The History of Neuroscience in Autobiography
Volume 6

Edited by Larry R. Squire
Published by Society for Neuroscience
ISBN: 0-12-538010-1

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pp. 0–31

https://doi.org/10.1093/acprof:oso/9780195380101.003.0001

Bernard W. Agranoff

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June 26, 1926

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University of Michigan, B.S.
Wayne State Medical School, M.D. (1950)
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Appointments:

Laboratory of Neurochemistry, National Institute of Neurological Diseases and Blindness (1954–1960)
Mental Health Research Institute and Department of Biological Chemistry, University of Michigan (1960–2003)
Director, MHRI (1985–1995)
Director UM Neuroscience Research Building (1983–2002)
Ralph Waldo Gerard Professor of Neurosciences in Psychiatry (1995–2003)

Honors and Awards (Selected):

President, American Society for Neurochemistry (1973)
Fogarty Scholar-in-Residence, NIH (1988)
Henry Russell Lecturer, University of Michigan, (1988)
Chairman, International Society for Neurochemistry (1989)
Institute of Medicine (1991)
Distinguished Alumnus Award, Wayne State University (1993)
American Academy of Arts and Sciences (2002)

Bernard Agranoff initially became known for his elucidation of the enzymatic synthesis of inositol lipids via the liponucleotide precursor CDP-diacylglycerol, a crucial step in signal transduction cycling. He also pioneered studies in memory and more generally neuroplasticity. His behavioral studies in the goldfish employed puromycin and other inhibitors of macromolecular synthesis to demonstrate that acquisition of a light coupled-to-shock avoidance task did not require ongoing brain protein synthesis, whereas in contrast, long-term memory formation did. He and his colleagues demonstrated the decay of short-term memory as well as an environmental trigger that initiated the memory fixation process. He also employed the goldfish visual system to identify proteins associated with nerve regrowth and synaptogenesis in the adult vertebrate brain following optic nerve crush.

Bernard W. Agranoff

After looking through autobiographies of fellow neuroscientists in this series, as well as those of fellow biochemists elsewhere, I find that my childhood is not as unique as I had thought: son of Jewish immigrants from Eastern Europe, influenced in my teens by books about biomedical discoveries, and so on. Yet, from our origins, each of us travels a different path. My research career unfolded in the last half-century during which neuroscience arose as a discipline. I will relate here how I became a biochemist, a neurochemist, and then a neuroscientist. Now, in my retirement, I am honored to have been invited to share my reminiscences. I apologize in advance for errors or omissions that may have crept into or out of my memory.

Early Years

I was born in Detroit, Michigan, in 1926, the youngest of three, with an older sister, and a brother who died in infancy. My mother was born in Dovid Horodok, a shtetl near Minsk. She crossed the ocean alone and disembarked at Ellis Island. She then traveled to Detroit, where an older brother and other relatives preceded her. She soon found work as an assistant in the Detroit Public Library. My father was born in Pogorelitz, a village in the Ukraine near Kiev. He came to Detroit in his teens around 1910. He entered the United States at Galveston, Texas, and found his way to Detroit, where he had relatives. He soon was happily on the Ford Motor Company assembly line, a beneficiary of the Henry Ford $5-a-day policy. He eventually had a job at Parke, Davis and Company as a shipping clerk, then in partnership with his brother started a grocery store that was to sustain our families for the next 40 years. We lost our home during the Great Depression and lived in rented flats thereafter but never went hungry.

My parents had met through a circle of friends who can best be described as Yiddish-speaking immigrant anarchists (not communists, to my good fortune, as will be elaborated). In retrospect, they were hard-working, independent-thinking, secular Jews. They shared a common atheistic bent, were married in civil ceremonies, but were unlikely to have wed a gentile. None of them, including my mother, wore a wedding ring. Our parents spoke Russian only occasionally, as an infuriating parental secret code. My mother was a "culture vulture," and I am grateful now for the concerts and plays, English and Yiddish, to which we were dragged. She was an ardent supporter of

territorialism, a movement seeking to establish a Jewish Homeland. I recall Tasmania and Uganda, among other suggestions. I'm sure that part of the appeal for her was the secular nature of Jewish territorialism. The movement declined sharply in 1948, when Israel was recognized as a Jewish state. Like most neighbors, my parents loved Roosevelt, and we listened together on the radio to his "Fireside Chats."

I attended public schools but also went to a secular Yiddish school for an hour each day after public school let out. I learned to read and write in Yiddish. In our high school years, we had classes on weekends, reading Yiddish newspapers and novels, occasionally slightly sexy ones that alleviated the boredom. We read the Old Testament, translated into Yiddish, as literature.

My mother was loving, intelligent, a good cook, and had a great sense of humor, shared with my father. There was often much laughter among us. Unfortunately, she suffered off and on from severe depression. She was subjected to various treatments, including electroshock and insulin shock therapies, and convalescent stays. There were no mood-modulating drugs other than barbiturates and bromides for insomnia. During such periods, it was hard on all of us, off to school or work, leaving her at home alone, disconsolate. This may have influenced my sister's decision to become a psychiatric social worker and resulted in my being exposed by osmosis to the mysteries of psychoanalysis and psychobabble, perhaps replacing a craving for occult fantasies that religion might have provided. For me, this fitted in well with my aunt Anna's library. Anna, like my mother, was an assistant librarian at the Detroit Public Library. She lived nearby and had a large, crammed bookcase. Only many years later did it occur to me that much of her home library must have consisted of deacquisitioned public library books that now served a purely decorative role. There were books on Mesmerism, phrenology, and animal magnetism that piqued my curiosity and engendered an interest in the mind and the brain. I tried hypnotizing myself and some of my friends without success.

I had two major interests growing up: art and science. My sister was a born musician. She began playing the piano by ear at age 3 or 4 and had a beautiful singing voice. I had no such talent but staked out drawing and painting for which I had some talent. This landed me in a Saturday morning art class in the Detroit Institute of Arts for 20 or so lucky city school students, who were given unlimited access to art supplies and, should we request it, guidance. Across Woodward Avenue from the Art Museum was the Main Public Library. There was a room filled with U.S. patents that fascinated me, and I thought that maybe I would be an inventor. I was especially into stratospheric balloons and rockets (a Jules Verne influence). My major passion was chemistry, learned almost entirely from library books. Like several of my friends, I had set up a little lab in our basement and bought, traded, or blew my own glassware and scrounged chemicals from pharmacies and local

commercial vendors. A common pursuit among budding basement chemists was, of course, making explosives, starting with gunpowder, as well as stink bombs and hydrogen gas to put into balloons that were launched with stamped postcards, This was back in the Zeppelin days, before helium became freely available.

When I was about 14, I learned of a college student, about 6 years my senior, who lived across Monterey Street who, it was rumored, once had a basement chemistry lab. I was interested in what he might be willing to sell or give me, but we didn't connect until 20 years later when we met in Washington, D.C., as fellow neurochemists. Eugene Roberts (see Volume 2 in this series) is well known for his elucidation of the structure and function of γ-aminobutyric acid (GABA) and more generally for his keen insights over the years into the molecular basis of brain function and dysfunction. We met thereafter at various scientific committees and meetings and remain close friends. Each of us served as president of the American Society for Neurochemistry. The nearby public schools from elementary through high school were of high quality, but my closest friends and I opted to attend Cass Technical High School, three of them in the Science curriculum, and I in Art, actually called Commercial Art.

Two disturbing events during that first semester in the fall of 1941 stand out in my memory. The first relates to my first day of classes in a course titled Mathematics for Art Students. The teacher, who had written a textbook of the same name, stood at the blackboard, having drawn two triangles that she declared to be similar. I raised my hand and asked what the proof was? She answered, "You feel it in your bones." I was able to switch to the Science curriculum math course that day but was already shaken regarding my choice of the Art curriculum. I found myself unhappily drawing letter fonts, not what I had envisioned as part of becoming an artist. On the positive side, there was a wonderful art history course, in which a competent and enthusiastic teacher reviewed the emergence of art, primarily architecture, by means of hundreds of beautiful lantern slides, from Egyptian, Grecian, and Roman eras, through the middle ages, renaissance, and on to the twentieth century.

The second event occurred a day after the Sunday, December 7, 1941, when Japanese aircraft launched a surprise attack on Pearl Harbor. On Monday morning, our art curriculum homeroom teacher instructed the 20 or so of us 15-year-olds to pull our stools into a semicircle. She then launched into a venomous racial rant that even outrage over the attack could not justify. Her tirade, and a lack of any disbelief or embarrassment I could infer on the part of my fellow art students, reinforced my conclusion that I needed to reconsider my educational prerogatives. I switched to the Architecture curriculum, which replaced my tedious lettering with drafting. I should add that neatness was not my forte. Fortunately, by the time I graduated, I had been able to finish 3 years of chemistry, 2 of math, as well as a year each of

Physics, Biology, and Bacteriology, all with excellent grades, more than satisfying the requirements for graduation, but not for college entry, because I had not fulfilled a foreign language requirement. This was not a worry for me, because I would turn 18 in the month I graduated, and would doubtless soon be serving in the armed forces. Military service against the Nazi-led Axis in World War II was clearly a just cause. I applied to the Air Force Cadet program, under the assumption that my envisioned demise by plummeting from the sky would be more merciful than would be sinking into infantry mud. There was a long shot—the Navy V-12 program that would send one directly from high school to an officer's training program at a university. I would guess that a third or more of the males in our graduating class of about 500 applied for this. I saw my chances as bleak, based on poor grades as an art/ architecture student during my first year of high school, and a neurasthenic, unathletic affect that probably didn't look much like one's concept of officer material. In addition, the Navy required a supporting letter from a clergyman. I managed to get a letter from my (atheistic) Jewish school teacher but was not hopeful that it would withstand scrutiny. I was thus pleasantly surprised to learn from our Monterey Street neighbors that federal agents had made inquiries about my family's political affiliations—my application was being considered! The agents were looking for possible communists in our family who might also be enemy foreign agents, as the USSR had initially been allied with Germany. This remained an issue even after Russia had been invaded in Hitler's Operation Barbarossa (by then 1944). Sometimes the enemy of your enemy is still your enemy.

Our neighbors reassured the feds that we were merely socialists or anarchists, and that apparently made everything O.K. At any rate I was even more amazed when a thorough physical exam found me to be fit. I believe I was one of only two graduating seniors to be admitted to the V-12 program. During the enlistment process, I discovered that what I thought was my birth certificate was just a souvenir from the hospital. When I obtained a valid one from the State, I found out that I had a middle name, my father's. It was a surprise to all of us.

Thus, a week after my high school graduation, I found myself living in a University of Michigan dormitory in Ann Arbor, 30 miles from Detroit, in a white sailor suit, ideal for hitch-hiking home on weekends, and uncertain of how, or whom, to salute. I was an apprentice seaman in the U.S. Navy and a freshman at the University, one of about 15 V-12'ers in an accelerated premedical program that was to put us in medical school in 2 years.

I had not envisioned a career as a physician. On the other hand, as alluded to in my introduction, I had indeed been inspired in my early teens by two books: *Arrowsmith*, by Sinclair Lewis, which dealt with a scientist who discovered bacteriophage, and *Microbe Hunters* by Paul de Kruif, which described the exciting discoveries of Louis Pasteur, Robert Koch, Ehrlich, and many others. Only later did I learn that Lewis and de Kruif had been acquaintances

at the University of Michigan and had inspired one another regarding the thrill of biomedical research. The fictional Dr. Max Gottlieb in *Arrowsmith* was said to be the combination of bacteriologist Frederick Novy and chemist Moses Gomberg, both world-acclaimed professors at the University at the time. In October of 1945, 16 months after I entered the Navy, the war was over, and I suddenly became an impoverished undergraduate student, living in an Ann Arbor student co-op. I worked part-time in the Chemistry Building, filling student laboratory reagent bottles at night, and occasionally dispensing supplies from the Chemistry Building store. I was thrilled to fill an order (I recall it was for ammonium chloride) for a pleasant emeritus professor—it was Moses Gomberg!

I learned that I would have to wait at least a year for entry into the UM Medical School. I surmised that there were many returning Jewish war veterans who filled the unspoken Jewish quota and decided, rather than wait, to attend Wayne State Medical School, a decision that had the additional financial advantage of free room and board with my parents, and more opportunities for part-time work as an "extern" at night in various small Detroit hospitals during my last 3 years of medical school. Most of my medical school classmates were war veterans, 4 to 10 years my senior, and academically a bit rusty. I found medical school unexciting and reconsidered my future. I made plans to drop out after my second year, to pursue a future in histochemistry, a quest that began with my infatuation with the beauty and the mystery of stained eosinophilic white blood cells. What were those microscopic red jewels made of? I lined up a graduate student fellowship at the University of Minnesota but was dissuaded by my Professor of Medicine, who urged me to finish the M.D. degree before pursuing my scientific interests. My girlfriend at the time concurred. Professor Gordon Scott, who taught my Histology course, took an interest in me and arranged for me to spend the summer of my sophomore year in the laboratory of Anatomy Professor Ernest Gardner, looking for stained nerve endings in joint capsules of cats.

My third-year clinical lectures were boring, but to my surprise I enjoyed seeing and treating patients, in the medical school setting and moonlighting as an extern. I was thrilled on the rare occasions when I detected a major treatable medical condition that had been overlooked. I interned at the Robert Packer Hospital and Guthrie Clinic in Sayre, PA. Its attractions for me included a month's rotation in a Pathology laboratory. There were connections with the Mayo Clinic, should I elect further clinical training. Last, the rustic setting appealed to me. In a few months, I disabused myself of a fantasy that I could spend my life as a country doctor, although I did become enthusiastic about horseback riding in the beautiful surrounding hillsides. During that internship year, my father came out to visit me. I was delighted and touched. He was a kind person, worked hard, and was worn down by my mother's illness, leaving little time for dad and son time, growing up. We had some good talks in Sayre that made up for years of uncommunicativeness.

Over the year, I came to recognize that my future was to be in experimental bioscience and preferably in an urban setting. I contacted Dr. Scott (he eventually became Dean of Wayne State Medical School), who had offered to help me should I opt for a research career. He suggested the names of two colleagues from his past: Keffer Hartline at Johns Hopkins University, and Francis O. Schmitt, at MIT. I decided to visit MIT first, and was so impressed with the fancy and massive equipment that I might be able to put my mitts on, such as the electron microscope and the analytical ultracentrifuge, that I did not look further. Some of this love of big equipment I attribute to the elusive toy electric train I campaigned for unsuccessfully as a child.

I arrived in Cambridge, Massachusetts, in the fall of 1951 pretty much broke but had lucked into the position of night physician at the MIT Homberg Infirmary before arriving. This took care of my room and board. I would take an elevator in what was then the main MIT building to the "roof level," where the elevator lobby opened into a single room and bath, with the Infirmary one flight down. There were usually two to five students in the Infirmary with flu or stomach upset, and the occasional appendicitis, which in the latter instance meant that I'd do a white blood cell count and, if high, contact an on-call surgeon to confirm the diagnosis and ship the patient off to a hospital. I continued this until I was able to secure a research fellowship. I recall being interviewed before a sizeable group of reviewers at a conference room in the Roosevelt Hotel in Manhattan. My application was directed at training in basic research in the nervous system but was not very specific. I was asked why The Infantile Paralysis Foundation (now March of Dimes) should sponsor me. I responded that only by training more basic research scientists would the treatment or prevention of polio be advanced. There was a silence, followed by a perfunctory "thank you very much." I interpreted this as a death knell for the application. To my surprise, it was awarded. That permitted me to devote more of my time to graduate study and uninterrupted sleep. Schmitt, my sponsor, was also Chair of the Department of Biology. The departmental research emphasis was on ultrastructure of proteins, using mostly biophysical techniques. The study of proteins of the giant axon of the squid, as well as of collagen and myosin from various other sources, were major themes. There was little research on living creatures or even on cultured cells. I recall a framed sign on the wall over the desk of one of the postdoctoral fellows that said it all: "If it moves, step on it."

Schmitt and I agreed on several graduate courses that I would take, including a physics course for MIT students from elsewhere, a physiology course on size and shape of proteins, electron microscopy and physical chemistry, but not the biochemistry course, which at that time was part of the departmental Microbiology program. Although I had not considered going for a Ph.D., at Schmitt's suggestion I took and passed the graduate prelim exam. After I delivered a graduate seminar on the physical properties of white blood cells, including my beloved eosinophil, Bert Vallee, a faculty

member, approached me about a possible research project to physically separate white cells. I was happy to get my hands wet and devised a differential centrifugation method on a sucrose gradient that we eventually published. I never did get back to the eosinophil. My future plans were curtailed by the Korean conflict (war). It seems that my V-12 stint had included an obligation to serve as a Naval physician if called up. The Navy was quite good about delaying my orders to report for duty, but then my draft board insisted that I report for induction as an Army private. When it became clear to me that they meant business, I reluctantly asked the Navy to reissue my orders, cutting my stay at MIT short. In October 1952, I reported to the Naval Medical School in Bethesda, Maryland, as a naval officer.

Bethesda: The Naval Medical Center, Then National Institutes of Health

It turned out that I had been assigned to what was then called the Naval Medical School to lecture on topics in medical biochemistry, such as acid-base balance, laboratory tests, and so on. This was part of a refresher course for Navy physicians, who were delighted with a month or two of respite from sea duty. The chemistry lab was responsible for all of the hospital blood analyses, and miscellaneous other duties, including supervising the hospital's blood drawing facility, and training courses for Navy lab techs. Mostly, we let experienced petty officers who knew the ropes do their thing, and to step in when a Medical Officer's approval was needed.

My predecessor as Officer-in-Charge was Roscoe Brady, who had been researching fatty acid synthesis at the University of Pennsylvania, and was also fulfilling a 2-year military obligation. When his tour of duty was over, he moved across the road to the National Institutes of Health (NIH) to join a large newly established Laboratory of Neurochemistry as head of a Section on Lipid Chemistry. The Scientific Director of the new facility was Seymour S. Kety, famous for his development and application of the nitrous oxide method for measuring cerebral brain flow. He was, in addition, Scientific Director of the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness. This is described in detail in the autobiographies of Seymour Kety, and also of Louis Sokoloff (both are in Volume 1 of this series). When my tour of duty was over, I accepted an offer from Brady to join his Section on Lipid Chemistry. This appealed to me more than did the option of returning to MIT. My immediate neighbors on the third floor of the newly constructed Building 10 of NIH included Alex Rich's Section on Physical Chemistry, Kety's (later Sokoloff's) Laboratory of Cerebral Metabolism, and Giulio Cantoni's Laboratory of Cellular Pharmacology. An orthogonal wing of the third floor housed the Laboratories of Biophysics, and Neurophysiology, which included the laboratories of Ichiji Tasaki, "K. C." Cole, and Wade Marshall. The geographical separation of the

neurochemical and neuropharmacological sections from the biophysical and electrophysiological sections mirrored a long tradition in brain research that has been referred to as "soups" and "sparks" (see section on Gerard). We had in common a bank of elevators. The new labs at NIH included psychologists and anatomists, including Bill Windle, also in Building 10, and a bit more distant, geographically and otherwise. Some 10 years later, we would all be referred to as neuroscientists. Much later, in 1988, I was a Fogarty Scholar-in-Residence at the NIH. We lived in the same apartment house as Seymour and Josie Kety and got to know and enjoy their company again after a 30-year hiatus.

The years from the fall of 1954 to the fall of 1958 were busy ones for me at NIH. I had the freedom to engage in a project of my choosing, preferably one having relevance to the brain, lipids, or both. Most important, it was expected that findings would be written up, approved, and coauthored by Brady, my section chief, and would be published in a respected journal. A prior interest in carbohydrate metabolism led me to an unsolved mystery: how inositol lipids were synthesized. This was an exciting problem to me for many reasons. The brain was known to be enriched in phosphoinositides, and I found the stereochemistry of inositol, its isomers, and their phosphate esters intriguing. The laboratory of Eugene Kennedy had already made the important discovery that cytidine nucleotides played a central role in the formation of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine, but how phosphatidylinositol and its further phosphorylated family members were formed remained an enigma. An added point of great interest to me was the report of Hokin and Hokin (1953) that carbamylcholine stimulated the incorporation of radiolabeled inorganic phosphate selectively into phosphatidylinositol in pancreatic tissue slices. The concentrations of carbamylcholine required to produce this effect were high (millimolar), casting doubt on the physiological significance of the effect. However, it was blocked by 10 micromolar atropine, an indication to me that their observations had great physiological relevance.

After many false leads, I experienced that rare eureka moment that was at once exhilarating and fulfilling. I had initially assumed that a hypothetical cytidine diphosphate (CDP)-inositol would react with diacylglycerol to form phosphatidylinositol in analogy to the biosynthesis of the other known phospholipids. My results suggested otherwise: They were compatible with the existence of a cytidine liponucleotide intermediate that would react enzymatically with free inositol, with the production of phosphatidylinositol and cytidine monophosphate (CMP). I performed the critical experiment with a fragile sense of confidence. When it worked out as predicted, I felt at last that I was a player in the game of biochemical research. Brady was not directly involved in the research project or writing the paper but wisely insisted that I submit the paper before going off for a year on an NIH off-campus assignment to work in the laboratory of Feodor Lynen, in the

fall of 1958. During that year away, Kennedy's lab confirmed the proposed liponucleotide intermediate and its role in phosphatidylinositol synthesis. I could have been scooped.

Many other events important for me transpired in those first 4 years at NIH. In those early days, the NIH Library was also in Building 10, and I routinely spent Saturday mornings scanning the latest journals. I was also looking for ways to more directly relate my research to brain function. One such morning, I read what was then known about Miltown (meprobamate), a blockbuster prescription drug described as a tranquilizer. Despite the fact that it was being prescribed widely, nothing had been reported regarding its disposition in the body. It appeared to be a highly stable lipophilic molecule, the dicarbamate of a branched-chain propanediol. I was sure it would be excreted pretty much intact.

I consulted a pharmacologist neighbor in Building 10 who was pretty much a one-man operation at NIH and who had received his doctorate only after he had published independently. I told him that I was able to produce a colored product by heating the drug in sulfuric acid but was disappointed that it wasn't fluorescent and would not lead to a sensitive assay. He convinced me that the visible spectrum would suffice and agreed it mostly likely would be excreted largely intact, as a glucuronide. So I swallowed four Miltowns, collected my urine for several days, added glucuronidase to samples, extracted the lipid material with ether, reacted it with sulfuric acid, and voila, a paper by me, my technician, and Julius Axelrod (14 years before he won the Nobel Prize, not for this!) with the first evidence of human metabolic disposition of meprobamate (using an *N* of 1, myself).

This paper had an interesting consequence. Some months later, a tall slim reddish-haired man stormed into my lab module, shouting with a Germanic/Balkan accent, "I am looking for Berrrnard Agrrranoff." He was Frank Berger, "Mr. Miltown," president of Wallace Laboratories, who was visiting NIH, and had decided to look me up. He was grateful for what we had done and invited me to consult with his company, which I did, once I left the Public Health Service. He enters my story by way of a meeting he organized in 1956 at the New York Academy of Sciences on Meprobamate (Miltown). As it happened, I had been radiolabeling a number of substances of interest by "Wilzbaching," subjecting them to highly radioactive tritium gas, which resulted in displacement of covalently linked hydrogen atoms by tritium. One of the substances that I labeled was meprobamate. At the meeting, I heard a talk by Eckhart Hess of the University of Chicago on the effects of meprobamate on imprinting of ducklings. I had been searching for an animal model of memory that could be studied biochemically, and imprinting ducklings sounded attractive. Hess offered to show me his setup in a bird sanctuary that by my good fortune was located in nearby Maryland. I was impressed with the demonstration and accepted his offer of a few eggs near hatching along with

instructions about how to imprint the newly hatched ducklings. I took the eggs back to my NIH lab and, as instructed, I was the first moving thing the ducklings saw after hatching. As I walked away, they followed. In fact they subsequently followed anyone with a long white lab coat, with preference for males. On further consideration of proceeding further, I concluded that though meprobamate prolonged the period in which the ducklings could be imprinted, this was likely a nonspecific effect of delaying an anxiety response, and was not specifically related to memory formation. I also disabused myself of the naïve idea that labeled meprobamate would be localized in brain regions directing the imprinting response. Our dishwashing assistant was not enthusiastic about cleaning the duck cages, and eventually "a place in the country was found for them," a fate that befell some Easter chicks of my childhood. My initial foray into animal behavior had failed.

In March of 1957, I met a beautiful and charming young woman at a party. We went on many walks through Georgetown, talking into the wee hours about her childhood in Boston, of living in the Philippines for several years with her father, and our many mutual interests. Ricky (Raquel Schwartz) and I were married that September, and a year later, we were off for a year in Germany.

Munich

The Max Planck Institut für Zellchemie was then located in central Munich, and I was privileged to participate in an exciting race to elucidate the biosynthesis of cholesterol. Feodor Lynen was a brilliant and inspiring scientist, with a good sense of humor. By the end of the year, he was a good friend as well. In addition to work, the year provided a good way to improve my German language skills. Before leaving for Europe, I contacted Lyle Packard of Packard Instruments to locate a liquid scintillation counter near Lynen's Institute. There indeed was one, in a Munich hospital. This information, my experience in scintillation counting, and the generosity of the hospital proved helpful during the year in counting radioactivity in volatile metabolic intermediates. I worked on the isomerization of a terpene precurser, isopentenyl pyrophosphate to dimethylallyl pyrophosphate, an early step in the biosynthesis of sterols, including cholesterol.

We were fortunate to be able to travel on weekends to neighboring Austria, Switzerland, France, and Italy in our VW convertible. In the summer, we drove and camped our way to Ricky's father and family in Barcelona. During this year, my budding interest in behavior was on hold. However, I did manage to visit Konrad Lorenz, who was a neighbor of Lynen in the outskirts of Munich. I am hazy on the details of our discussion, but fish behavior did come up because I remember him telling me that he had been bitten by a parrotfish while swimming.

When we returned to Bethesda, it became clear that it was time to move on. My working relationship with Brady had soured, and I wanted to be on my own. Prospects for new independent positions at NIH were some years off.

I look back at my NIH years as happy ones. The community was filled with bright scientists, senior and junior. Guilio Cantoni's journal club and the meetings of the NIH-Johns Hopkins Enzyme Club were informative and convivial. We had many good friends. Even so, I began to explore possible moves.

Moving to Ann Arbor

I was attracted by an offer at the University of Michigan. I knew and liked Ann Arbor. In addition, my parents were getting on and still lived in Detroit, and I felt Ricky and I could be of help when needed. The offer was from the University of Michigan's Mental Health Research Institute, a wide-ranging microcosm of academia put together by James G. Miller, an M.D./Ph.D. psychiatrist, and psychologist, who left the Psychology Chair at the University of Chicago to form the Institute in 1955 under the aegis of Raymond Waggoner, Chair of Psychiatry at the University of Michigan Medical School. Miller brought with him several University of Chicago colleagues, among them Ralph W. Gerard, as Director of Laboratories.

Ralph Waldo Gerard

I interrupt my narrative to pay homage to the remarkable man who offered me the position. Gerard had been a *bona fide* child prodigy, receiving his Ph.D. from the University of Chicago when he was 21. Among his many discoveries, he is perhaps best known for developing the microelectrode together with Gilbert Ling. He also wrote several well-received readable books that clearly presented what was then known about cellular biology and especially about the brain. I had first heard him speak at scientific meetings in Washington, D.C., in the mid-1950s. He spoke unhesitatingly, without notes and in measured tones, as if from a script. When asked in advance for a manuscript, he would suggest that his words be recorded and transcribed. The commas and periods seemed in place, and no infinitives had been split. Gerard was frequently invited to present a summary of a morning or afternoon program. His genius shone; without notes, he would accurately restate each speaker's salient points, often better than did the speaker, and would weave the talks together into an aesthetic whole. If you had the temerity to ask a question after he spoke, as I once did, you took your life in your hands—he cut me off at the knees.

It was thus with some apprehension that I entered my interview with him in Ann Arbor. Fortunately, he seemed not to remember me. I was also a bit concerned that he might press me into a scientific collaboration at a time that I was looking forward to being completely independent. There was no problem. Ralph was, and remained, cordial and helpful. He was at the

time engaged in a large project at a state mental hospital that involved extensive questionnaires, laboratory tests and measurements, and by design without an hypothesis. Answers were to appear via correlations, using a new and magical tool: the computer, and tens of thousands of punch cards. The approach seems inelegant today, but in the late 1950s it was cutting-edge stuff to psychiatrists. Gerard also kept a small lab and, with a student, was developing a spinal learning paradigm in frogs. He asked me for advice about a possible biochemical intervention. I recommended trying 8-azaguanine, based on studies by Dingman and Sporn (1961; also cited by Sam Barondes in Volume 5 of this series). I first heard from Ralph about the historical "soups and sparks" dichotomy in approaches to understanding neurotransmission. The "soups" were the biochemists and pharmacologists, who identified chemical messengers, and the "sparks" were the neurophysiologists who recorded nerve impulses. The orthogonal corridors on the third floor of Building 10 at the NIH came to mind. It is unclear who originated the "soups and sparks" phrase (perhaps it was Gerard), chronicled by Valenstein and also by Van der Kloot, who credits Ling and Gerard's micropipets as key in demonstrating chemical transmission at the synapse and resolving the issue. Gerard had been well prepared in both camps. After completing his Ph.D. and M.D., he studied nerve impulses in the laboratory of A. V. Hill in Cambridge, England, then nerve metabolism in the laboratory of renowned biochemist Otto Meyerhof, in Germany. In his travels, Gerard also visited Ivan Pavlov in Moscow, and shortly thereafter Sigmund Freud, in Vienna. Three years after I came to Ann Arbor, Gerard left to become Dean of Graduate Studies at UC Irvine, where he remained until his death in 1974.

A Dual Research Career

For me, an attraction of the Michigan offer was that I would have a tenured joint appointment in the Department of Biological Chemistry and could remain a card-carrying biochemist, and at the same time wade into murky waters, that is, to pursue my conviction that biochemistry could make an important contribution to our understanding of behavior. Because my labs were in the Institute rather in Biological Chemistry Departmental space, I would be spared the possible embarrassment of being categorized by my biochemist colleagues as an odd duck or as it turned out, a strange fish. I found the lab space I was being offered more than adequate, but somewhat isolated. I suggested the Institute also recruit Norman Radin, a colleague I had met through Federation of American Societies for Experimental Biology (FASEB) and other meetings, who studied brain glycolipids, then at Northwestern University in Chicago. This worked out very well.

Thus I began my independent professional life with two divergent interests: phospholipids and behavior, with precious little overlap. I had no idea this would continue for my entire professional career. It was a bit like Sophie's choice: which child would I desert? I have cautioned my students and postdoctoral

fellows not to pursue this double research strategy. "Do as I say and not as I do!" In today's climate of restricted grant support, I probably would not have so easily been able to pursue divergent interests. Shortly after arriving, I applied for and was awarded an NIH grant to further explore phospholipids. I also began to consider how I would at last get into brain and behavior. I began by determining the amounts of total deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in brain tissue. Quantitative methods then used were based on phosphorus content and worked well for DNA and RNA of most organs but were troublesome in brain. We found this was mostly due to the contamination of nucleic acid preparations with the very acidic phosphoinositides. We devised a new method that worked well for rat brain. To apply the method, I turned to Tryon maze-bright and maze-dull rats that were being bred and studied anatomically by David Krech, Mark Rosenzweig, and their collaborators. Mark suggested sending me frozen brains, but I preferred, and he agreed, that he send me live rats because I was concerned about the time interval following death that the brains would be frozen. I was surprised to see that the two inbred strains that he sent us looked very different in appearance. My naïve concept of specific genes that regulated maze behavior quickly evaporated. We found no significant differences in total brain DNA or RNA between the two strains.

Flatworms and Memory Transfer

Shortly after coming to Ann Arbor, I met Jim McConnell, a psychologist who had attracted considerable attention as a result of his behavioral experiments on the flatworm, planaria. The paradigm was simple. Light from a gooseneck lamp over a small glass dish containing a planarian was paired with an electric shock administered through the water, resulting in a whole body contraction. After many trials, the worms were reported to have been conditioned: they "scrunched up" following light alone. McConnell further claimed that if trained worms were cut in half, and the head and tail segments were allowed to regenerate so that each formed a complete planarian, both regenerated halves displayed the trained response. Additional variants, including feeding chopped up bits of trained worms to naïve ones, reportedly worked as well. Much of this was published in McConnell's *Worm Runner's Digest*, a circulated pamphlet/periodical with separate experimental findings and humor sections.

I observed inexperienced undergraduate students collecting data firsthand. They were motivated to get positive results and, in my opinion, were poorly monitored to boot. I concluded that the results I saw being gathered from McConnell's lab were untrustworthy. Yet I remained hopeful that these simple creatures might serve well as experimental subjects, if a more objective means of measurement of the response could be devised, other than deciding whether the little critters scrunched up or not. I hired a

lab assistant, Paul Klinger, and had him build a multicompartmented apparatus that would allow six planaria to each escape from the lighted end of a small chamber to the dark end to avoid electric shock. The chambers' illumination was directed by a relay from a toy train set sitting in the image plane of a photographic enlarger. A summer student whom I hired from the McConnell lab mob spent a summer working for me faithfully with this apparatus, and we gradually lost hope of seeing an escape response, let alone a learned avoidance. At long last, I sent him to the pet store to purchase a dozen guppies. They were about the same size as planaria but with eyeballs, a brain, spinal cord, and so on. It was truly amazing to see the guppies demonstrate the escape and even some shock avoidance behavior after only a few trials.

This marked the end of my interest in flatworms. We didn't publish our failure. Over the subsequent years, people would occasionally confuse my goldfish research with McConnell's worms. On occasions when asked for my opinion of the planaria research, I attempted to be diplomatic and not criticize a colleague at the same institution. My stance was, and is, that if a reproducible robust experimental paradigm produced clear data supporting memory transfer, I would be willing to listen. McConnell once proposed to bet a bottle of Scotch on whether memory transfer in planaria would ever be widely accepted. I asked him how we would make the decision, say 5 years hence. He proposed that we sum up all of the papers that are confirmatory and those that are not, winner take all. We got hung up on the details and never made the wager. I recall discussing this issue with Ralph Gerard. He told me about the mitogenetic rays of Alexander Gurevitch, a Soviet scientist who proposed in the 1940s that dividing cells emit faint ultraviolet light that stimulate mitotic activity in cells in their optical path. There were dozens of papers, even doctoral theses, elaborating on the reported observations. Ralph made the point that, though no one categorically disproved the hypothesis, fewer and fewer citations and publications on the topic appeared. Authors are not as motivated to publish a failure to reproduce a scientific claim as to report a new discovery. He predicted accurately the demise of memory transfer research. The reports of Georges Ungar in the 1960s and 1970s that injection of a peptide extracted from the brains of mice trained in an auditory extinction task into naïve mice conferred the learned response, created much excitement. Despite Ungar's published structure of the peptide, interest waned, probably because of the lack of a robust objective behavioral assay. Louis Irwin has summarized his attempts and those of others in search of a demonstration of memory transfer.

Training Fish

Paul Klinger and I continued working with fish after the guppies trounced the flatworms. We began training giant danios (related to zebrafish) to

maintain a fixed position in a donut-shaped rotating tank, as measured by a photodetector and recorder. I don't know where this project was taking us, but a freeze in Florida put an end to our fish supply, and we needed a new experimental species. I was drawn to the ready availability of goldfish and only then discovered a rich literature on training them. At this time I had became intrigued by the experiments of Louis and Josepha Flexner on the block of memory formation in mice by the protein synthesis inhibitor puromycin. Gabriel de la Haba, a former NIH colleague who had codiscovered the mechanism of action of this antibiotic, and was now in Flexner's Department of Anatomy at the University of Pennsylvania, had recommended the use of the agent to them. As it happened, I was now making regular visits to nearby Cranbury, New Jersey, to consult for Frank Berger on the development of a cholesterol-lowering drug. In connection with one such trip, I arranged with Gabe to visit the Flexners' lab in the morning and made an appointment for that afternoon to meet with psychologist Geoff Bitterman in his lab at Bryn Mawr, a few miles away. Bitterman showed me his many goldfish setups and remarked that one of his problems with using goldfish, for example in establishing visual or appetitive preferences, was their memory, which interfered with his experiments. Memory! I recall leaving in a daze. I walked, deep in thought, to the train station, found a payphone, and called Geoff back to be sure I had heard correctly what I thought I had. When I got back to Ann Arbor, I had Paul build a bank of six goldfish-size shuttle boxes, each fitted with photodetector beams on either side of a midtank barrier We could inject enough puromycin intracranially to block brain protein synthesis in a 10 μL volume quickly and reproducibly by means of a Hamilton gas chromatography syringe. We soon demonstrated that the puromycin had no measurable effect on acquisition of a light coupled-to-shock avoidance task but did block long-term memory formation, as measured in a retraining session a few days later. We reported this in *Science*, as well as at an American Association for the Advancement of Science (AAAS) National Meeting in Berkeley, in 1964. Memory disruption became insusceptible to the injected agent an hour after training. Roger Davis, a zoologist, joined as a postdoctoral fellow and brought much needed fish and behavioral expertise. He designed and conducted experiments to demonstrate the time course of decay of short-term memory and also characterized an "environmental trigger" that was required for the onset of the memory fixation process. We surmised that disruption of protein synthesis in the fish brain had no measurable effect on acquisition of the light–shock avoidance response, but blocked the process whereby long-term memory is formed in a consolidation process that began after the training. The process was complete in about an hour, after which the fish were no longer susceptible to the blocker. We later learned that initiation of the consolidation process required that the fish be removed from the stressful training environment. A similar phenomenon, called "detention," has been described in rodents.

Fig. 1 This lithograph by Honoré Daumier (1808 -1879) of fish being trained came from a Paris bookstall. Daumier's intent was to satirize the establishment of a scientific oceanographic station in Concourneau, Brittany, according to a letter to the author from the late Professor A. Fessard. A companion lithograph depicts fish dancing to the teacher's toodling.

Memory consolidation of an aversive task did not begin until the animals were removed from the experimental environment and returned to the safety of their home cages. A hypothesis that there was a "shreckstoffe" in the training tank water that kept the fish aroused was short lived; it turned out that the delaying cues were probably visual. Roger later found that the vulnerability of memory to various blocking agents could be reinstated for a period some time after protein blockers were thought to be no longer effective.

In 1967, I was invited to write an article for *Scientific American* magazine on our work on goldfish memory. The magazine reprinted over 100,000 copies of the article, presumably many of them for high school and college classes. It has been rewarding over the years to be approached by neuroscientists at a Society for Neuroscience meeting, recognizing me from my nametag, to tell me how this essay was their introduction to neuroscience. The fact that research was being performed on fish memory engendered public and academic interest, some of it in unexpected ways. Following an invited lecture at Harvard, my host, E. O. Wilson, presented me with a John Macdonald

detective novel. The plot turned out to be relevant to our research. There were many invitations to lecture, often at symposia where other ongoing biochemical and pharmacological studies on memory were reported. I met Sam Barondes and his former mentor Murray Jarvik, as well as Ed Glassman, Art Cherkin, Jim McGaugh, Felix Strumwasser, Eric Kandel, Stephen Rose, and numerous others at such "road shows," each of us working on his favorite creature, most commonly rodents. For the next 5 years, we examined many parameters of the behavior of various other macromolecular synthesis blockers and began to look for possible changes in goldfish brain protein synthesis that could be correlated with behavior.

The Neuroscience Research Program

Francis Otto Schmitt had by now formed his Neuroscience Research Program (NRP) and convened meetings periodically on exciting subjects in a "castle" in Brookline, a Boston suburb. He was not only the Scientific Director, but also impresario, and developmental officer rolled into one. He was also the prime student. He sat in the front row of each session, took notes, and asked good questions. He foresaw not only that the "soups" and "sparks," but the microscopists, biophysicists, and behaviorists as well had intersecting interests. It has been said that Ralph Gerard coined the term "neurosciences," but Schmitt and his NRP group must be credited with bringing neuroscience to the fore as an entity. Following NRP meetings, always on timely topics, the NRP circulated blue and white-covered meeting summary bulletins, which were widely circulated.

After participating in one of his thematic meetings, Schmitt invited me to a week-long course to be held in the summer of 1965 at MIT, to which about 10 world-famous scientists, unfamiliar with the nervous system were to immerse themselves in the excitement of neuroscience by dissecting a human brain—one apiece. I was invited as a kind of docent, already having a medical degree, and being relatively knowledgeable on brain structure. The instructor was Walle Nauta. His assistants were Jay Angevine and Gardner Quarton, a psychiatrist and NRP Staff Director. Ricky and our 4-month-old son Will stayed at a cottage on Cape Ann overlooking a cemetery and beyond that the Atlantic. I was billeted at an MIT dormitory next door to Melvin Calvin, celebrated for his discovery of the mechanism of carbon dioxide fixation in photosynthesis. His laboratory at U.C. Berkeley had an ongoing interest in brain and behavior, headed by Edward Bennett.

I have tried in these pages not to wander off my narrative too much but am tempted to tell a little side story. Calvin and I were dorm neighbors. As I left my room one morning, I found him in the hallway, talking on a payphone. He motioned to me that it wouldn't take long and to wait for him, so I stood there, waiting. I overheard him say, "Well, tell 'em to put 'em in a plastic bag" and then hung up. As we started to walk toward the classroom

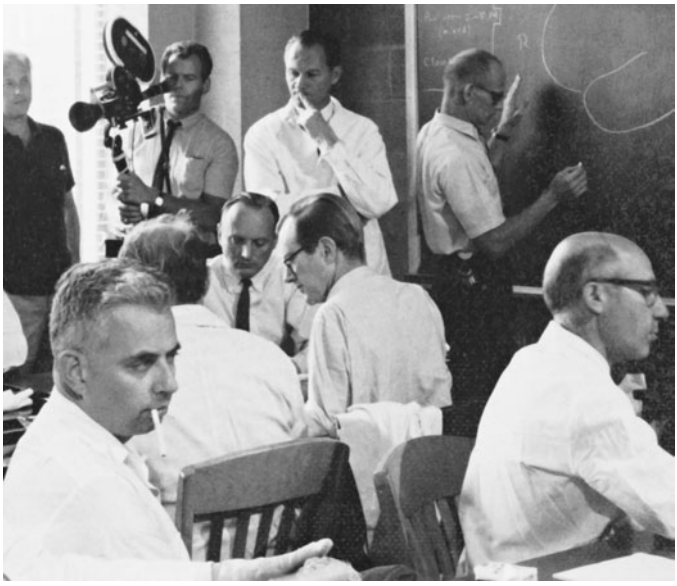

Fig. 2 Photographs from The NRP's Brain Dissection Course, in 1965. An F. O. Schmitt production, being filmed, perhaps for television. The instructor, Walle Nauta, in white lab coat, Jay Angevine at the blackboard. Seated facing the camera is Gardner Quarton. In the foreground, left, myself; right, Melvin Calvin.

building, my curiosity got the better of me. At last I said, "What was that all about?" Calvin replied, "Oh, there are these astronauts meeting down in Wood's Hole. They're trying to figure out how to handle the Moon rocks." At the time there was much speculation among scientists and in the press about potential chemically toxic or infectious perils of anything brought back to Earth from the Moon. I had just borne witness to how such weighty problems end up being handled in the real world. Fortunately, we seem to have survived—this time.

Another attendee was the late Seymour Benzer, who had not yet begun (as far as anyone knew) his move from bacterial genetics at Purdue to his ingenious behavioral studies with drosophila at Cal Tech. We enjoyed interesting food and tested Boston's most obscure restaurants together. A few years later, he invited me to give a talk at Cal Tech and asked me to select the kind of cuisine I'd like to sample for dinner. In an attempt to stump him, I suggested Albanian. Unfortunately, he found a place.

Two years after the MIT brain dissection course, Schmitt and his NRP staff convened a month-long NRP meeting in Boulder, Colorado, the first of four to be held over the next few years. I was invited to the first of them in 1967, with my wife and children as well as my postdoctoral fellow, Roger

Davis and his family. It was a stimulating month-long adventure in science and a wonderful treat for our families. I presented a lecture on our goldfish research and prepared a chapter for the resulting massive tome, the first the series of four. My chapter included further confirmatory results of our original goldfish study with a different protein synthesis blocking agent, acetoxycycloheximide. I was so favorably impressed with the skills of Helene Jordan Wadell, an editor assigned to the book, that I contacted her a few years later to edit the first edition of the textbook *Basic Neurochemistry*. She served in this capacity for the next three editions as well, working closely with the chief editor, George Siegel.

Schmitt had asked me, in addition to my own lecture and book chapter, to take on a review of recent studies on memory transfer, that is, McConnell's planaria experiments, Ungar's studies in mice, and so on. I balked at the assignment, and the task fell on Gardner Quarton, Schmitt's NRP associate. I knew "Q," as he was called, from my previous NRP activities, including the "brain dissection" class. Eventually, Q moved to Ann Arbor in 1969 as Director of the University of Michigan Mental Health Research Institute (MHRI), succeeding Jim Miller. He remained in this position until his death in 1985. Q was a great colleague and friend. He was idolized by the psychiatry residents, whom he enjoyed counseling. At Boulder, Melvin Calvin introduced me to David Samuel, a biochemist at the Weizmann Institute in Israel, then on sabbatical with him in Berkeley. Samuel later invited me to teach a 6-week neurochemistry course at the Weizmann Institute in Rehovot in 1971.

Neuroplasticity

For the next 5 years, we examined many parameters of the behavior of various other macromolecular synthesis blockers and began to look for detectable changes in protein synthesis that could be correlated with behavior. Our research on goldfish memory and protein synthesis blockers can be categorized as interventive, more pharmacological than biochemical. Interventive approaches permit investigation of complex phenomena such as animal behavior but bear the serious caveat that the agents being administered may have multiple effects not directly related to the process being addressed. Molecular genetic interventions may have similar drawbacks. The ideal complementary experiment would be correlative: to observe memory formation without disrupting it (a bit like astronomy). Such a correlative biochemical approach is offered by the administration of radioisotopically labeled precursors followed by a search for changes in precursor incorporation, under experimental, compared with control conditions. We had been able to distinguish short-term from long-term forms of memory behaviorally but had no inkling of where in the brain to look biochemically nor what the magnitude of putative relevant biochemical changes might be. We nevertheless felt

obligated to examine incorporation of amino acid precursors into protein with the tools then in hand, gel electrophoresis of proteins from brain regions, subcellular fractions, and so on. We concluded that this was not a useful approach.

We stepped back and sought a model system that would permit us to detect proteins that are being made in the developed adult brain undergoing neuroplastic synaptogenesis, analogous to what we infer happens during memory formation. These conditions are met in regeneration of the teleost optic nerve. In memory formation and in regeneration, we are dealing with an adaptive response of an adult nervous system to an external input that we believe involves synaptogenesis. The optic tracts are completely crossed, so we began by injecting labeled amino acids intraocularly and looking for labeled proteins arriving at various times in the contralateral tectum. We found that the sensitivity of this procedure was compromised by the use of labeled amino acids that leave the eye via the circulation and then enter both right and left tecta, where they are incorporated into tectal proteins that were not transported from the retina. We overcame this problem by using [^{3}H]-proline, a nonessential amino acid for which the brain had no transport system through the blood–brain barrier. This proved to be an ideal agent for radiolabeling nerve pathways, and an improvement over the then prevalent use of essential amino acids, that do cross the barrier, such as [^{3}H]-leucine. At this point, in 1974, we went on sabbatical to the laboratory of R.M. Gaze, at the National Health Institute at Mill Hill in England. I tried my hand at tissue culture, using adult frog retinal explants, with little success. Tadpole eyes did better but were too tiny to manipulate. Mike Gaze suggested crushing the optic nerve in an adult frog, waiting a few days, and then explanting. This worked very well, and we did the same with goldfish when we returned to Ann Arbor. The goldfish retinas were large enough to cut into multiple squares by means of a McIlwain tissue chopper, yielding retinal "baklava" for explant culture. We studied the microscopic behavior of neurites, and the effects of the growth media and matrix. Anne Heacock observed a marked tendency for the outgrowing neurites to rotate clockwise along the culture dish surface, which we attributed to the sliding of growing and spiraling helical fibers over the matrix.

We returned to comparing 2-D gels of [^{3}H]-proline-labeled, axonally transported proteins produced in intact retinas that of retinas following nerve crush. We decided to pursue a labeled doublet that appeared a few days after nerve crush and began to wane in 2 weeks after nerve crush, a time that optic nerve regeneration was reaching completion. This doublet was known to be axonally transported as well. That is, it originated in the denervated retinal ganglion cells. We isolated the doublet, and dubbed the pair G68 and G80, based on their presumptive molecular weights (kDas). We employed an antibody to the doublet to verify its localization in retinal ganglion cells during regeneration. A partial sequence was used by Mike Uhler's

lab to clone complementary deoxyribonucleic acid (cDNAs). These RICH (Regeneration-Induced-CNPase-Homolog) proteins are neuronal in origin and are part of a superfamily that includes 2′-3′ cyclic nucleotide 3′phosphodiesterase (CNPase). RICH protein is present in zebrafish as a single protein (zRICH). This is as far as we got. The biological bases of vertebrate memory formation have come a long way since then but are still far from understood. Molecular biology and genetics, together with innovations in in vivo imaging, ranging from the microscopic level to human brain imaging, presage exciting challenges and discoveries. There will be plenty to do for quite a while.

Phospholipids

I maintained my interest in inositol and phospholipids, trying to go beyond our work on phosphatidylinostol synthesis to relate it to cholinergic signaling. It was ultimately the contributions of Berridge and of Nishizuka and their collaborators that finally unraveled the role of inositol lipids in signal transduction, with the demonstration of inositol 1,4,5-trisphosphate and diacylglycerol as second messengers. We had made much use of a high voltage paper electrophoresis (HVE) technique for separating [^{32}P]-labeled inositol phosphates. Using it, we confirmed the release of [^{32}P]-labeled inositol trisphosphate, in this case from human platelets (mine).

myo-inositol is one of six possible stereoisomers of hexahydoxycyclohexane. It is the most common isomer and the one present in the inositol lipids. It has one axial and five equatorial hydroxyls. There are many phosphorylated derivatives of inositol that play roles in signal tranduction. To clarify a then existing confusion in numbering the six ring positions of phosphorylated inositol, I proposed the use of a three-dimensional turtle cartoon, in which the axial hydroxyl is the head, and the four limbs plus the tail constitute the five equatorial hydroxyl groups. This visual device has been associated with my name and ironically may well outlive my other contributions to science. My lipid research is detailed in a forthcoming "Reflections" essay in *The Journal of Biological Chemistry*.

Neurochemistry and Neuroscience

With attendance of the Society for Neuroscience annual meeting exceeding 30,000, it is bemusing to recall that one of the justifications for starting the Society in the early 1970s was that the annual meeting of the FASEB, which had over 10,000 registrants in the 1960s, was thought to be getting too large. It cannot be denied, however, that the interdisciplinary approach to basic questions regarding brain function has proven exciting and rewarding. As a biochemist working in the nervous system, "neurochemistry" pretty much

describes my scientific interests. I first heard the term in 1953 as the name of Kety's new laboratory at NIH. He was also a founding editor of the *Journal of Neurochemistry*. The International Society for Neurochemistry (ISN) was formed as an outcome of several international symposia, the first of which was held at Magdalen College, Oxford, in 1954 (also described by Kety in Volume 1 of this series). The first ISN meeting was held in Strasbourg, France, in 1967. There was considerable interest on the part of several U.S. members of the ISN to form an American Neurochemical Society (ASN), and its first meeting was held in Albuquerque, New Mexico, in 1970. The first meeting of the Society for Neuroscience was held in Washington, D.C., in 1971. Ralph Gerard was named its first (honorary) president. The ASN annual meetings were, and have remained, relatively small, about a thousand attendees, and are focused on biochemical and molecular neuroscience. They are usually held in the spring in relatively small towns. This is in sharp contrast to Society for Neuroscience meetings, which are limited to one of a few large convention centers. Attendees select from a huge menu of scientific offerings, with little possibility of absorbing more than a fraction of the program. Yet its breadth is also its strength. My research on biochemical correlates of behavior found a receptive home at these meetings.

For the Society for Neuroscience meeting in Atlanta, Georgia, in 1979, I was invited to host a neurochemical evening mixer. For this, I organized a light-hearted, yet scientific symposium on Molecular Gastronomy. Invited speakers addressed the chemical properties of a specific food. The speakers and subjects of their talks were Henry Mahler on truffles, myself on onions, and Louis Sokoloff on glucose. It was well received, and I was persuaded to organize a second such symposium for the 1980 Society for Neuroscience meeting in Cincinnati. To my knowledge, though tongue-in-cheek, this marked the first use of the term *molecular gastronomy*, now employed somewhat more seriously. For neurochemists, there is an additional connection. J. L. W. Thudichum is considered by many of us to be the founder of neurochemistry. His identification of various phospholipids, sphingolipids, and brain fatty acids, as well as his treatise on brain chemistry is a neurochemical historical cornerstone. He also wrote treatises on the chemistry of wine, on gallstones, and a cookbook.

The ISN meetings have brought together colleagues throughout the world that had known one another only by name. In addition, of course, we have traveled to places we might never have experienced and gained insight into how others live. Participation as a council member and society officer was educational in scientific matters as well as diplomacy (and sometimes lack thereof) as well. I am convinced that international professional organizations are valuable channels for breaking down national and ethnic barriers that become increasingly important issues as the world shrinks.

Table 1. Students, Postdoctoral Fellows 1960–2003

Inositol and Phosphoinositides, Signal Transduction

Joyce A. Benjamins
Gary A. Davis
Stephen K. Fisher
William Jackinovich, Jr.
Yaakov Lavie
Prushpa P. N. Murthy
James E. Novak
Gary Petzold
Harry Rittenhouse
Ulrich Seiffert
R. Michael Snider
Evan B. Stubbs, Jr.
Lucio A. A. Van Rooijen

Fatty Acids, Acyl Dihydroxyacetone Phosphate (DHAP), other Lipids

John E. Bleasdale
Carl A. Boast
Cinda Sue Davis
J. Lindsley Foote
Amiya K. Hajra
Joshua Hollander
John M. Hollenbeck
Frank R. Masiarz
Robert J. Pollack
William D. Suomi

Brain Imaging

Lance L. Altenau
Oliver G. Cameron
Kirk A. Frey

Biochemical and Behavioral Correlates of Memory

Fred Baskin
Jerry J. Brink
Harry R. Burrell
Luigi Casola
Roger E. Davis
Linda A. Dokas
Howard Eichenbaum
Ramon Lim
Elaine A. Neale
Joseph H. Neale
Richard J. Santen
Jochen Schacht
W. Michael Schoel
Alan Springer

Goldfish Retinal Regeneration, Explants, Axonal Transport RICH Protein

Rafael P. Ballestero
Keith A. Cauley
Joseph A. Dybowski
John S. Elam
Eva L. Feldman
Thomas Ford-Holevinski
Anne M. Heacock
James M. Hopkins
Shinichi Kohsaka
Gary E. Landreth
Kenneth C. Leskawa
Michael L. Leski
Pamela R. Raymond
Michal Schwartz
Lawrence R. Williams
George R. Wilmot
James L. Olds
Barry L. Shulkin

I am indebted to the doctoral students and postdoctoral fellows with whom I shared my laboratory, ideas, and collegiality. I was extremely fortunate to have had the able technical assistance of Roy M. Bradley at the National Institutes of Health, and at the University of Michigan Edward B. Seguin (in lipid biochemistry) for 38 years, and Paul K. Klinger (in behavioral equipment design, measurements and statistical analysis) for over 25 years.

Acknowledgments

I have been fortunate in many ways. By a stroke of luck, I was assigned by the Navy to the University of Michigan right out of high school. My medical education served me well; it piqued my interest in biomedical research and did not deter me from continuing my preparation for a research career. At the NIH, I was immersed in a stimulating environment created by Seymour Kety,

an inspiring role model. When we moved to Ann Arbor from Bethesda in 1950, I thought that we would not stay more than a few years. We had several opportunities to leave over the years for warmer climates, particularly in the winter, and for the excitement of big-city life. The anchors have been my happy professional life with friendly colleagues, good students and postdocs, and excellent facilities. Ricky became deeply involved in various culinary activities, culminating in, together with two other faculty wives, a restaurant named the Moveable Feast that was set in an historic house and that continued on for 20 years, until it was sold and renamed. I thank her for putting up with me these past 50 years.

The schools for our two boys were excellent. Will is a graphic designer and creative director of a communications company in Seattle, Washington. Adam is a physician and lives nearby. Each of them and their wives have provided us with a grandson and a granddaughter (four total).

I am particularly grateful to the NIH and NSF, the Markey Charitable Trust, and to the late Ralph and Elsie Colton, for research support. I thank my successors, codirectors, Huda Akil and Stan Watson, who renamed MHRI as MBNI (Molecular and Behavioral Research Institute) for leaving the welcome mat out. Thanks to Mary Driscoll for help with the bibliography and James Beals with the graphics.

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