certainly severed the ascending dopamine fibers innervating the caudate, thereby releasing them from the dopamine afferent effects. This paper for the *Journal of Pharmacology and Experimental Therapeutics* gave me a good qualifying start for eventual membership in the Pharmacology Society, my first professional society.

This last burst of productivity greatly elevated my interests in single-cell neuropharmacology, and the review I wrote for *Science* with Salmoiraghi, and the review article that Salmoiraghi, Costa, and I were invited to do for the *Annual Reviews of Pharmacology* made me start to wonder whether I really wanted to go back to patient care or take another path forward. Reluctantly, I returned to St. Louis and told Dr. Moore I had decided not to continue with my residency training. He asked with some consternation what I intended to do instead, and I said I wanted to work out chemical methods to visualize synapses containing norepinephrine so I could be certain that I was aiming the 5-barrel micropipets at the right target neurons. Although I suspect he was skeptical that I could accomplish that, he wished me well and often wrote me to comment on the papers I wrote.

In the final weeks I spent at St. Elizabeths, I applied for a special fellowship to undertake training in electron microscopy and histochemistry with Professor Russell Barrnett at Yale. Since it was too late to start a new series of experiments at St. Elizabeths, I decided to see if I could learn some of the rudimentary methods of electron microscopy by becoming a guest worker in the NIH Campus laboratory of Professor Keith Richardson, head of the Section on Neurocytology. He agreed I could come over, and he walked me through the details of brain perfusion fixation, dissection for electron microscopy, orientation of the tissue blocks for embedding in epoxy plastics, and how to make glass knives from whole sheets of glass in order to do ultramicrotomy to acquire the less than 1000 Angstrom thick sections that could be placed on copper grids and examined in the electron microscope.

Richardson had been the head research assistant in the neurocytology laboratories at University College London before coming to the NIH. Because he was one of the few Section heads who didn't have a doctoral degree, he called himself "Professor Richardson" in the NIH Directory. (Julius Axelrod was another until he got his degree a few years before his Nobel Prize). These weeks of training were quite enjoyable, and they showed me a major strategic advantage that neurocytology provided over physiology: In physiological experiments, the investigator was obliged to stay with the animal until enough valid data had been obtained to warrant the nonrecovery surgery of early neurophysiology. But in neurocytology, once you had your material to examine, you could turn off the microscope and nothing was lost; the investigator could come back hours or days later and restart the analysis as though nothing had ever intervened.

In addition to teaching me the fundamentals of electron microscopy, Richardson had been one of the first people to examine tissues of the peripheral autonomic nervous system. He had observed that immersion fixation with a mixture of osmium tetroxide and potassium dichromate produced sympathetic nerve fibers containing synaptic vesicles with dense granular cores, rather than the electron lucent synaptic vesicles that epitomized the nerve terminals at the neuro-muscular junction where acetylcholine was the recognized neurotransmitter. Then just before I left NIH for Yale, Richardson published a report in *Science* with Julius Axelrod and Lincoln Potter showing a second method for detecting norepinephrine by ultrastructural autoradiography of nerve terminals in the pineal exposed to ^{3}H-norepinephrine; there the sympathetic nerves actively transported the norepinephrine into the nerve terminals, where it was stored in the synaptic vesicles. I was eager to test these approaches in the brain.

The Yale Experience (1964–1968)

My 4 years at Yale were another highly enjoyable period of learning, productive research, and growing confidence on what rigorous investigation could reveal, especially when the protocol seemed to have been followed exactly as planned but the results came out quite different than had been anticipated going in. I had been attracted to Professor Russell Barrnett in the Yale Department of Anatomy because of his finding that glutaraldehyde could provide an alternative fixative to the typically employed "formalin," with better structural preservation and retention of enzymatic activity suitable for performing enzyme histochemistry on the fixed tissues. Tissue fixation generally had been considered the result of protein denaturation through exposure to alcohols, ethanol, or methanol. Formalin was a mixture of formaldehyde and methanol. By dissolving formaldehyde powder in heated buffers, one could obtain nearly pure formaldehyde solutions that were an excellent fixative that formed carbon-carbon bonds across proteins, but some enzymes such as acetylcholinesterase were badly affected. Glutaraldehyde and an even longer dialdehyde, hydroxyadipaldehyde, retained intracellular structural details and also preserved enzymatic activity by linking across broader domains of the enzyme proteins. Then after the first fixation, and after the enzymatic histochemical reaction had been run, the tissues could be secondarily "postfixed" with osmium and appeared in the electron microscope just like the same tissue would have if fixed only in osmium.

Working with Russ, as he was known to all trainees, students, and fellow faculty, I was introduced to a very creative environment. We decided to pursue two goals in parallel: I would use glutaraldehyde as a prefixative to localize acetylcholinesterase in the brain, starting by working out the proper fixation and incubation details with the eel electroplax, and in the second series of work, I would use glutaraldehyde as a prefixative and try to

replicate Keith Richardson's studies on autonomic nerve endings detected by dichromate and osmium. If either or both lines were successful, we could then carry that protocol to the brain. The eel electroplax tissue was kindly provided by the laboratory of Professor David Nachmansohn at Columbia University College of Physicians and Surgeons, but watching the lab technicians harvest the tissue was a bit "shocking," and not just because these were electric fish. The tech would reach into the tank, lay the eels (some of which were 5 feet long originally), cut off a 4- or 5-inch long segment, hand it to me to dissect and immerse in the jars of glutaraldehyde I had brought up with me on the New Haven railroad, and then cauterize the blood vessels on the eel's side with a soldering iron, before throwing the eel back into the holding tank.

Both of my initial projects succeeded on the trial tissues, and I got my first publication in the *Journal of Cell Biology* on the EM localization of acetylcholinesterase in the electroplax. My studies of the vas deferens, in which the reaction product of the small granular vesicles seen after glutaraldehyde-dichromate fixation was absent if the animal had been treated with drugs to block synthesis or storage of norepinephrine, became my first *Nature* paper.

That same year, I was invited by Seymour Kety to participate in a 2-day meeting at the Neuroscience Research Program (NRP) in Brookline, Massachusetts, that would examine the evidence for biogenic amines as neurotransmitters in the central nervous system. There I met for the first time, the principal founder of the NRP, Francis O. Schmitt, with whom I developed an immediate rapport. We both worked in electron microscopy, although he was a pioneer developer of the device, and we both had ties to Washington University in St. Louis, where he had been a graduate student in physiology and later a faculty member, before becoming the first Professor of Biology at MIT. Also participating in this meeting was Kjell Fuxe, representing the Hillarp-Falck-Carlsson laboratories at the Karolinska Institute and Lund University, the foremost practitioners of the freeze-dry formaldehyde-induced fluorescence method. This group had begun to map all three monoamine systems (norepinephrine, dopamine, and serotonin) in the rat brain. At the beginning of their studies, their data were regarded skeptically by the classical neuroanatomists because none of the pathways they described had ever been seen by the traditional silver stain or postlesion degeneration metal stains on which most detailed circuitry in the brain had been based. This meeting was an outstanding event for me because I was able to meet and develop relationships with many of the leading scientists in the field of synaptic transmission and assess my competition up close.

In my second year at Yale, George Aghajanian, a graduate of the Yale Psychiatry residency program, returned from his military service at the Edgewood Arsenal and joined me in the quest to see the norepinephrine synapses in brain. George had close ties to Daniel X. Freedman, a Professor

of Psychiatry, and I was invited to join them whenever Danny was in town to discuss recent papers in the brain research literature that might be relevant to psychiatry.

As I was now nearing the end of my NIMH Special Fellowship, I had to decide what to do and where to go next. Because of Russ and Danny, in 1966 I was invited to join the Yale Faculty as an Assistant Professor appointed jointly in Anatomy, Psychiatry, and Pharmacology, where one of Danny's close collaborators, Nicholas Giarman was the senior figure in Neuropharmacology.

I learned a great deal from all three of these gentlemen and their Departments. From Russell, I learned that teaching histology, while readily accomplishable, was not something I found rewarding. As the new appointee, even though I was on a Research Career Development Award that was supposed to give me 90% of my time for research, I was assigned the parts of the histology course no one else wanted. I found it took me 6 or 7 hours to prepare my lectures and slides for every hour I was assigned to teach, and this made it very hard to get to my research program.

Fortunately, Russ traveled a lot and to keep his lab assistant Carolyn Lee occupied, he lent her to me. Because she had trouble reading my handwriting, I was given one of my best discoveries in the Yale years. Searching for reagents that might selectively label catecholamines, I had devised a protocol to try ethanolic phosphotungstic acid, a reagent that had been used to emphasize synaptic specializations with osmium fixation. Carolyn followed my protocol precisely, but when I thin sectioned the blocks and put them in the microscope, all I saw were the pre- and postsynaptic specializations, because I had neglected to say "and then postfix with osmium." George Aghajanian and I used this "E-PTA" method to follow the development of synapses in the cerebral cortex and showed that hypothyroidism could slow that rate. Carolyn later went to medical school and entered private practice in Cleveland.

From Nick, I learned not only how to create a happy lab group, but how to build a group. The Chairman of Pharmacology at Yale was Arnold Welch, and the department he built was composed of faculty members who had been his or other senior faculty members postdoctoral fellows. Nick's lab was built the same way, with the better graduate students staying to be postdocs, and the better postdocs being invited to join the faculty as junior members. I generally followed a similar course in recruitment and hiring and learned the hard way that when I didn't do it that way, the results were suboptimal. For Nick's introductory course to first year pharmacology graduate students at Yale, he enlisted two of the other Yale Pharmacology faculty, Jack Cooper and Bob Roth, and me to give a few of the lectures. When he died tragically in the aftermath of a terrible automobile accident, Jack, Bob, and I took our lecture notes to write, and dedicate to Nick, the first edition of the Cooper, Bloom, and Roth irreverent paperback text *The Biochemical Basis of Neuropharmacology*, which has lasted through eight

editions at Oxford University Press and has reemerged as *Introduction to Neuropsychopharmacology* with Les and Sue Iversen as co-authors.

From Danny, I learned a great deal of people assessing and managing, as well as an unfailing love of learning and life. I served on my first Study Section with Dan as the Chairman, who kept the discussions focused on the science and not the applicant, and who would tolerate no commentary that was irrelevant to the evaluation of the proposal. In my third year at Yale, Danny agreed to become the Chairman of the Department of Psychiatry at the University of Chicago and within a year had offered both George and I appointments. Traveling to Chicago and seeing where we would have been obliged to live, I knew I could not commit my wife and two young children to the South Side Kenwood area, despite the progressive school at the University they could have attended. After a suitable and respectful period of deliberation, both George and I opted to stay in New Haven. Thanks to Danny, the Yale Psychiatry Department was awarded a training grant in the biological sciences, and George and I were hired to do the teaching of the residents, an opportunity that connected me with David Kupfer when he was a resident, and with his mentor Tom Detre, before they left to reinvigorate Psychiatry at the University of Pittsburgh. But Danny remained a friend and mentor for his next 30 years, and he was my best man when I married Jody Corey in 1980.

Nevertheless, the offer from Dan had served to awaken my thoughts as to what I really wanted to do and where I wanted to do it. With my Career Development Award I had 5 years of assured funding that I could take with me, and the pressures of teaching were still impeding the time I could devote to research. The one medical student who chose to do a thesis project with me, Stuart Schorr, helped me broaden my knowledge of the histology of the pancreas by detecting autonomic nerves to the islets that were not described in our textbooks. Stuart went into the practice of pediatrics in Seattle. I found that kind of bench-side teaching much more to my liking as it also allowed me to see research progress at the same time. After declining an opportunity at Case Western Reserve, I was still uncertain where my future lay.

However, the collaborations with George Aghajanian were highly successful. For one of our early projects, we decided we should try to use the method of Potter, Axelrod, and Richardson, namely EM-Autoradiography of terminals that accumulated ^{3}H-norepinephrine. Undoubtedly we were stimulated by a lecture at Yale by Jacques Glowinski, a postdoctoral fellow in Axelrod's lab who with Les Iversen had characterized the uptake, distribution, and metabolism of the catecholamines after intraventricular injection. Les described many of my collaborations with him in Volume 6 of this autobiographical series, and the three of us have remained close friends for the past half century.

While George and I figured we could work out the intraventricular injection part, neither of us had ever done EM-autoradiography. A search of the

literature identified Professor Beatrix Kopriwa at McGill University, and I wrote her to ask if I might visit for 2 or 3 days to learn the method. She agreed, but she noted that it was a complex and lengthy procedure that might take a bit longer to learn. She was correct, of course, but I figured after watching her for 3 days that it would still take trial and error in my lab to get it right. So George and I plunged ahead and developed autoradiographs of thick sections a week after making our first intraventricular injections. We selected the paraventricular nucleus of the hypothalamus as it was close to the third ventricle and, as I knew from my early work at St. Elizabeths, it was known to be rich in norepinephrine. The light microscopy of thick sections developed for autoradiography after a couple of weeks showed that the neuropil of the paraventricular nucleus was studded with grains. Two months later we developed the thin-section autoradiographs and successfully transferred onto EM grids the thin celloidin membranes bearing the thin sections coated with the now-developed emulsion. To verify that the grains we saw over nerve terminals were selectively localized, we did stereological comparisons of the area occupied by all nerve terminals, and the area occupied by nerve terminals with large granular vesicles, with the area occupied by dendrites, glia, and blood vessels. More than 90% of the grains were over the large dense vesicle nerve terminals, which was less than 5% of the area we surveyed.

Highly pleased, we wrote our paper to submit to *Science,* where the Potter, Axelrod, and Richardson paper had been, and decided to leave the manuscript alone for the weekend and then submit it after we read it cold again on Monday. We left it on the corner of my desk. But when we came in on Monday morning, the paper was gone. Horrified, we concluded that maybe it had been knocked off the desk and into the trash by the janitor, and we spent several hours opening the collected trash baskets and finally found our paper and the envelope ready to send off. It was accepted.

George and I were then invited to develop a joint laboratory in the newly completed Connecticut Mental Health Center that had been built on the north edge of the medical school campus on land purchased for the project by the State of Connecticut. We went to the FASEB meetings in Atlantic City that spring looking to buy the equipment we would need, including an electron microscope. Prowling the halls of the Exhibits, we came to the Karl Zeiss exhibit and their new model, the EM-9. Mr. Rudolph Partsch, who identified himself as the Director of Microscope Development, offered to show us what it could do—quite a feat since most electron microscopes were housed in completely darkened rooms, and here we were in the bright lights of the Exhibit Hall. As he completed his demo, he asked us if we were now prepared to make a purchase, and at exactly that moment, the public address system announced that the Exhibit Hall would be closing for the day in 15 minutes. We responded to Mr. Partsch that if he could disassemble the microscope, insert a fresh filament, and get the electron beam aligned to the

screen before the Hall closed, we would seriously consider it. He did. Six months later we had our Zeiss microscope in our new labs.

In the spring of 1968, I was contacted by my old boss, Nino Salmoiraghi, to see if I might be interested in returning to St. Elizabeths. He informed me that the Director of the National Institute of Mental Health, Stanley Yolles, was forming a new administrative unit to be called the National Institutes of Mental Health, soon to be joined by the National Institute of Drug Abuse, and the National Institute of Alcoholism and Alcohol Abuse, and that our former Clinical Neuropharmacology Research Center was now the Division of Special Mental Health Research, within which would be the Laboratory of Neuropharmacology. He suggested I could form a Section for which I proposed the title Cytochemical Neuropharmacology, and of course the benefits of Intramural Program budget support at a level far above what I could ever have hoped for on my grants. Furthermore, there would be 26 vacant positions that I could fill as I saw fit. He also implied that since he would be very busy as Division Director, that I would for all practical purposes be directing the Laboratory of Neuropharmacology. Lastly, he played a trump card in stating he was pretty certain that Erminio Costa, our former collaborator, would be joining the division to create the Laboratory of Preclinical Psychopharmacology. It took me a very brief time to recognize that this was an undeniable invitation, and I accepted.

In an effort to keep me at Yale, Russell and Nick nominated me for promotion to Associate Professor, to which I responded somewhat curtly that if they really wanted me to stay they should make me a postdoctoral fellow again. It was momentarily attractive because Yale had hired Paul Greengard to the Pharmacology Department, and his work on the roles that cyclic adenosine monophosphate might be playing in synaptic signaling was becoming very interesting. The promotion did come through in the last month I spent at Yale, but I was committed to new horizons with a return to St. Elizabeths Hospital.

St. Elizabeths Again (1968–1975)

A number of disturbing events happened in the spring and early summer of 1968—the Tet offensive in Viet Nam led to Lyndon Johnson declaring that we couldn't afford both guns and butter and that he was eliminating all vacant government positions effective July 1. That posed a serious problem for the three young women I had hired in New Haven to be research technicians in the new labs in DC. I found these women through Mildred Gordon, a mid-40s graduate student in Russ's labs, who taught Biology at the Connecticut College for Women (now Connecticut College), one of the "little Ivies," when I asked her if any of her graduating biology seniors might want a job in Washington. Three came for interviews, and I hired all three. When Johnson decided to cancel all vacant positions, they were able to get to

Washington to sign in before the end of June, so I only lost 23 vacancies. One of those three, Elena Fasano Crawford, still works with me, and she has been a co-author and technical guidance guru for every one of my fellows and visitors for the past four decades.

Then in April, on one of my visits to assess the lab remodeling, Washington, DC underwent rioting following the assassination of Martin Luther King Jr., and still more civil unrest after the assassination of Robert Kennedy in June. Since the laboratories at St. Elizabeths were located in southwest Washington, DC, just across the Potomac River from National Airport, there was no chance that anyone I would hire would choose to live anywhere near there. We were also told to expect to be at St. Elizabeths for no more than 2 or 3 years, because there would be a new campus for the National Institutes of Mental Health in Colombia, Maryland, a new community being developed half way between DC and Baltimore on the far northeast side of DC. The advice on where to pick a home was to go to Montgomery County, the upscale community that included the NIH and Naval Medical Center, as it would be a much shorter drive. My choice was to reside in Rockville, close to the Capitol Beltway and the NIH Campus. The Colombia Campus was never built.

When I arrived in my new laboratories and office, things were much more conveniently arranged than when I had worked at St. Elizabeths the first time. Then the labs were in the basement, and the offices were on the fifth floor. Now my office and those of the staff and fellows were all together on the first floor, and our new and old labs nearly adjacent as well as in the basement. I was now responsible for three permanent staff members who had been hired by Salmoiraghi: Forrest W. Weight, who had taken my Research Associate slot when I departed for Yale and then spent 2 years in Sweden learning intracellular recording in the cat spinal cord; and two invertebrate neurophysiologists, Anthony Gorman and Maurizio Mirolli. Had I been able to use the 23 positions that were a part of my invitation agreement, the two invertebrate neurophysiology groups would have been tolerable. Now, however, they looked to me much like resources that needed redirection, and I made clear to them that their present budgets were as much as they would ever be.

Fortunately, I did have six postdoctoral colleagues, three of whom were ready for their second and final years: John Connor who had been studying the caudate nucleus and went on to become a Professor of Physiology at Penn State University, Jim Couch who did the first iontophoretic investigation of the serotonin neurons of the raphe nuclei and went on to become the Chairman of Neurology at the University of Oklahoma School of Medicine, and John Crayton who had been doing electron microscopy with Dr. Mirolli but who was eager to learn some electrophysiology. John went on to a residency in Psychiatry with Daniel Freedman in Chicago, but for his last year in St. Elizabeths he collaborated with one of the new fellows, Roger Nicoll, who had worked at St. Elizabeths with Salmoiraghi as a medical student

from the University of Rochester on the rabbit olfactory bulb after I left. Returning now after getting his M.D. degree, Roger wanted a new preparation and so he and John Crayton started anew on the paraventricular nucleus of the hypothalamus, using my old para-esophageal exposure, and another first year fellow, Jeffrey Barker, came over from the Neurological Institute to join them. Roger has had a spectacular career and is now a member of the National Academy of Sciences at UC San Francisco, a leader in the field of long-term potentiation and its pertinent synaptic plasticity, and has been awarded the 2010 Neuroscience Prize of the National Academy of Sciences. Jeffrey stayed at NIH, eventually becoming Chief of the NINDS Laboratory of Neurophysiology.

In addition to those good people, the two with whom I worked the most closely for the next several years were Barry Hoffer and George Siggins. Barry had been at St. Elizabeths as a medical student from the University of Rochester during my second summer at St. Elizabeths and began to learn some of the methods of microiontophoresis research. After completing his M.D. and Ph.D. degree work in Rochester, Barry was ready to come back. Joining us was George Siggins, the last new fellow selected by Salmoiraghi before moving to his new position. Siggins had done a Ph.D. at Boston University in pharmacology, and was especially skilled with fine control of his fingers, no doubt a byproduct of his highly practiced musical talent on a variety of stringed instruments. When I knew I would be coming back to St. Elizabeths, and that Barry would be one of my new Fellows, I wrote to him proposing we look for the target of the norepinephrine innervation of the cerebellar cortex, the brain region he had studied for his thesis, and perhaps in that era, the best understood cellular system in the brain. Siggins, after meeting Barry, opted to join with us.

Not knowing where the norepinephrine fibers to the cerebellum would make their synapses, our initial studies were focused on seeing what norepinephrine would do to neurons whose identity could be determined through their discharge patterns. The most pertinent neuron was the Purkinje cell, the main efferent neuron of the cerebellar cortex that fired in rapid ($\sim$ 60Hz) single spikes occasionally interrupted by a complex spike caused by discharge of the climbing fiber to each Purkinje cell. Using a method that Barry and his Rochester colleague Don Woodward developed, measuring the interval between spikes instead of the overall average rate of firing, we were surprised to see that what norepinephrine did was to increase the number of interspike intervals longer than 125 msec but without affecting the response to the climbing fiber or the median single spike discharge pattern.

While Barry and George were busy testing the neurons of the cerebellar cortex, I was trying to bring the tricks I had learned at Yale to bear on determining the synaptic target in cerebellum for the norepinephrine fibers. Doing freeze-dry formaldehyde-induced fluorescence histochemistry in Washington, DC, in the hot humid summer was hopeless, and we needed to

know sooner than that. The autoradiographs of sites of ^{3}H-norepinephrine accumulation seemed to target Purkinje cell apical dendrites, so we proceeded under that assumption, aided by a new tool that allowed for somewhat more immediate feedback—localization of degenerating terminals 8 hours or 1 week after intracisternal injection of the selective noradrenergic neurotoxin, 6-hydroxy-dopamine. Within a few months, the Purkinje cell was confirmed as the norepinephrine target cell by all three approaches.

Barry and Siggins went on to characterize the effects of norepinephrine on these neurons, observing that the effects of iontophoretic norepinephrine could be blocked with a beta-receptor antagonist. This led them immediately to evaluate whether the effects of norepinephrine could be mediated by cyclic adenosine monophosphate (cAMP), a process being intensively investigated throughout the NIH, including in the labs of our neighbors in the Costa lab. With their pharmacological support, we observed that cAMP replicated the effects of norepinephrine, and that the effects of norepinephrine were prolonged by drugs that inhibited the enzyme phosphodiesterase that catabolized cAMP. We published these observations in a series of papers in *Science*, and then in 1971, in three back-to-back comprehensive papers in *Brain Research* to confirm the anatomy, physiology, and pharmacology of the adrenergic innervation of the cerebellar cortex. That summer we presented these data at the International Physiology Congress and at a satellite meeting in Basel organized by Leo Hösli. I had a 15-minute presentation that, with questions from John Eccles and his wife, went on for over an hour before Dom Purpura who was chairing called a break. During the break, Bill Douglas, a Professor of Pharmacology I knew at Yale, suggested that I ask Eccles if he wasn't the same person who once held that synapses were all electrical.

This was a propitious time to have convergent evidence for the function of specific brain circuits, for 1971 was the inaugural year for the Society for Neuroscience. I served on the Program Committee for that first meeting in Washington, DC, and then as Assistant Program Committee Chairman for the second meeting in Houston that a few less people attended, causing concern that perhaps such an endeavor was premature. However, by 1973, when the third meeting was held in San Diego, the President, Walle Nauta, instructed me as Program Committee Chair to apologize to the audience at the Presidential Symposium for the lack of space in the presentation rooms—The Society had rapidly grown to exceed the capacity of the San Diego Town and Country Convention Center. At any rate, without further interruption of the career narrative, the Society continued to grow at an average annual rate of around 7% for more than three decades.

To resume our progress path, the next two major advances came through friends. At Washington University, Dr. Charles Parker and one of his Fellows, Jim Wedner, a former Barnes medical resident, had developed an immunoassay for cAMP. I asked Jim whether he might come to Washington

and see if we could develop an immunohistochemical assay to detect cAMP formation and binding, and it worked to our amazement. With George and Barry we then worked out a means to do this in living animals, taking frozen biopsies of the exposed cerebellum before and after activation of the noradrenergic afferents.

That step worked too, but it benefited from what I had learned on a quick visit to Kjell Fuxe, Tomas Hökfelt, and Lars Olsen at the Karolinska Institute. This visit was immediately after my microsabbatical with Les Iversen when we localized GABA uptake sites, and the announcement that Axelrod and von Euler had won the Nobel Prize along with Bernard Katz. Our very happy Swedish colleagues told me that they had been able to trace the origin of the noradrenergic nerve fibers to the cerebellum, the hippocampal formation, and cerebral cortex to a nucleus in the pons named the locus coeruleus. It had that name because in primates the neurons in this nucleus exhibit a blue pigment. I immediately faxed that information back to Barry and George, and when I returned they asked, "Where's that?" We found it, and stimulated it, and reproduced the effects we had observed for iontophoretic norepinephrine.

In achieving relatively long duration intracellular recordings from Purkinje cells before, during, and after stimulation of the locus coeruleus, Siggins confirmed what we had seen with intracellular recordings and iontophoretic administration of norepinephrine: The neuron hyperpolarized, but the membrane resistance increased, as did the size of the climbing fiber postsynaptic potential. This was a most unusual combination of results, and we hypothesized that the intracellular mediation of the norepinephrine effect by cAMP led to modification of active ion channels, subsequently known as the "Hyperpolarizing Cyclic Nucleotide" effect.

At this point, the question uppermost in my mind was to determine when the neurons of the locus coeruleus would discharge in an awake behaving animal. The choice at that time was still the cat, given their tolerance for neurosurgical procedure, and their very thick skulls permitting movable microelectrode assemblies to be mounted and supported. We tried this with two fellows, Nai-Shin Chu who recorded cat locus coeruleus neurons in unrestrained awake cats, and Yung-Shi Sheu, who did the same experiment recording from raphe neurons. However, because the neurochemistry of these nuclei was heterogeneous, unlike the case in rat, monkey, or human, these results were difficult to interpret.

Meanwhile, Jean Lauder used the autoradiographic thymidine birthdating method she had employed for her thesis at Purdue to define the moments during gestation when the locus coeruleus and other monoamine neurons underwent their final cell division relative to the neurons we had begun to define as their synaptic targets. Virginia Pickel, Story Landis, and Menahem Segal performed a series of experiments to confirm the

efferent trajectories of the locus coeruleus with orthograde and retrograde tracer methods. Virginia and Menahem did a heroic experiment, defining by selective transection the cerebellar peduncle through which the norepinephrine fibers entered the cerebellum, and then showing that partial transection of one superior cerebellar peduncle not only activated axonal sprouting of norepinephrine within the cerebellar cortex, it also stimulated similarly intense sprouting within the hippocampal formation. Virginia went on to become the leading U.S. practitioner of electron microscopic immunohistochemistry, identifying with different-sized gold particles two or three antigens in a given field of view.

Menahem did a series of experiments on the hippocampus and the interactions with the locus coeruleus that replicated what we had found in cerebellum, and then examined the interactions in awake behaving rats, similar to the work he had done with Jim Olds at CalTech for his Ph.D. thesis. Menahem's crowning observation to me was that the stimulation of the locus coeruleus could amplify whatever synaptic messages were operating on the hippocampal neurons: If an environmental signal was inhibiting, then that signal with locus stimulation enhanced the inhibition. If the signal were paired with food and the hippocampal neuron accelerated, signaling food with locus stimulation enhanced the activation. If the signal came to be meaningless through extinction, the locus coeruleus stimulation did not change the firing. These studies and the results we observed on membrane properties during the actions of norepinephrine or the locus were then confirmed in studies that Barry did with Don Woodward, showing again that either excitation or inhibition could be enhanced by the locus. They termed this effect "neuromodulation." I preferred to call it "enabling," which sounded to me like a more precise description of this contextual enhancing effect.

When Steve Foote joined the lab from his thesis studies with Hans-Lukas Teuber at MIT, and lent his expertise in training and recording from awake behaving monkeys, he observed even greater complexity in the norepinephrine response effect. His observations were based on the spontaneous activity of neurons in the auditory cortex before and after responding to the playing of a natural squirrel monkey vocalization; here, norepinephrine reduced the background activity and enhanced the vocalization response, thereby increasing the signal to noise ratio of the acoustic response. Menahem rapidly rose through the ranks at The Weizmann Institute and has been a leading neuroscientist there. Steve remained with us throughout the years at St. Elizabeths and joined us when we moved west, which I shall describe in the next section. Working with Steve on a part of this project, and also with Barry, was Bob Freedman. After his time with us, Bob completed a psychiatric residency with Daniel Freedman at the University of Chicago and then established himself at the University of Colorado, where

he has been Chairman of Psychiatry and is the current Editor-in-Chief of the *American Journal of Psychiatry*.

When our colleagues in Sweden reported an even better method for visualizing norepinephrine and dopamine, using glyoxylic acid instead of the freeze-dried formaldehyde procedure that was so problematic in Washington, Elena Crawford and I refined the approach to work with cryostat sections, which were far easier to control than the vibratome sectioning procedure used by the Swedes. Story Landis, then finishing her Harvard Ph.D. thesis with us, applied the norepinephrine localizing methods to her cerebellar mutant mice, confirming anatomically and electrophysiologically with George Siggins and Steve Henriksen that the NE fibers and responses followed the Purkinje neurons, wherever they came to lie in the cerebellar cortex. Her subsequent career has also been distinguished, becoming the chairperson of the Department of Neurobiology at Case Western Reserve, and now the Director of the National Institute for Neurological Disease and Stroke. Bob Robinson came to us in the middle of his psychiatry residency at Johns Hopkins, specifically to work on two problems that he had observed in his patients: the weight gain after treatment with antipsychotics, and the inappropriate euphoria he observed after certain frontal right-sided cerebral infarctions. The rats were not a good subject for the former question, but he has pursued the latter subject for most of his career, serving as well as Chairman of Psychiatry at the University of Iowa.

Having already noted why I wear bow ties, some readers may be interested in why I have a mustache. When my daughter celebrated her ninth birthday, her wish was for a roller skating party, and I reserved the Gaithersburg Roller Skating rink for her and nine of her friends. After we had arrived and the girls were on the rink, the manager asked if I wouldn't like to have a pair of skates to join them. Knowing my inner klutziness, I declined, but the manager persisted, saying that since I had rented the whole rink for the day, my skates would be on the house. I said, "If I try to skate, I'm going to break a leg." The manager said, "Nonsense." So I put on a pair of roller skates and tried the rink. Not more than 10 steps later, I felt myself falling and threw my right foot out to try to regain balance. As I did, I heard a sound like a thin pencil breaking, and I knew I had broken my leg at the ankle. I did a very good job of that, fracturing the tibia, the fibula, and the calcaneous bones, for which the orthopedic surgeon put me in a long leg cast for 6 months and warned me I might never be able to walk without a limp. I recovered fully but, while my leg was in the cast, I grew the mustache so I could see something growing. I later completed three Honolulu marathons without a limp, and the mustache has become one of my biomarkers.

Two other achievements during the St. Elizabeths period merit inclusion, both derived from Neuroscience Research Program (NRP) meetings that I attended. Les Iversen and I organized a meeting on "Neuropeptides and Amino Acids as Neurotransmitters." The participants included

Susan Leeman who had just reported that Substance P, an inhibitory material found in acetone extracts of the gut by Ulf Von Euler in 1934 was actually a 12-amino acid peptide. Roger Guillemin attended and described the isolation of two hypothalamic releasing factors that when chemically characterized and replicated synthetically were also shown to be peptides, thyrotropin releasing hormone, and somatostatin, a 14–amino acid peptide that blocked the actions of growth hormone releasing factor and was interfering with its isolation. While most of the attendees were quite willing to consider that neuropeptides could be transmitters, there was much skepticism that amino acids such as glutamate or aspartate could so function because the argument went, how could a neuron segregate the amino acids it needed for protein synthesis from those it might reserve for synaptic signaling. Gamma-amino butyrate (GABA) was considered an exception.

The meeting with Guillemin opened a new door. Shortly after that I was approached by Frederic de Hoffman, the President of The Salk Institute, who inquired whether I might consider moving our group and, if so, what would I estimate to be the cost of moving and establishing a new lab. I had been asked that question several times before, and my stock answer was at least $5 million. That usually ended the inquiries, but de Hoffman just paused briefly and said, "Let me get back to you on that." A week later, he called me again and said he thought he might be able to do that, and if I would commit to coming he would get right to work on it.

The second NRP meeting of note was one organized by Sol Snyder of Johns Hopkins that brought together a highly competitive group of investigators who were attempting to isolate an endogenous brain factor that acted in bioassays as though it were a congener of morphine. While the evidence was quite impressive that such a factor existed, its chemical nature remained elusive. At the meeting Hans Kosterlitz and John Hughes stated that they knew what the factor was but because of its importance couldn't tell us. A few weeks later, Avram Goldstein, a leading opiate researcher and the Dean of Molecular Pharmacology at Stanford University, invited me to give a summarizing discussion at the end of the First International Narcotics Research Club meeting, where the atmosphere was filled with intrigue on the nature of what all agreed would be called "endorphins" (endogenous morphine).

These peptides were really starting to attract my interest, and since we had answered most of our original questions on the circuits and functions of norepinephrine in the brain, I felt it was time to take a new direction. Salmoiraghi had resigned as Director of the Division in 1973 to become Commissioner of Mental Health Research for the State of New York, and I had been made Acting Division Director. That was acceptable for awhile, and I enjoyed hosting visiting dignitaries such as Roger Egeberg, the Assistant Secretary for Health in Nixon's Department of Health, Education and Welfare, and Charles Edwards, the Commissioner of the Food and Drug

Administration when they came to see our labs (see Fig. 1.2). But it was clear that if I remained the Acting Director, I would soon be made the Director. In November of 1975, I resigned my position at St. Elizabeths Hospital and, with my daughter and son, began our move west to The Salk Institute.

The Salk Institute (1975–1983)

After I committed to Dr. De Hoffman that I would come if he could raise the funds to build the new labs to my specifications and equip them, I had to study a whole new profession: lab architecture. Scientists rarely get to design the labs they will occupy because most often the person who designed the labs just left (or they wouldn't be empty), and you are given the old space. At Salk we had the chance to really plan how we would use our 8000 square feet of empty space.

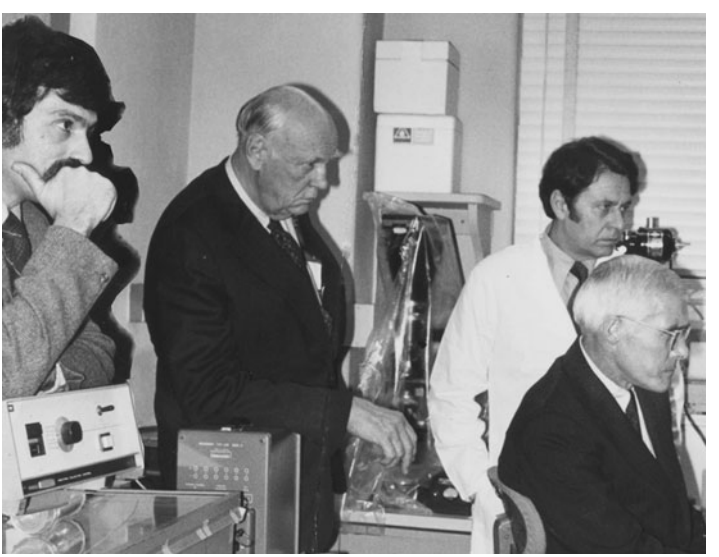


Fig. 1.2 The author as Acting Director, Division of Special Mental Health Research, National Institutes of Mental Health hosting Roger Egeberg (second from left) then Assistant Secretary for Health, and Charles Edwards (far right) then Commissioner of the Food and Drug Administration and soon to be Assistant Secretary for Health. Erminio Costa, Chief Laboratory for Preclinical Psychopharmacology is second from right.

In the months before we were to make the move, after I had assessed which lab members I would invite to come with me, The Salk Institute sent out the lab architect Donald Reeves to come up with some plans. Don stayed 3 or 4 days, carefully photographing the selected lab personnel doing their routines in our existing labs, and then went back to San Diego to create floor plans. When he came back to me, it was clear that while he got some things that needed to be adjacent to be efficient, other details of his plan were just not right. The biggest constraint is that we were budgeted for one PDP-11 computer, but we had hoped to have four labs undertaking electrophysiological recordings, and they all needed to be close enough to that computer to acquire and then analyze the data.

Don came back twice with plans that to me were still conventional and not quite as efficient as I thought they could be. After the last cycle, when I showed him what the remaining problems were, he threw up his hands in frustration and said, "I give up. What you need is a lab shaped like a Kodak Carousel." To which I responded, "Let's pursue that." We sketched a computer center, with the electrophysiology rooms as pie-shaped wedges facing into the center. We placed the neurochemistry areas where they would have maximum illumination from the large windows, and the microscopy areas where they could be shielded from the light (see Fig. 1.3). There were only two problems. The first was a financial decision as to whether we would have another lab door or more memory for our computer. The lab doors at The Salk were specially casted stainless steel doors and hinges and in 1975 they were priced at $5000 a door. I opted for the memory, which cost the same then for 8 kilobytes of random access memory.

The second problem was that having such an unconventionally configured space broke one of the spatial principles that Jonas Salk had worked out with his architect Louis Kahn: that the labs should be very flexible and nothing should be regarded as permanent. For that reason, every lab floor had an interstitial floor above and below, so that any new requirement for gas, vacuum, water, or special plumbing could be installed at any location in any lab anytime. Before de Hoffman was willing to submit the "carousel" plans to a construction estimate, it would be necessary for me to get Jonas's approval. I had started off with a very warm relationship with Jonas, and he had taken the time to interview me before I was invited to join the faculty, so I felt his evaluation of our proposed plans would be given an objective evaluation. I laid out the plans on the table in the conference room next to his office and showed him why this was ideal for the various parts of the lab I wanted to create. He stared at the plans silently for a considerable time and then looked up and said, "That Louis Kahn, such a genius. His plans allow for anything." Construction proceeded.

The labs were to be constructed next door to Roger Guillemin's lab, on the ground floor of the south building at Salk. When I went to visit the space after the final plans had been approved, Reeves and his assistant Dean

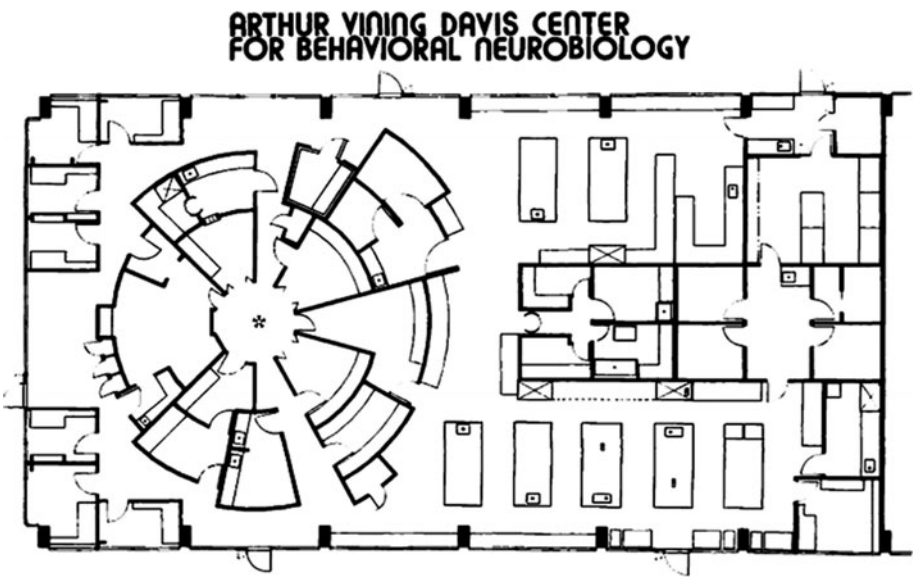


Fig. 1.3 Room layout of the Arthur Vining Davis Center for Behavioral Neurobiology, the author's laboratories at The Salk Institute, 1976–1983. The central computer core is labeled with an asterisk. The author's office was in the lower left corner.

Amantea had chalked out on the floor the placement of the walls for the offices, the central computer, the pie-shaped electrophysiology labs, and all the other rooms; when I entered they were playing the music from Stanley Kubrick's movie *2001: A Space Odyssey*, and they told me our labs-to-be bore a strong similarity to level 5 of the Starship Enterprise. That became a kind of underlying theme for the new labs, formally named the Arthur Vining Davis Center for Behavioral Neurobiology, to recognize the support of the Arthur Vining Davis Foundation in its construction. In fact, we named our weekly journal and scientific progress meetings "STARTREC" that stood for Special Thursday AM Training, Research, and Education Conferences.

Every faculty member and every trainee was required to make presentations of what they were doing and, if they weren't yet in possession of data to present, they had to present a paper from the literature. They were video taped both in making their presentations and as members of the audience asking questions of the speakers. Those tapes were often the subject of the STARTREC meetings as well, to improve how to deliver a scientific presentation and how to behave as members of the audience.

The science in the new labs was also both an extension of what we had been doing at St. Elizabeths Hospital and new endeavors. Realizing we had

to get substantial grant support before our starting dowry was consumed, I spent most of my days trying to determine what we could do to be competitive. A first focus was to investigate comprehensively the effects of lithium treatment on the functions of the locus coeruleus and its efferents, feeding the animals with Li-containing food pellets (Bill Shoemaker had been trained in the Department of Nutrition at MIT) and for long periods of time, since the antimania effects took 2–3 weeks to be observed in patients. Lithium had the great advantage that it was not metabolized, and brain and blood levels were easily measured. The grant was funded after a site visit by big-time neuroscientists who came out to see what we had built.

When I had arrived at The Salk, and before my labs were ready, I began a collaboration with Roger Guillemin, who had by now gotten interested in the endogenous opioids. As I was driving from DC to California, the paper by Kosterlitz and Hughes appeared in *Nature* defining what they termed enkephalins as two pentapeptides, differing only in whether the C-terminal was a leucine or methionine. A friend of Guillemin's at UC San Francisco's Hormone Research Laboratory, C. H. Li, had been studying a pituitary peptide, β-lipotropin, and Guillemin creatively incubated this peptide with brain homogenates, isolated the proteolysis fragments, and, having identified them, synthesized them as pure materials. Whenever his colleague Nick Ling would synthesize one of these long endorphins, I would take them to the labs of a close friend at UC San Diego, David Segal, who graciously let me use his lab space, and we would test the peptides for behavioral effects after intracisternal injections following brief ether anesthesia. The astounding result was that the 31–amino acid fragment, β-endorphin, was extraordinarily potent, inducing hypothermia and a rigid catatonic posture for hours at what we thought were extremely low doses, an effect that was almost immediately reversed with naloxone, the classical opiate antagonist. With these observations, we had a *Science* paper before my new labs were ready to occupy.

To describe in any detail all of the exciting science we were able to explore at The Salk would take more space than this entire essay and, since all of those observations were promptly published, the results are all "out there." But, given that the lithium grant had gone well, and that the opioid peptides seemed like the coming hot item, we used the exact same application and substituted opioid peptide for lithium, adding mapping and reward analysis as well. By this time, George Koob had joined us from his postdoctoral period with the Iversens, lending substance to the term "behavioral" in the Center's name. F. O. Schmitt paid a visit to the delight of all (see Fig. 1.4).

Shortly after his visit, I was called by Ed Evarts who was then the immediate Past-President of the Society for Neuroscience, who wanted to know if I would agree to be nominated for President in the 1976 election cycle. I had been Secretary for 3 years by then and had declined to run when I had been invited to do so in 1975 because of the move west. This time I agreed, and a

Fig. 1.4 Francis O. Schmitt visits the Davis Center founding staff in June 1978. Pictured left to right are as follows: (Back row) George F. Koob, Klaus Liebold, Nancy Callahan, Ed French, George Siggins, Steve Foote, Walter Zieglgänsberger, Bill Shoemaker, Joe Rogers, Leonard Koda, Steve Henriksen; (front row) Viveca Lindefors, Elena Crawford (then Battenberg), Dora Games, Raana Asad, Francis O. Schmitt, and the author.

few months later, was told that I had been elected. For my Presidential Symposium at the 1977 annual meeting, I was able to get a grant from the Arthur Vining Davis Foundation to rent a television satellite ground station for the Public Broadcast TV channel in Anaheim, and I got permission from the NIH to use their National Library of Medicine television studio to do a bicoastal true satellite meeting with Julius Axelrod and Marshall Nirenberg in Bethesda, communicating interactively with the audience and the panel in Anaheim (see Fig. 1.5). We also had Tom Bryant, Chief of Staff to Mrs. Carter, President Carter's wife, to report on the then ongoing President's Commission on Mental Health. To me this was (and is) the best of scientific meetings, and it predicted a time when we may not need to travel, although we haven't gotten there yet.

Back to the scientific program, we also began to explore with George Koob the results obtained by workers in The Netherlands claiming that the

Fig. 1.5 Video image from the Presidential Symposium of the 1977 Society for Neuroscience meeting, from the Anaheim Convention Center. Pictured in front row (left to right): Max Cowan, Robert Doty, Masao Ito, and Francis O. Schmitt. Also visible James McGaugh (behind Doty), Robert Moore (behind Ito), and Michael Bennett (behind Moore).

subcutaneous injection of the posterior pituitary hormone vasopressin had the ability to enhance learning and memory. With Aaron Ettenberg, Derek van der Kooy, Michel LeMoal, and George, we found this claim to be a misinterpretation and showed that the learning effect could be blocked by antagonists that didn't enter the brain. Later with Scott Deyo and Bill Shoemaker, we showed that the amounts that did enter the brain after subcutaneous injection were extremely small.

While I was fascinated with these neuropeptides, Steve Foote began a series of arduous experiments attempting to record from the locus coeruleus of awake behaving monkeys. Our NSF grant application to fund this work was rejected with the assertion from the reviewer that "nothing useful will ever be learned by recording from the locus coeruleus!". Steve also used orthograde and retrograde tracers to work out the efferent projections of the locus coeruleus with Sandra (Sandy) Loughlin. Other work on identifying norepinephrine in the hilus of the dentate gyrus was accomplished by Leonard Koda, and my first UC San Diego neuroscience graduate student, Jesse Shulman, who was also the stepson of Robert Galambos, a Professor of Neurosciences at UCSD. Jesse started a postdoctoral fellowship with Les Iversen but decided bench work may not be his calling. He then did broadcasting from the combat of the first Persian Gulf War for CBS radio and

later became a consultant for biotech investing in London. Jean Rossier and Alejandro Bayon worked out many of the regional differences and neuroendocrinological specificities between the peptides of the pro-endorphin series, and those of the pro-enkephalin family. Jean has become a distinguished neuroscientist in France, but Alejandro and his family died tragically in a plane crash in Nepal.

Working with Jesse, Sandy, and with some of the other students and postdocs helped me generate my two most-often asked questions when we were reviewing data, and they almost always were greeted with a blank stare. The first was, "Now that you know that, what does it mean and what can you now do?" The second question was, "What is the thesis of your thesis?" Students almost never could come up with an overriding question that encompassed their body of work but rather generated a series of observations with limited connectivity. Part of my mentoring attitude was to get them to see where their smaller pieces of observation fit into a larger picture of our neuroscience.

The whole lab was transformed in 1977, when Ernest Noble, the Director of the National Institute of Alcoholism and Alcohol Abuse, came to visit and proposed that instead of an RO-1 on alcohol actions at the neuronal level, I apply for an Alcohol Research Center. This much larger grant would allow me to bring in collaborators from other parts of the Salk faculty such as Hyam Leffert, who had developed ways to grow pure hepatocytes in culture, and Helen Neville, a neuropsychologist interested in cortical plasticity. When the Center was funded, we applied for a Training Grant, and with that we could hire six postdoctoral fellows a year, further expanding the range of experiments we could pursue. Almost all of them turned out to be rich veins of discovery.

The group of fellows we had in 1980 were particularly noteworthy for their zeal and subsequent productivity. The group included Joseph Rogers, now Director of Research for the Sun City Research Foundation; Pierre Magistretti, Director of the Brain Mind Institute at Ecole Polytechnique Federale in Lausanne and a former President of the Federation of European Neuroscience Societies; and John Morrison, formerly the Chairman of the Department of Neuroscience and now Dean of Basic Sciences and the Graduate School of Biological Sciences at Mount Sinai School of Medicine. Their studies on the localization of neuropeptide fibers in aging and Alzheimer brains gave us our first opportunity to apply our methods to human brains, and Pierre's work with John exposed the intersections between norepinephrine fibers and those containing Vasoactive Intestinal Polypeptide. Pierre also showed that VIP and norepinephrine could both activate cAMP synthesis, another hint at an enabling mechanism. Pierre's work for his thesis at UC San Diego set the stage for his career-long pursuit of astrocyte-neuronal exchanges in energy metabolism and for the first advances in the molecular mechanisms underling functional magnetic resonance imaging.

Two more events must be included in this abbreviated overview of the years at The Salk. Gary Jones had been a graduate student with the famous experimental psychologist Jim Olds at CalTech, who had also been Menahem Segal's mentor. Jim was well known for his discovery of the internal reward pathways of the lateral hypothalamus and intracranial self-stimulation. When Jim died tragically while swimming in the Pacific, CalTech gave Gary the option to go to any lab he wished to complete his CalTech Ph.D. After considerable looking about, he opted to come with us at The Salk, and he chose for his project to record from locus coeruleus neurons in the awake behaving rat, a task that seemed as daunting as Steve's efforts in the monkey, given the tiny size of the nucleus in a rat and the fact that their spontaneous locomotion made it almost impossible to record one unit long enough to try to define its environmental repertoire. Thankfully, Gary's girlfriend Stephanie Aston made little leather hammocks that Gary trained the rats to lie still in, reinforced by flavored milk when they did. Gary became Aston-Jones when they married, and his thesis was published in two classical papers on locus coeruleus physiology in the first volume of the *Journal of Neuroscience.*

By this time, Steve Foote's efforts in the monkey had paid off, and we were able to report that in both species, locus coeruleus neurons in awake, behaviorally responsive animals responded to novel events in the environment of any sensory modality, that they were most active when the animal was alert and focused on the environment, and slowed progressively with inattention, stopping completely during rapid eye movement sleep.

Gary has persisted with this problem, and his 2005 *Annual Review of Neuroscience* paper with Jonathon Cohen of Princeton establishes a far richer and more profound explanation of the locus coeruleus than I would ever have imagined we would know. Steve pursued the effects of corticotropin releasing factor on the locus coeruleus with Rita Valentino, and he later moved his labs to UCSD before he joined the Extramural Research Program of the National Institute of Mental Health. He quickly rose to become the Director of the Neuroscience Branch before taking an early retirement.

In early 1979, Rob Milner joined our lab from Gerald Edelman's labs at The Rockefeller University, specifically to try to develop monoclonal antibody technology to enrich our studies of the neuropeptides. As he was developing these approaches with a Visiting Scholar from Israel, Ilana Gozes, a paper appeared in *Nature* from the Kyoto laboratory of Professor Numa showing that with cloning technology it was possible to determine the entire amino acid sequence of the common precursor of β-lipotropin and the adrenocorticotrophic hormone, ACTH, from the messenger RNA extracted from a dozen pituitary glands. Moreover, in analyzing the sequence of this precursor, they uncovered a third repeat of the melanocyte stimulating hormone that they proposed as a new signaling molecule waiting to be characterized.

I took this issue to my friend Richard Lerner at The Research Institute of the Scripps Clinic, only about three blocks away, and asked him why we couldn't use a similar approach to find as yet undiscovered neuropeptides in the brain. He thought that was a crazy but possibly fruitful line and introduced me to his new postdoc, Greg Sutcliffe, who had just completed his Ph.D. at Harvard in the labs of Wally Gilbert by sequencing the most used cloning vehicle, the pBR322 plasmid. We agreed to a collaboration, and Greg and Rob did the work while Richard and I dreamed of the results.

By now, the growth of our group was making our 8000 square foot laboratory feel tight, and with the grant success that we had accumulated, our group could move with a lot less risk than when we left the NIH in 1976. I began to look around and accepted some invitations to visit. The search was made more pressing by the gossip that some of the professors at The Salk didn't think alcohol research was a fitting topic for the Institute. When the colleagues at Scripps heard of this, Richard and his boss, Frank Dixon, suggested I consider moving around the corner. When I took them seriously and really started to explore the opportunity, the more exciting it seemed to be—we might now be able to carry our results from experimental animals to humans. But Dr. De Hoffman was incensed to think I would abandon what he had helped me create. While I was entitled to take with me all of the equipment I had purchased on my grants, I had no basic right to the equipment that he had purchased to get us started. Therein lay a year's worth of negotiations, until it was agreed I could buy the start up equipment, since it was unlikely to be used by anyone else at Salk. In November, 1983, *Nature* ran a News Item saying "Bloom Moves South," but they had mistaken the Research Institute of Scripps Clinic for the Scripps Institute of Oceanography; and we moved the three blocks north. As soon as we left, our Salk "carousel" labs were completely dismantled and refitted as conventional labs.

Leaving The Salk was a mixed emotional affair because I had made a lot of friends while there, and almost all of them remained my friends after the move. It had been a great place to receive visiting scientists, and we were pleased to get to know better some of the world's leading scientists. The Iversens came at least three times in the summers and helped us work out in vitro peptide release assays. Kjell Fuxe and Torgny Svensson both spent winters from the Karolinska, with Kjell mostly playing tennis, while Torgny helped us recognize that alpha receptors in the cerebellum also played a role in the norepinephrine effects there. Guy Chouvet came from the Jouvet sleep labs in Lyon to work with Steve Henriksen, as did Alim (Ben) Benabid, a neurosurgeon from Grenoble who wanted to examine thalamic stimulation techniques—the start of deep brain stimulation as a treatment. The Salk was our home when I was elected President of the Society for Neuroscience, when I was elected to the National Academy of Sciences, and when I married Jody Corey. But it was time to move on.

The Scripps Years (1983 to the Present)

Given that I have spent the last 27 years at The Scripps Research Institute, it goes without saying that only the most superficial coverage of the research carried out here by my many colleagues is possible. We moved from The Salk during the Christmas break of 1983. Thanks to the hard work of the fellows like Charles Chavkin, Jakie McGinty, Jorge Mancillas, Lisa Giovanneli, and Franco Vaccarino, the labs were back in full operation quickly. These new labs were now divided into four separate working areas—neurohistology for light and electron microscopy with John Morrison and visits from Steve Foote; neurophysiology with George Siggins, Steve Henriksen, and Donna Gruol; neurochemistry with Rob Milner; and behavioral pharmacology under George Koob.

Our overall lab group was called the Division of Preclinical Endocrinology and Neuroscience, a part of Ernest Beutler's Department of Clinical Medicine; the "endocrinology" term allowed us to be supported from two endowments under Beutler's control. It was the first time we had any hard moneys we could count on since our startup days at Salk, and it was put to good advantage equipping the labs since we now had more than 50% more space than we had had previously. The four research groups now more or less ran their own shows, allowing the faculty to mature, but we maintained our training grant, the Alcohol Research Center, and the STARTREC sessions that were the main training vehicle.

For the first 6 years at Scripps, our more notable achievements were in undertaking highly detailed maps of the monoamine systems in nonhuman primate, a move pioneered by John Morrison with strong support from Steve Foote. With his fellows Mike Campbell and David Lewis, Morrison and Foote made detailed maps of the cortical regions, documented the interregional innervation density differences, and applied the latest methods of circuitry tracing to define the target neurons. After 2 years, David was recruited to the Psychiatry Department at the University of Pittsburgh, where he has just been appointed Chairman. With Ana de Lima, John Morrison defined with serial reconstructions the immunohistochemically defined serotonin terminals in cortex and the very tiny zones of synaptic specializations they possessed. Such an approach was necessary if one wanted to see those specializations that many others had denied existed.

When John had been a graduate student at Johns Hopkins, he had been in a serious automobile accident that traumatized his cervical spine, and the head-down position used to examine tissues in a microscope severely exacerbated his neck pains. This struck me as an unnecessary burden to place on my collaborator, and so we invested in an effort to modernize microscopic analysis by using high-definition video capture of images, and stepping motors to move the slides. This allowed us to do quantitative mapping and stereological analysis, for which Warren Young was able to write highly

effective software. These investments earned us a berth in the Human Brain Mapping project when the brain-centric Institutes at NIH recognized they needed something to compare to the investment that had been made in the Human Genome Project.

John was also a major supporter in the project that Rob Milner and I undertook with Greg Sutcliffe, namely to employ differential and subtractive mRNA cloning to identify genes that were expressed in the brain but not in other tissues. From the calculations based on the first hundred or so such genes, Greg estimated that well over half of the mammalian genome could be either brain specific or brain enriched. There were so many brain-specific genes that, to gain a toehold, Greg and Rob started playing one brain region against another, using John's knowledge of the primate brain regions and their higher but different degrees of cellular specialization—frontal versus motor versus visual cortex, for example. When such genes were identified with Greg's help, we would seek to develop either antibodies to fragments of the proteins they encoded or to use in situ hybridization to map them out. This effort was supported by a Program Project grant in which Rob, Greg, John, and I each had component projects.

In my unit, we concentrated on technical developments that would allow the mapping of new brain-specific gene expression sites more quickly and more completely. The original approach had been to try to raise antibodies against synthetic fragments of the newly discovered gene product. But even when coupled to highly foreign proteins like keyhole limpet hemocyanin, antibodies with titers high enough and avidity high enough failed to be acceptable for immunohistochemistry. In 1989, Gustave Jirikowski came to work with us on a Heisenberg Fellowship and brought with him an excellent monoclonal antibody to Bromo-deoxyuridine, a tag that could be incorporated into in situ hybridization probes, and then localized with Gustave's antibody. His studies led us to find that for some neurons, such as the magnocellular hypothalamic neurons, mRNA was found in axons and increased there with demands on the system, like water deprivation. His studies with Pietro Sanna (who came to us with the recommendation of Rita Levi-Montalcini) and Dominique Maciejewski-Lenoir also demonstrated an uptake by neurons of some selected mRNAs, a finding that remains to be replicated, but to me was one of enormous potential. Marisela Morales and Alain Trembleau developed methods to bring in situ hybridization to even higher resolution using multiple oligonucleotide probes and fluorescent labeling. Marisela collaborated with scientists at The Salk to map out and define the population of interneurons bearing the 5HT-3 receptor, the only monoamine receptor not to be a G protein–coupled receptor. Marisela is now a tenured scientist at the National Institute of Drug Abuse, and Alain was recently appointed at College de France.

In Rob's unit, the focus initially was on myelin and astrocytes, and his trainees Cary Lai and Klaus Nave each acquired exemplary observations

that have launched distinguished careers—Klaus as Director of the Max Planck Institute for Experimental Medicine at the University of Göttingen, and Cary as Professor of Neuroscience and Genetics at the University of Indiana. Rob left us to become Chairman of Neuroscience at the Penn State University School of Medicine. In Greg's Unit, the effort was focused on finding brain-region selective gene expression, and such genes were found to be abundant. The apex of this emerged from studies of hypothalamically enriched gene expression, one of which on initial in situ hybridization was clearly localized to a bilaterally symmetrical nucleus that was near to but was not the paraventricular nucleus. Sequencing revealed this gene to encode a secretin-like peptide and, since it was in the hypothalamus, Greg named it hypocretin. Interestingly, these neurons have a limited efferent circuitry, one of their targets being the locus coeruleus. The hypocretin neurons seem to play a role in a variety of vegetative functions, including appetite, blood pressure, and sleep. Mutations of the peptide or its receptor have been reported to cause narcolepsy, and drugs based on the peptide are being developed to treat the disease.

Although John was trained in neuroanatomy, my knowledge of circuitry was loosely based on what I had learned in medical school, supplemented by many trips to the library. Every time we identified an interesting new brain-specific gene, and John and I attempted to map it out, a new complete analysis from olfactory bulb to spinal cord was required. It frustrated me to have to look up so many circuits so many times. Then the thought occurred to me that maybe I could create a database of the known circuitry, transmitters, and receptors. I could then attribute to the circuits the cellular and system properties they were thought to regulate, and the behaviors in which they were thought to participate, so that when the next new one came along we could gain insight just from the mapping. After all, in neuroscience "Where?" is a very important question. This line of reasoning led to many attempts to employ computer databases, but none that were available to me could handle the known complexity of real brains, that is, until Hypercard was released by Apple. On a trip home from a meeting at NIH, I bought the software, read the manual, and sketched out the major organization of the database that Warren Young and I later published as the Brain Browser (several years before there were Internet browsers). Although Brain Browser was not a real database, it was an easy-to-use, intuitive way to organize information about the brain's circuitry that has never been replicated. It is now obsolete since Apple did not maintain the program to work with current operating systems.

Another very large program of research came our way when the National Institute of Mental Health put out a request for proposals to develop research centers to study the basis for the effects of HIV infection on the brain. While other NIH Institutes had invested heavily in this area of work, the NIMH had not, and now they wanted to catch up. We at Scripps had considerable

assets in this area, with several noted virologists who had been studying viruses known to attack the nervous system (Mike Oldstone and his colleagues Jay Nelson and Michael Buchmeier) and another investigator, John Elder, who had been one of the first to identify the comparable retroviral disease in cats, the feline immunodeficiency virus. In addition, we had Tom Edgington and his colleagues who were expert in the cellular and molecular aspects of inflammatory reactions. We competed, and we were funded in one of the largest grants to that point that had ever come to Scripps. As a reward, we were designated the Department of Neuropharmacology and given the entire first floor of a new research building that Scripps had leased on the eastern part of our campus. At this point we had grown to more than five times the space we had occupied at The Salk Institute.

Science (1995–2000)

While all was going quite swimmingly in the laboratory on virtually every front, I began getting "feeler" messages inquiring whether I had any interest in becoming Editor-in-Chief at *Science*, the weekly magazine of general science owned and operated by the American Association for the Advancement of Science (AAAS). It is one of the two most widely read journals in the world, with a subscriber list perhaps four times that of the other such journal, *Nature*. Daniel Koshland, who had been the Editor-in-Chief, had announced his retirement, and the Board of the AAAS had formed a search committee. Although I had made a previous arrangement with Elsevier Publishers to take on the Chief Editorship of their five journals in Brain Research (*Brain Research*, *Molecular Brain Research*, *Developmental Brain Research*, *Cognitive Brain Research*, and *Brain Research Reviews*), the opportunity to work at *Science* was too important to dismiss, and so I expressed a sincere interest.

At the Society for Neuroscience meeting in the fall of 1994, the *Science* news reporter Marcia Barinaga and I were chatting, and I asked her what the status of the Editor search was. She told me she thought I was the choice, although no one had said anything to me. Then in December that year, Rich Nicholson, the Executive Officer of AAAS, asked if he could fly in from Washington to speak to me, and he offered me the job. I flew up to see Dan Koshland at Berkeley to begin to understand what I had to learn, and I asked him how much of my time I should set aside to do the job. He told me he thought I could do it in about 25% of my time. That seemed reasonable, and I thought the easiest way to gain 25% of my time back for this new opportunity was to relinquish being Director of the Alcohol Research Center. George Koob agreed to take it on. After enough delay to indicate I had thought seriously about it, I agreed to accept the AAAS offer, effective July 1.

However, since I didn't want to live in Washington, DC, where AAAS and *Science* are based, there was a sizable chunk of budget that had been set aside for the new Editor's moving expenses that could now be reinvested.

In the spring of 1995, Ellis Rubinstein, the head of the News Department at *Science*, came to Scripps to start briefing me about the job's responsibilities, the internal politics of the organization, the decisions that were going to have to be made, and the opportunities that lie ahead. In February, I went to Washington to meet some of the 200 staff members and get a feel for the work ahead. My introduction was facilitated greatly by Monica Bradford, who was then the Managing Editor and responsible for the review and production of the elements in the original research and research commentary parts of *Science*. Although most scientists, if asked why they read *Science*, would respond that it was for the science, the magazine covered all of science but had the space to publish only 15 articles a week. Thus, most issues would have very little to offer any given field. In reality, the front half of the magazine, carrying the global news of science and the scientific community, had something for everyone. The one weak spot to me was the Book Reviews section, which chose to review books that to me were less than appealing and that were often divisive, pitting one philosophy of science against another. I resolved to see how this might be improved.

The Editor-in-Chief at *Science* is there primarily to represent the academic scientific community when it comes to resolving disputes between authors and reviewers, helping the review editors render fair and prompt decisions about submittals, but rarely helping the news side see broader perspectives on some issues being covered. In the scientific disciplines, the original research submittals were handled by 18 or so editors with Ph.D. degrees in the fields that were their responsibility. The review process installed by Dan Koshland employed a Board of Reviewing Editors—known to the staff as the BoRE—who had the current expertise of an active bench scientist (I had been one of the BoRE in neuroscience). Each week BoRE members were FedEx-ed a packet of submittals and asked to comment on them under the proposition: If the results claimed in this paper were true, would that be significant and important enough to be a *Science* paper? If the answer were yes, what scientists would make the best reviewers? Those comments were supposed to be returned by fax, or by e-mail for those who did it, within 48 hours.

The original research editors would send their papers out for review, nudge the reviewers for their decisions, then make a tentative decision and once a week present their current portfolio to the other editors to gain group support for an acceptance, given that they were all competing for the constrained space of the weekly table of contents. Original research editors were working either in Washington, DC, or in the European office based in Cambridge, England, so the entire meeting was a teleconference, which

either the Editor-in-Chief or the Managing Editor would chair. From what I learned, these meetings were frequently quite intense events that could evoke anger and sour working relations.

Armed with these early insights into the operations, when I reported for duty in July, I was faced with an unexpected immediate need for a decision: It seemed that the estimated costs of the paper used to print the magazine were going to be raised above budget, and the costs of the postal and air deliveries for the weekly issues were also going up. However the AAAS was a nonprofit organization, so this also meant it was a no-loss organization. Where in the magazine's budget would I propose to trim the extra sums needed?

Searching about, I learned that in Koshland's last year, the editors had looked closely at ways to start transmitting *Science* over the Internet but, knowing that he would leave, those ideas had been put on hold. As we began to think about the possible budget shortfall, we received a request to meet with John Sack and Mike Keller from Stanford University's library, who were developing an electronic publishing service named HighWire Press, aimed initially at nonprofit societies with journals. We were immediately captivated, and after a demo and a lot of discussion, despite the upfront costs incurred, we were on board. In October of 1995, *Science* went online, the third journal to do so after the *Journal of Biological Chemistry* and the *Journal of Neuroscience*. Once that decision had been taken, the door opened on what the online journal should and could be. We resolved from the beginning that *Science* online would be more than just a digital version of the printed magazine, but would offer tools for scholars that could empower the dissemination of knowledge.

Before this new job in Washington, it used to be said that the two things you never wanted to watch being made were sausages and laws. To that, after my experiences, I would add a weekly science magazine. Plans for properly filling the pages, and placing the ads—necessary for support of the magazine and the society—extend weeks into the future. The ability to lay out the original research articles in the no-space-is-wasted format that *Science* employs will look even harder when one knows that, unless all the authors approve and return their galley proofs on time, that the space designated for one article cannot exactly be filled by any other. All of these problems and more came into play when it became necessary to expand the weekly workflow to convert the text and graphics into the hypertext markup language (HTML) that is used to present information on the World Wide Web, and that in 1995 was not exactly well understood. Then we eventually came to realize that, while putting the journal online might reduce the cost of dissemination, it did not lessen the costs of production and that creating the software to implement the tools for scholars that the Editors and I creatively flung at our readers could become quite costly.

Rather than dwell on the enormous number of issues that arose and were solved, I will just note that the book review section was changed, and a

new way for each original research editor to handle the submittals in his or her field was found. As the most senior of those editors, Mrs. Eleanore Butz, used to point out, the best papers came when the editors spoke to the leaders in their fields of coverage to find out what exciting new data they had heard about and got that author to consider sending his or her work to *Science*. She called this "shmoozing." It was her view that if they waited for the papers to come in on their own, the best would go elsewhere and it was much too late. Of the matters I was pleased to have had more than a hand in, the creation of *Science*'s NextWave and the *Science* signal transduction knowledge environment (STKE) are right at the top of the list.

Science's NextWave as an online-only publication started even sooner than the time when *Science* itself went online. It was based on an idea brought to me by Ellis and one of his news editors, John Benditt, that we should do something for graduate students and postdoctoral fellows who were trying to determine what they should do with their scientific education when they grew up, and maybe even help graduate students select the areas where they might work. That site, now combined with the *Science* employment opportunities in Science Careers, is supported by graduate universities and educational systems globally and has been warmly received by students and faculty, especially those who may have grown dissatisfied with their current line of work.

Science's STKE was another opportunity for an online information system to emerge. Our editors found that the same principal signal transduction pathways were often being pursued in many different experimental systems and in each one, the various components had different names and those communities rarely spoke to each other. The STKE was conceived as a way to portray graphically these signal transduction pathways and allow species-specific terminology to be compared and contrasted. Those connection maps can be seen today, and the reviews and special articles that illuminate the pathways are still leaps and bounds ahead of any other summarizing system for signal transduction. I note that in the past year, the STKE has also begun to publish original research in the area of signal transduction.

In my final year as Editor-in-Chief, *Science* did a "Pathways of Discovery" series as special coverage of the calendrical transition into the next millennium, portraying the pathways of discovery across all of science from quantum physics to cosmology and from genomics to atmospheric sciences. For each topic covered, distinguished scientists reviewed what they saw as the major past heuristic accomplishments along the intellectual pathways of that field and then attempted an extrapolation into the future from discoveries unfolding then. My inspiration for this series arose when my wife and I visited the original site of the Hong Kong University Medical School where the Hong Kong Radiological Society had erected a display of how Roentgen's observations on the physics of X-ray led to the development of medical imaging, and it then occurred to me to document how the 20th century was filled

with examples of advances in one field of science creating opportunities for advances in many other fields. My neuroscience mentor, F. O. Schmitt, often pointed out how the neurosciences frequently exploited advances in other fields to move ahead. My editors at *Science* agreed and we moved ahead with this plan.

To help lay out our year of Pathways essays, *Science*'s editors assembled a graphical timeline of major past events and agents of discovery. These timelines served as convenient simplifications of the spectacular and progressive accumulation of insight and understanding scientists have achieved. In my editorial announcing these plans I invoked a visual metaphor of this progress as an intricate circulatory system with multiple ever-finer branchings that often interconnect with other parts of the nexus. While science has indeed become a process of continuous specialization, each new capillary of investigation contributes to the overall understanding. Each new branch of science can open wondrous new opportunities while posing societal challenges that will require vigilance and insightful management. For me, the most remarkable conclusion to emerge from this exercise was the realization that in the millennium we were about to leave, humanity's knowledge of its place in the universe had moved from St. Thomas Aquinas's view that knowledge was of two types—that which man could know and that which was "higher than man's knowledge" and not to be sought through reason—to the belief begun with Newton's Principia that our universe and all within it are indeed knowable.

After 4 years of being Editor-in-Chief, I had grown weary from the time spent commuting between California and Washington, DC. I also recognized that this was not the final post I wished to hold and asked to be replaced after my fifth year on the job. In my final editorial, of the 50 or so that I wrote, I offered some reflections on the interesting times (in the Chinese sense of the term) through which we had traveled. It was my good fortune to witness truly amazing discoveries and achievements. Among those that remain most intensely etched in my mind are the evidence for possible life on Mars, the Bose-Einstein condensate, the emergence of nanotechnology, the expanding universe, the basis for nearby planetary chaos, and remarkable archaeological insights into human origins. Equally thrilling to recall are the whole bacterial and plant genomes already sequenced, as well as *C. elegans*, *Drosophila*, and soon the human genome; the atomic coordinates of complex molecules such as cytochrome C, erythropoietin, immunoglobulin enfolding its antigens, and the potassium channel; the chemokines and their receptors through which HIV infects; numerous new regulatory peptides and markers of oncogenic vulnerability; the cloning of whole animals; the isolation of adult totipotent stem cells; and many, many more. As a life scientist, I always shuddered when the popular press found the articles about bones and rocks more interesting than the insights into biology and medicine.

Unquestionably, those 5 years were most vividly epitomized by the ascent of the Internet and the significant changes that it was and still is imposing on scholarly publishing, as well as on almost every other aspect of our society. I concluded by noting that *Science* will likely continue to refine and evolve these adaptations as new and better means of communication emerge. I eschewed technology that merely intensifies the information glut faced by scientists because the Internet makes possible such accelerated information access. Mountainous collections of information, unorganized, unanalyzed, and uncategorized, become useful only when experts take over and interpret the mountains with perspective. Drawing knowledge from information remains an overarching goal for *Science*.

Current Activities and Conclusions

Returning to my responsibilities at Scripps, I found myself with no grants, no postdoctoral fellows, and no active research except for that being done in the Alcohol Research Center and the Neuro-AIDS Center, and even there I was not current with recent developments. I knew that I dare not try to write new grants, for surely among those grants' peer reviewers would be authors whose papers had been rejected while I was at *Science*, and scientists do take those things personally. I therefore looked for other ways to apply my experience.

Greg Sutcliffe had by now started a biotech company, Digital Gene Technology, based on work done in his labs to make the high throughput comparison of specific mRNAs much more sensitive and accurate than the gene array technologies of the time, and he invited me to serve on his scientific advisory committee. This committee was charged with evaluating proposals from academic labs to take up some unused capacity in their assay systems, and to popularize what the technology could do. My comment after many of those reviews was that if you can identify this unique gene whose expression is changed by this perturbation, then the next goal should be to map it. After repeating that assertion innumerable times, the CEO, Greg's brother Bob, said to me, "What don't you start a company to do that?" It seemed like a great idea and, with his help, we raised the funds to launch Neurome, Inc., to develop high throughput means to map and compare gene expression in mouse transgenic models of human neurological diseases, to spot the earliest sites of neuropathology, and to use that information to assess the ability of a therapeutic intervention to halt or reverse the pathology.

The founders with me were my colleagues John Morrison and Warren Young. Through a variety of contracts with Elan Pharmaceuticals, we were able to study their mouse model of amyloid accumulation as a form of Alzheimer disease. This mouse model incidentally had been developed by Dora Games, one of the original research technicians at the Davis Center

labs at The Salk (see Fig. 1.4), who had then gone to graduate school and obtained a Ph.D. Our Neurome scientists, Jeff Redwine, John Reilly, Ron Broide, and Chi-Cheng Wu, developed excellent stereological quantification methods that grew into compelling and comprehensive quantitative documentation that, in this mouse model, the earliest changes in synapses and dendritic spines occurred in the outer molecular layer of the dentate gyrus weeks before any amyloid accumulations were detectable. Work on different mouse models resulted in a contract with Wyeth Pharmaceuticals, intended to lead up to a therapeutic intervention study, and work with Merck seemed to have gone well enough to support the in-licensing of an antistroke medication. Nevertheless, because the bubble had long since burst in biotech, sufficient financing was impossible to arrange, and Neurome was forced to close in 2006. Nevertheless, the thrill of discovery and applying new quantitative methods to discern the earliest pathological changes in the brains of mice expressing the familial form of Alzheimer disease allowed me to take another swing at the application of neuroscience to neurological disease. It was not the science that failed here but the lack of proper business training that allowed me to make managerial mistakes that might have been avoided and allowed the company a longer life.

My activities have now turned mainly to consultation and the offering of advice. At the 2004 meeting of the Society for Neuroscience, my colleagues created for me a massive "Bloom Science Family Tree" that illustrated how those who had been trainees with me, then trained others, who trained others, and so on for four generations, and encompassing more than a thousand scientists. Having mentored that stream of discoverers, I have to admit to a feeling of some self-satisfaction.

Today, I serve as a Trustee for Washington University in St. Louis and chair their National Council for the School of Medicine. I completed 3 years on President Bush's Presidential Council on Bioethics, and I am in my third year as a member of the Independent Citizens Oversight Committee for the California Institute of Regenerative Medicine (the Proposition 71 Stem Cell initiative).

These transitions in my role as a scientist have not gone unnoticed. I liken my evolution to the progression of the workers in Vannevar Bush's quarry of science essay, "Science Is Not Enough." He conceives of knowledge as an edifice that once existed and whose parts have been scattered, hidden, and buried, awaiting scientists to find them and reassemble an organized science. He identifies some workers in this quarry as "those content to dig away, unearth odd blocks, pile them up for others to view and caring not whether they fit in now" and others as "those who sit by and give advice, and those who just sit." But he also describes "those men of rare vision who can grasp well in advance just the block that is needed to advance construction rapidly and can tell by some subtle sense where it will be found." I feel I was once one of those men of rare vision, and occasionally still am. Perhaps some

readers may be inspired by what my colleagues and I were able to find and reassemble, and gain confidence to move along their own chosen paths.

Selected Bibliography

Original Research

Aghajanian, G.K., and Bloom, F.E. Electron-microscopic autoradiography of rat hypothalamus after intraventricular 3H-norepinephrine. Science, 153: 308–310, 1966.

Arnsten, A.F.T., Segal, D.S., Janowsky, D.S., Judd, L.L., Hillyard, S.T., Neville, H.J., and Bloom, F.E. Naloxone augments electrophysiological signs of selective attention in man. Nature, 304: 725–727, 1983.

Aston-Jones, G., and Bloom, F.E. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. J. Neurosci., 1: 876–886, 1981.

Aston-Jones, G., and Bloom, F.E. Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced response to non-noxious environmental stimuli. J. Neurosci., 1: 887–900, 1981.

Aston-Jones, G., Foote, S., and Bloom, F. Low doses of ethanol disrupt sensory responses of brain noradrenergic neurones. Nature, 296: 857–860, 1982.

Bayon, A., Koda, L., Battenberg, E., and Bloom, F.E. Redistribution of endorphin and enkephalin immunoreactivity in the rat brain and pituitary after in vivo treatment with colchicine or cytochalasin B. Brain Res., 183: 103–111, 1980.

Bayon, A., Rossier, J., Mauss, A., Bloom, F.E., Iversen, L.L., Ling, N., and Guillemin, R. In vitro release of [5-methionine] enkephalin and [5-leucine]-enkephalin from the rat globus pallidus. Proc. Natl. Acad. Sci. U.S.A., 75: 3503–3506, 1978.

Benabid, A.L., Henriksen, S.J., McGinty, J.F., and Bloom, F.E. Thalamic nucleus ventro postero-lateralis inhibits nucleus parafascicularis response to noxious stimuli through a non-opioid pathway. Brain Res., 280: 217–231, 1983.

Bloch, B., Brazeau, P., Ling, N., Bohlen, P., Esch, F., Wehrenberg, W., Benoit, R., Bloom, F., and Guillemin, R. Immunohistochemical detection of growth hormone releasing factor in brain. Nature, 301: 607–608, 1983.

Bloom, F., Battenberg, E., Rossier, J., Ling, N., and Guillemin, R. Neurons containing β-endorphin in rat brain exist separately from those containing enkephalin: Immunocytochemical studies. Proc. Natl. Acad. Sci. U.S.A., 75: 1591–1595, 1978.

Bloom, F., Segal, D., Ling, N., and Guillemin, R. Endorphins: Profound behavioral effects in rats suggest new etiological factors in mental illness. Science, 194: 630–632, 1976.

Bloom, F.E. Science as a way of life: Perplexities of a physician-scientist. Science, 300: 1680–1685, 2003.

Bloom, F.E., Algeri, S., Groppetti, A., Revuelta, A., and Costa, E. Lesions of central norepinephrine terminals with 6-OH-Dopamine: Biochemistry and fine structure. Science, 166: 1284–1286, 1969.

Bloom, F.E., and Aghajanian, G.K. An electron microscopic analysis of large granular synaptic vesicles of the brain in relation to monoamine content. J. Pharmacol., 159: 261–273, 1968.

Bloom, F.E., and Aghajanian, G.K. Fine structural and cytochemical analysis of the staining of synaptic junctions with phosphotungstic acid. J. Ultr. Res., 22: 361–376, 1968.

Bloom, F.E., and Barrnett, R.J. Fine structural localization of acetylcholinesterase in the electroplaque of the electric eel. J. Cell Biol., 29: 475–496, 1966.

Bloom, F.E., and Barrnett, R.J. Fine structural localization of noradrenaline in nerve ending vesicles of the autonomic nervous system. Nature, 210: 599–601, 1966.

Bloom, F.E., and Battenberg, E.L.F. A rapid, simple and more sensitive method for the demonstration of central catecholamine-containing neurons and axons by glyoxylic acid induced fluorescence: II. A detailed description of methodology. J. Histochem. Cytochem., 24: 561–571, 1976.

Bloom, F.E., and Iversen, L.L. Localizing 3H-GABA in nerve terminals of rat cerebral cortex by electron microscopic autoradiography. Nature, 229: 628–630, 1971.

Bloom, F.E., and Schoepfle, G.M. Kinetics of procaine-acetylcholine antagonism. Am. J. Physiol., 204: 73–76, 1963.

Bloom, F.E., Battenberg, E.L.F., Milner, R.J., and Sutcliffe, J.G. Immunocytochemical mapping of 1B236, a brain specific neuronal polypeptide deduced from the sequence of a cloned mRNA. J. Neurosci., 5: 1781–1802, 1985.

Bloom, F.E., Costa, E., and Salmoiraghi, G.C. Analysis of individual rabbit olfactory bulb neuron response to microelectrophoresis of acetylcholine, norepinephrine and serotonin synergists and antagonists. J. Pharmacol., 146: 16–23, 1964.

Bloom, F.E., Costa, E., and Salmoiraghi, G.C. Anesthesia and the responsiveness of individual neurons of the cat's caudate nucleus to acetylcholine, norepinephrine, and dopamine administered by microelectrophoresis. J. Pharmacol., 150: 244–255, 1965.

Bloom, F.E., Hoffer, B.J., and Siggins, G.R. Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum: I. Localization of the fibers and their synapses. Brain Res., 25: 501–521, 1971.

Bloom, F.E., Hoffer, B.J., Battenberg, E.F., Siggins, G.R., Steiner, A.L., Parker, C.W., and Wedner, H.J. Adenosine 3,'5'-monophosphate is localized in cerebellar neurons: Immunofluorescence evidence. Science, 177: 436–438, 1972.

Bloom, F.E., Stone, T.W., and Taylor, D.A. Responses of identified cerebral cortical neurones to cyclic GMP and cyclic AMP. J. Physiol., 246: 103–104, 1974.

Broide, R.S., Redwine, J.M., Aftahi, N., Young, W., Bloom, F.E., and Winrow, C.J. Distribution of histone deacetylases 1–11 in the rat brain. J Mol Neurosci., 31(1): 47–58, 2007.

Chavkin, C., Bakhit, C., Weber, E., and Bloom, F.E. Relative contents and concomitant releases of prodynorphin/neoendorphin-derived peptides in rat hippocampus. Proc. Natl. Acad. Sci. U.S.A., 80: 7669–7673, 1983.

Chu, N-s. and Bloom, F.E. Norepinephrine-containing neurons: Changes in spontaneous discharge patterns during unrestrained sleeping and waking. Science, 179: 908–910, 1973.

de Lecea, L., Kilduff, T.S., Peyron, C., Gao, X.-B., Foye, P.E., Danielson, P.E., Fukuhara, C., Battenberg, E.L.F., Gautvik, V.T., Bartlett, F.S., Frankel, W.N., Pol, A.N., Bloom, F.E., Gautvik, K.M., and Sutcliffe, J.G. The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. Proc. Natl. Acad. Sci. U.S.A., 95: 322–327, 1998.

DeCamilli, P., Ueda, T., Bloom, F.E., Battenberg, E. and Greengard, P. Widespread distribution of Protein I in the central and peripheral nervous system. Proc. Natl. Acad. Sci., 76: 5977–5981, 1979.

Deyo, S.N., Shoemaker, W.J., Ettenberg, A., Bloom, F.E., and Koob, G.F. Subcutaneous administration of behaviorally effective doses of arginine vasopressin change brain AVP content only in median eminence. Neuroendocrinology, 42: 260–266, 1986.

Elmasion, R., Neville, H., Woods, D., Schuckit, M., and Bloom, F. Event-related brain potentials are different in individuals at high and low risk for developing alcoholism. Proc. Natl. Acad. Sci. U.S.A., 79: 7900–7903, 1982.

Ferron, A., Siggins, G.R., and Bloom, F.E. Vasoactive intestinal polypeptide acts synergistically with norepinephrine to depress spontaneous discharge rate in cerebral cortical neurons. Proc. Natl. Acad. Sci. U.S.A., 82: 8810–8812, 1985.

Foote, S.L., Aston-Jones, G., and Bloom, F.E. Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. Proc. Natl. Acad. Sci. U.S.A., 77: 3033–3037, 1980.

Fox, H.S., Gold, L.H., Henriksen, S.J., and Bloom, F.E. Simian immunodeficiency virus: A model for NeuroAIDS. Neurobiol. Dis., 4: 265–274, 1997.

Freedman, R., Foote, S.L., and Bloom, F.E. Histochemical characterization of the neocortical projection of the nucleus locus coeruleus in the squirrel monkey. J. Comp. Neurol., 164: 209–232, 1975.

Gautvik, K.M., de Lecea, L., Gautvik, V.T., Danielson, P.E., Tranque, P., Dopazo, A., Bloom, F.E., and Sutcliffe, J.G. Overview of the most prevalent hypothalamus-specific mRNAs, as identified by directional tag PCR subtraction. Proc. Natl. Acad. Sci. U.S.A., 93: 8733–8738, 1996.

Granholm, A-C., Backman, C., Bloom, F., Ebendal, T., Gerhardt, A., Hoffer, B., Mackerlova, L., Olson, L., Soderstrom, S., Walus, L.R., and Friden, P.M. NGF and anti-transferrin receptor antibody conjugate: Short and long-term effects on survival of cholinergic neurons in intraocular septal transplants. J. Pharmacol. Exper. Therapeutics, 268: 448–459, 1994.

Hoffer, B.J., Siggins, G.R., and Bloom, F.E. Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum: II. Sensitivity of Purkinje cells to norepinephrine and related substances administered by microiontophoresis. Brain Res., 25: 523–534, 1971.

Hoffer, B.J., Siggins, G.R., Oliver, A.P., and Bloom, F.E. Activation of the pathway from locus coeruleus to rat cerebellar Purkinje neurons: Pharmacological evidence of noradrenergic central inhibition. J. Pharmacol. Exp. Therap., 184: 553–569, 1973.

Iversen, L.L., and Bloom, F.E. Studies of the uptake of 3H-GABA and 3H-Glycine in slices and homogenates of rat brain and spinal cord by electron microscopic autoradiography. Brain Res., 41: 131–143, 1972.

Iversen, L.L., Iversen, S.D., and Bloom, F.E. Opiate receptors influence vasopressin release from nerve terminals in rat neurohypophysis. Nature, 284: 350–351, 1980.

Iversen, L.L., Rossor, M.N., Reynolds, G.P., Hills, R., Roth, M., Mountjoy, C.J., Foote, S.L., Morrison, J.H., and Bloom, F.E. Loss of pigmented dopamine-β-hydroxylase positive cells from locus coeruleus in senile dementia of Alzheimer's type. Neurosci. Lett., 39: 95–100, 1983.

Jacobsen, J.S., Wu, C.C., Redwine, J.M., Comery, T.A., Arias, R., Bowlby, M., Martone, R., Morrison, J.H., Pangalos, M.N., Reinhart, P.H., and Bloom, F.E. Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. Proc. Natl. Acad. Sci. U.S.A., 103(13): 5161–5166, 2006.

Jirikowski, G.F., Sanna, P.P., and Bloom, F.E. mRNA coding for oxytocin is present in axons of the hypothalamo-neurohypophysial tract. Proc. Natl. Acad. Sci. U.S.A., 87: 7400–7404, 1990.

Jirikowski, G.F., Sanna, P.P., Maciejewski-Lenoir, D., and Bloom, F.E. Reversal of diabetes insipidus in Brattleboro rat after intrahypothalamic injection of vasopressin mRNA. Science, 255: 996–998, 1992.

Koda, L.Y., Schulman, J.A., and Bloom, F.E. Ultrastructural identification of noradrenergic terminals in rat hippocampus, unilateral destruction of the locus coeruleus with 6-hydroxydopamine. Brain Res., 145: 190–195, 1978.

Lai, C., Brow, M.A., Nave, K-A., Noronha, A.B., Quarles, R.H., Bloom, F.E., Milner, R.J., and Sutcliffe, J.G. Two forms of 1B236/myelin-associated glycoprotein (MAG), a cell adhesion molecule for postnatal neural development, are produced by alternative splicing. Proc. Natl. Acad. Sci. U.S.A., 84: 4337–4341, 1987.

Landis, S.C. and Bloom, F.E. Ultrastructural identification of noradrenergic boutons in mutant and normal mouse cerebellar cortex. Brain Res., 96: 299–306, 1975.

Le Moal, M., Koob, G.F., Koda, L.Y., Bloom, F.E., Manning, M., Sawyer, W.H., and Rivier, J. Vasopressor receptor antagonist prevents behavioural effects of vasopressin. Nature, 291: 491–493, 1981.

Loughlin, S.E., Foote, S.L., and Bloom, F.E. Efferent projections of nucleus locus coeruleus: topographic organization of cells or origin demonstrated by three-dimensional reconstruction. Neuroscience, 18: 291–306, 1986.

Malfroy, B., Bakhit, C., Bloom, F.E., Sutcliffe, J.G., and Milner, R.J. The brain specific polypeptide 1B236 exists in multiple molecular forms. Proc. Natl. Acad. Sci. U.S.A., 82: 2009–2013, 1985.

McGinty, J.F., Henriksen, S.J., Goldstein, A., Terenius, L., and Bloom, F.E. Dynorphin is contained within hippocampal mossy fibers: Immunochemical alterations after kainic acid administration and colchicine-induced neurotoxicity. Proc. Natl. Acad. Sci. U.S.A., 80: 589–593, 1983.

Miller, F.D., Naus, C.C.G., Higgins, G.A., Bloom, F.E., and Milner, R.J. Developmentally regulated rat brain mRNAs: Molecular and anatomical characterization. J. Neurosci., 7: 2433–2444, 1987.

Morales, M., and Bloom, F.E. The 5-HT3 receptor is present in different subpopulations of GABAergic neurons in the rat telencephalon. J. of Neurosci., 17(9): 3157–3167, 1997.

Morales, M., Battenberg, E., de Lecea, L., Sanna, P.P., and Bloom, F.E. Cellular and subcellular immunolocalization of the type 3 serotonin receptor in the rat central nervous system. Mol. Brain Res., 36: 251–260, 1996.

Morrison, J.H., Foote, S.L., Molliver, M.E., Bloom, F.E., and Lidov, H.G.W. Noradrenergic and serotonergic fibers innervate complementary layers in monkey primary visual cortex: An immunohistochemical study. Proc. Natl. Acad. Sci. U.S.A., 79: 2401–2405, 1982.

Morrison, J.H., Rogers, J., Scherr, S., Benoit, R., and Bloom, F.E. Neuritic plaques of Alzheimer's patients contain somatostatin immunoreactivity. Nature, 314: 90–92, 1985.

Nave, K-A., Lai, C., Bloom, F.E., and Milner, R.J. Splice site selection in the proteolipid protein (PLP) gene transcript and primary structure of the DM-20 protein of CNS myelin. Proc. Natl. Acad. Sci. U.S.A., 84: 5665–5669, 1987.

Nicholson, J.L., and Bloom, F.E. Ontogeny of monoamine neurons in the locus coeruleus, raphe nuclei and substantia nigra of the rat. I. Cell differentiation. J. Comp. Neurol., 155: 469–482, 1974.

Nicoll, R.A., Siggins, G.R., Ling, N., Bloom, F.E. and Guillemin, R. Neuronal actions of endorphins and enkephalins among brain regions: A comparative microiontophoretic study. Proc. Natl. Acad. Sci., 74(6): 2584–2588, 1977.

Nimchinsky, E.A., Young, W.G., Yeung, G., Shah, R.A., Gordon, J.W., Bloom, F.E., Morrison, J.H., and Hof, P.R. Differential vulnerability of oculomotor, facial, and hypoglossal nuclei in G86R superoxide dismutase transgenic mice. J. Comp. Neurol., 416: 112–125, 2000.

Oyler, G.A., Higgins, G.A., Hart, R.A., Battenberg, E., Billingsley, M., Bloom, F.E., and Wilson, M.C. The identification of a novel synaptosomal-associated protein, SNAP-25, differentially expressed by neuronal subpopulations. J Cell Biology, 109: 3039–3052, 1989.

Pickel, V.M., Krebs, W.H., and Bloom, F.E. Proliferation of norepinephrine-containing axons in rat cerebellar cortex after peduncle lesions. Brain Res., 59: 169–179, 1973.

Pickel, V.M., Segal, M., and Bloom, F.E. A radioautographic study of the efferent pathways of the nucleus locus coeruleus. J. Comp. Neurol., 155: 15–42, 1974.

Pickel, V.M., Segal, M., and Bloom, F.E. Axonal proliferation following lesions of cerebellar peduncles. A combined fluorescence microscopic and radioautographic study. J. Comp. Neurol., 155: 43–60, 1974.

Polich, J., and Bloom, F.E. P300 from normal and adult children of alcoholics. Alcohol, 4: 301–305, 1987.

Polich, J., Burns, T., and Bloom, F.E. P300 and the risk for alcoholism: Family history, task difficulty, and gender. Alcoholism: Clin. Exp. Res., 12: 248–254, 1988.

Redwine, J.M., Kosofsky, B., Jacobs, R.E., Games, D., Reilly, J.F., Morrison, J.H., Young, W.G., and Bloom, F.E. Dentate gyrus volume is reduced before onset of plaque formation in PDAPP mice: A magnetic resonance microscopy and stereologic analysis Proc. Natl. Acad. Sci. U.S.A., 100: 1381–1386, 2003.

Reilly, J.F., Games, D., Rydel, R.E., Freedman, S., Schenk, D., Young, W.G., Morrison, J.H., and Bloom, F.E. Amyloid deposition in the hippocampus and

entorhinal cortex: Quantitative analysis of a transgenic mouse model. Proc. Natl. Acad. Sci. U.S.A., 100: 4837–4842, 2003.

Robinson, R.G., and Bloom, F.E. Changes in Posterior Hypothalamic self-stimulation following experimental cerebral infarction in the rat. J. Comp. Psych. Physiol., 92(5): xx-xx, 1978.

Robinson, R.G., Shoemaker, W.J., Schlumpf, M., Valk, T., and Bloom, F.E. Effects of experimental cerebral infarction in rat brain: Catecholamines and behaviour. Nature, 255: 332–334, 1975.

Rogers, J., Siggins, G.R., Schulman, J.A., and Bloom, F.E. Physiological correlates of ethanol intoxication, tolerance, and dependence in rat cerebellar Purkinje cells. Brain Res., 196: 183–198, 1980.

Rogers, J., Silver, M.A., Shoemaker, W.J., and Bloom, F.E. Senescent changes in a neurobiological model system: Cerebellar Purkinje cell electrophysiology and correlative anatomy. Neurobiol. Aging, 1: 3–11, 1980.

Rogers, J., Wiener, S.G., and Bloom, F.E. Long-term ethanol administration methods for rats: Advantages of inhalation over intubation or liquid diets. Behav. Neural Biology, 27: 466–486, 1979.

Rogers, J., Zornetzer, S.F., and Bloom, F.E. Senescent pathology of cerebellum: Purkinje neurons and their parallel fiber afferents. Neurobiol. Aging, 2: 15–25, 1981.

Rossier, J., Bloom, F.E., Guillemin, R. Stimulation of human periaqueductal gray for pain relief increases immunoreactive β-endorphin in ventricular fluid. Science, 203: 279–281, 1979.

Rossier, J., Rogers, J., Shibasaki, T., Guillemin, R. and Bloom, F. Opioid peptides and alpha-MSH in genetically obese (ob/ob) mice during development. Proc. Natl. Acad. Sci., 76: 2077–2080, 1979.

Rossier, J., Vargo, T., Minick, S., Ling, N. Bloom, F. and Guillemin, R. Regional dissociation of β-endorphin and enkephalin contents in rat brain pituitary. Proc. Natl. Acad. Sci. U.S.A., 74(11): 5162–5165, 1977.

Ryabinin, A.E., Melia, K.R., Cole, M., Bloom, F.E., and Wilson, M.C. Alcohol selectively attenuates stress-induced c-fos expression in rat hippocampus J. Neurosci., 15: 721–730, 1995.

Schoepfle, G.M., and Bloom, F.E. Effects of cyanide and dinitrophenol on membrane properties of single nerve fibers. Am. J. Physiol., 197: 1131–1135, 1959.

Segal, David S., Browne, Ronald G., Bloom, Floyd, Ling, Nicholas, Guillemin, Roger. β-endorphin: Endogenous Opiate or Neuroleptic? Science, 198: 5411–414, 1977.

Segal, M., and Bloom, F.E. The action of norepinephrine in the rat hippocampus: I. Iontophoretic studies. Brain Res., 72: 79–97, 1974.

Segal, M., and Bloom, F.E. The action of norepinephrine in the rat hippocampus: II. Activation of the input pathway. Brain Res., 72: 99–114, 1974.

Segal, M., and Bloom, F.E. The action of norepinephrine in the rat hippocampus. III. Hippocampal cellular responses to locus coeruleus stimulation in the awake rat. Brain Res., 107: 499–511, 1976.

Segal, M., and Bloom, F.E. The action of norepinephrine in the rat hippocampus. IV. The effects of locus coeruleus stimulation on evoked hippocampal unit activity. Brain Res., 107: 513–525, 1976.

Shorr, S.S., and Bloom, F.E. Acino-insular cells in normal rat pancreas. Yale J. Biol. Med., 43: 47–49, 1970.

Shorr, S.S., and Bloom, F.E. Fine structure of islet-cell innervation in the pancreas of normal and alloxan-treated rat. Z. Zellforsch., 103: 12–25, 1970.

Siggins, G.R., Battenberg, E.F., Hoffer, B.J., Bloom, F.E., and Steiner, A.L. Noradrenergic stimulation of cyclic adenosine monophosphate in rat Purkinje neurons: An immuno-cytochemical study. Science, 179: 585–588, 1973.

Siggins, G.R., Hoffer, B.J., and Bloom, F.E. Cyclic 3'5' adenosine monophosphate: possible mediator for the response of cerebellar Purkinje cells to microelectrophoresis of norepinephrine. Science, 165: 1018–1020, 1969.

Siggins, G.R., Hoffer, B.J., and Bloom, F.E. Studies on norepinephrine-containing afferents to Purkinje cells of rat cerebellum: III. Evidence for mediation of norepinephrine effects by cyclic 3,'5'-adenosine monophosphate. Brain Res., 25: 535–553, 1971.

Siggins, G.R., Hoffer, B.J., Oliver, A.P., and Bloom, F.E. Activation of a central noradrenergic projection to cerebellum. Nature, 233: 481–483, 1971.

Siggins, G.R., Oliver, A.P., Hoffer, B.J., and Bloom, F.E. Cyclic adenosine monophosphate and norepinephrine: Effects on transmembrane properties of cerebellar Purkinje cells. Science, 171: 192, 1971.

Stone, T.W., Taylor, D.A., and Bloom, F.E. Cyclic AMP and cyclic GMP may mediate opposite neuronal responses in the rat cerebral cortex. Science, 187: 845–847, 1975.

Sutcliffe, J.G., Milner, R.J., Bloom, F.E., and Lerner, R.A. Common 82-nucleotide sequence unique to brain mRNA. Proc. Natl. Acad. Sci. U.S.A., 79: 4942–4946, 1982.

Sutcliffe, J.G., Milner, R.J., Shinnick, T.M., and Bloom, F.E. Identifying the protein products of brain-specific genes with antibodies to chemically synthesized peptides. Cell, 33: 671–682, 1983.

Travis, G.H., Naus, C.G., Morrison, J.H., Bloom, F.E., and Sutcliffe, J.G. Subtractive cDNA cloning and analysis of primate neocortex mRNAs with regionally-heterogeneous distributions. Neuropharmacology, 26: 845–854, 1987.

Trembleau, A., and Bloom, F.E. Enhanced sensitivity for light and electron microscopic in situ hybridization with multiple simultaneous non-radioactive oligodeoxynucleotide probes. J. Hist. Cytochem., 43(8): 829–841, 1995.

Trembleau, A., Morales, M., and Bloom, F.E. Aggregation of vasopressin mRNA in a subset of axonal swellings of the median eminence and posterior pituitary: Light and electron microscopic evidence. J. Neurosci., 14: 39–53, 1994.

Van Orden, L.S., Bloom, F.E., Barrnett, R.J., and Giarman, N.J. Histochemical and functional relationships of catecholamines in adrenergic nerve endings: I. Participation of granular vesicles. J. Pharmacol., 154: 185–193, 1966.

Wedner, H.J., Hoffer, B.J., Battenberg, E., Steiner, A.L., Parker, C.W., and Bloom, F.E. A method for detecting intracellular cyclic adenosine monophosphate by immunofluorescence. J. Histochem. Cytochem., 20(4): 293–295, 1972.

Weiss, F., Lorang, M.T., Bloom, F.E., and Koob, G.F. Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: Genetic and motivational determinants. J. Pharmacol. Exper. Therap., 267: 250–258, 1993.

Wu, C-C., Chawla, F., Games, D., Rydel, R.E., Freedman, S., Schenk, D., Young, W.G., Morrison, J.H., and Bloom, F.E. Selective vulnerability of dentate granule cells prior to amyloid deposition in PDAPP mice: Digital morphometric analyses. Proc. Natl. Acad. Sci. U.S.A., 101: 7141–7146, 2004.

Yang, T., Gallen, C.C., Schwartz, B., and Bloom, F.E. Noninvasive somatosensory homunculus mapping in humans by using a large array biomagnetometer. Proc. Natl. Acad. Sci. U.S.A., 90: 3098–3102, 1993.

Zieglgansberger, W., French, E.D., Siggins, G.R., and Bloom, F.E., Opioid peptides may excite hippocampal pyramidal neurons by inhibiting adjacent inhibitory interneurons. Science, 205: 415–417, 1979.

Reviews and Texts

Bloom, F.E. *The Gains in Brain Are Mainly in the Stain.* In The Neurosciences: Paths of Discovery. Worden, F.G, Swazey, J.P., and Adelman, G., Eds. MIT Press, Cambridge, 1975, pp. 211–227.

Bloom, F.E. The role of cyclic nucleotides in central synaptic function. Rev Physiol. Biochem. Pharmacol., 74:1–103, 1975.

Bloom, F.E. To spritz or not to spritz: The doubtful value of aimless iontophoresis. Life Sci., 14(10): 1819–1834, 1974.

Cooper, J.R., Bloom, F.E., and Roth, R.H. The Biochemical Basis of Neuropharmacology. Oxford University Press, Oxford, 8th Edition, 2003, p. 405.

Moore, R.Y., and Bloom, F.E. Central catecholamine neuron systems: Anatomy and physiology of the dopamine systems. Annu. Rev. Neurosci., 1: 129–169, 1978.

Moore, R.Y., and Bloom, F.E. Central catecholamine neuron systems: Anatomy and physiology of the norepinephrine and epinephrine systems. Annu. Rev. Neurosci., 2: 113–168, 1979.