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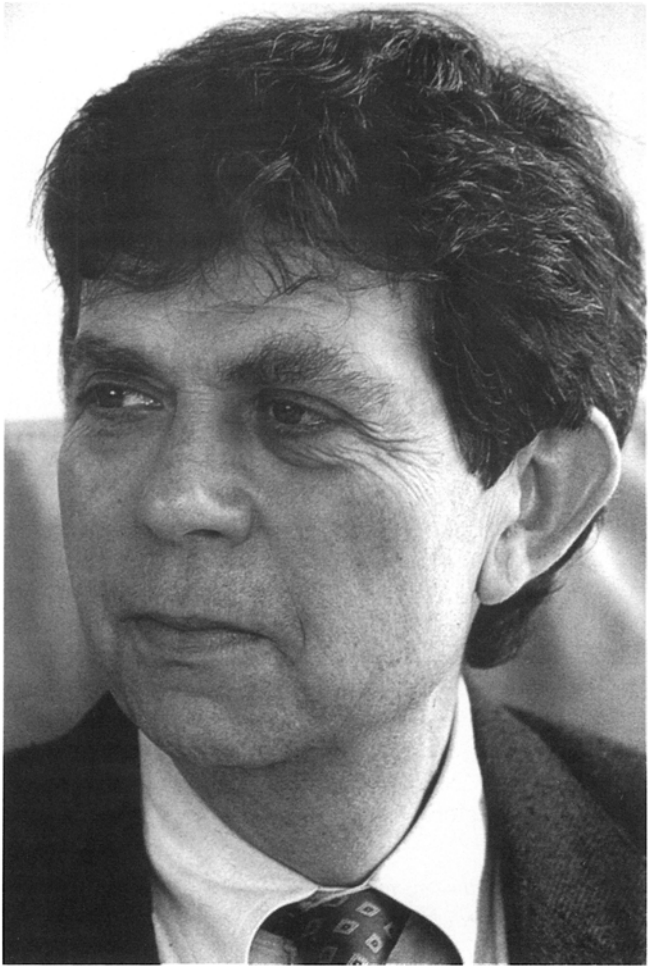

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Samuel Barondes played a major role in bringing a molecular and genetic approach to neuroscience and psychiatry. In early work he helped establish the requirement for brain protein synthesis in long-term memory and demonstrated the rapid transport of proteins in brain axons. Turning his attention to cellular interactions, he discovered discoidins—slime mold relatives of the discoidin-domain proteins involved in synaptogenesis—as well as galectins, a family of glycoconjugate-binding proteins, some of which are found in neurons. A gifted writer, he has published three books about psychiatric genetics and molecular psychiatry for a general audience.

Samuel H. Barondes

Brighton Beach Childhood

Writing this memoir has caused me to reflect on my good fortune. I have been very lucky to have had the privilege of participating in such an exciting period of discovery in neuroscience and psychiatry and of enjoying warm personal relationships with so many talented members of these rich scientific communities. I am particularly grateful to the mentors who shaped me, the colleagues and trainees who sustained me, and the continuing elaboration of our work by others. My parents were born in Eastern Europe in 1902, and each left for America in their late teens, in the aftermath of the First World War. My father, Solomon, was raised in Zbaraz, which was part of the Austro-Hungarian empire and is now in Ukraine. My mother, Yetta Kaplow, came from Kraisk in what is now Belarus. These were both Fiddler-on-the-Roof-type villages in which their families, each with eight children, eked out a living and were guided by the Jewish traditions of the time. Although my parents had almost no formal schooling they were literate in Yiddish, Russian, and Hebrew. As immigrants they went to night school and became fluent in English.

Both my parents came to America following in the footsteps of an older brother. My father's voyage was arranged by his brother Nathan who had settled in Quincy, Massachusetts and had become a junk dealer. But neither Quincy nor the junk business appealed to my father who soon moved to New York City with the hope of becoming a professional singer. He settled in the lower east side of Manhattan, which then had a thriving Yiddish theater, worked as a waiter in restaurants in this theater district, then as a salesman in a clothing store. His singing ambitions were not fulfilled until many years later.

My mother's immigration was made possible by her older brother, Joe, who arrived in New York City shortly before World War I and soon found himself in the US Army. Sent to France as an infantryman he was gassed in the trenches but survived without disability. Upon his discharge he was offered some schooling and became an accountant in New York and, over the years, a wealthy man. When my mother arrived she went to work in a clothing store near the one where my father was employed.

When my parents married several years later they moved to Brighton Beach, a seaside community of six-story brick apartment buildings in Brooklyn. Helped by a gift from Joe they opened a small fabric store on a

street lined with mom-and-pop businesses. Being in the store all day provided a great opportunity for reading, which my mother took full advantage of. The store and their apartment were just a few blocks from a wide beach and a splendid boardwalk, which both extended for several miles to Coney Island, Brooklyn's famous amusement park district. It was golden America, the promised land, even when the Depression came.

By the time I was born in 1933 the Depression was in full force. My parents told me that we were very poor during my early childhood, but I, of course, remember none of it. I do know that the bad economy influenced the elementary school I attended, a Jewish parochial school for boys called the Yeshiva of Brighton Beach, which provided religious studies in the morning and secular studies in the afternoon. The long school day was particularly attractive to my parents because they both worked in the store and it was a convenient way for them to have me, their only child, occupied all afternoon in those days when there were no after-school programs. My parents were also pleased that I would be getting a Biblical and Talmudic education as well as a secular one, but a school day that went until 5 PM was clearly a major attraction.

The Yeshiva of Brighton Beach was, for me, mainly a blessing. In the first grade it became clear that I was an enthusiastic student, the first in my class to read the Bible in Hebrew. By the time I was 10 I eagerly participated in discussions of ethical arguments in the Talmud, a series of volumes of commentaries by eminent rabbinical scholars, parts of which go back 2 millennia. These talents were greatly prized by my teachers who considered the study of the Bible and its Talmudic commentaries as an act of worship. I also did well in the usual elementary school curriculum, which got me a gold medal on graduation but was not valued as highly.

The downside of my schooling was that it was largely in the hands of orthodox rabbis who expected not just the study of the Bible but also the relentless practice of the way of life that it prescribed—a practice that was not always in tune with that of the greater world around me. Some of their demands were not hard to fulfill. For example they required that we always wear a traditional head covering, but they were willing to accept a baseball cap in its place. Others were more difficult to satisfy, especially those that concerned the observance of the Sabbath, because it is forbidden to do work of any kind on this day of rest, and working on the Sabbath is a concept that orthodox rabbis have interpreted very broadly. In the modern world they have extended this prohibition to such simple activities as flipping a switch to turn on the lights or the radio. Even as a child this seemed unreasonable to me. But the rabbis at my school had zero tolerance for any behavior they believed to be forbidden.

Despite my discomfort with the rules of orthodoxy I went to a high school that was organized along similar lines. I did this mainly to please my mother who had several eminent rabbinical relatives and who hoped

that I too would become a rabbi. I was already strongly inclined against this but bowed to her wishes, knowing that I would eventually conduct my life as I pleased.

My father also was in favor of this choice of high school but for a different reason. As the family store began to bring in a comfortable living he had the time and the means to indulge his passion for singing by studying with excellent teachers. With this training, his haunting lyric tenor voice, and a great talent improvising on traditional synagogue themes, he became a superb Cantor. In the process he befriended other Cantors, such as Jan Pierce and Richard Tucker, who studied operatic singing and became leading tenors at the Metropolitan Opera. My father, too, sang operatic arias, mainly by Puccini, Verdi, and Mozart, but his greatest talent was in interpreting Jewish liturgical music. Despite this he refused to become a full-time Cantor because he did not want to be dependent on the whims of a congregation. So he restricted his cantoring to special holidays and to making records, while guaranteeing his independence with the earnings from the store. Nevertheless, he believed that it was appropriate for the son of a Cantor to attend a religious high school, much to my mother's delight.

The high school I attended, Talmudical Academy, introduced me to a world outside of Brighton Beach. Located in a central part of Brooklyn, it was a 20-minute subway ride away. One of its attractions was that it was just a few blocks from Ebbetts Field, home of the Brooklyn Dodgers. Another attraction was its excellent secular afternoon classes that followed a morning of Talmud. Taught by teachers who were also employed by the public high schools, the afternoon curriculum was particularly strong in science. The success of our education was assessed each year when we, like all high school students in New York, took standardized achievement tests. Students like me, who scored close to the top in these exams, were viewed with respect by our classmates. Instead of being ostracized as a hopeless nerd I was elected president of the student council.

But it was to Brighton Beach that I returned every night and with happy anticipation. There was always the beach and the boardwalk where I liked to hang out. If I needed pocket money I would collect discarded soda bottles that were easy to find on the beach and brought 2 ¢ apiece, quite a bonanza at a time when a movie ticket cost only a dime. There were also fascinating discussions going on at various spots on the boardwalk where adults would congregate to dream together about the creation of a harmonious socialist world in the aftermath of World War II. And just down the boardwalk were the amusements of Coney Island with its rides, shows, and penny arcades.

My teenage years were also greatly enriched by 2 months each summer at camps in upstate New York. I started these adventures just before high school, and over the years I graduated to senior boys counselor. Going to

camp was 2 months of continuous outdoor activities in the countryside. And, for the first time in my life, there were girls, dances, and coed theatrical productions that I participated in avidly, often writing original skits and the lyrics for musicals. This new world facilitated my transition from the cloistered existence of all-boy parochial schools to the liberation of college.

There was, however, a final challenge: my mother was still interested in making me a rabbi and urged me to go to Yeshiva University. But I had decided to move into the greater world. Since I was only 16, and my parents insisted that I continue to live at home during college, I narrowed the choices down to Brooklyn College, which was only about 20 minutes away by subway, and Columbia, which would extend the ride by at least an hour more in each direction. Despite this inconvenience I liked the feel of the Columbia campus, and I was thrilled by the possibility of a daily escape to Manhattan. When Columbia admitted me I was ready to go, despite my mother's disappointment. My father was proud—an immigrant from Zbaraz with a son at Columbia.

As I look back on my experiences in Jewish parochial schools I consider them a valuable preparation for my subsequent life and career. Although I was, from a young age, skeptical about the aspects of my education that were based on revealed truth, I could put that aside while incorporating its emphasis on living a virtuous life and a life of learning. My father, who had a strong philosophical bent, would also talk with me about wisdom and morality on our frequent evening walks on the boardwalk. He sometimes liked to base our conversations on phrases from the Talmud, many of which have stayed with me ever since. One of his favorites, roughly translated: "Who is a rich man? He who rejoices in his portion."

College at Columbia

When I started Columbia College in the Fall of 1950 I had no clear plans for the future. This was just fine with the College, which did not require the selection of a major course of study. Instead it prided itself on offering a liberal education shaped by its famous core curriculum. This emphasis on great ideas of western civilization was particularly valuable for me because I was less informed about these matters than many of my classmates, and I was delighted to be offered so many samples of the wisdom of the ages. My 3 hours a day on the subway were regularly devoted to reading, and the jostling ride went unnoticed as I immersed myself in Aristotle, Sophocles, Spinoza, and Freud.

There was also a science course requirement that I began to satisfy in my sophomore year by taking the course in introductory psychology. Taught at Columbia as an experimental science, it was organized around *Principles of Psychology: A Systematic Text in the Science of Behavior* by Fred S. Keller and William N. Schoenfeld, the two professors in charge of the course.

Having just been published in 1950 this was a very unusual introductory textbook. Instead of providing a broad survey of approaches to psychology it confined its attention to behaviorism and emphasized the ideas of the world's leading behaviorist, B.F. Skinner, whom the authors idolized.

Discovering that psychology could be based on experimentation rather than introspection was very exciting to me. I was captivated by the simple experimental apparatus that was used to study bar-pressing by rats and the manipulation of their rates of response by schedules of reinforcement with food pellets. I was particularly impressed that the pattern of responses could be recorded graphically in the course of the experiment as a cumulative response curve, providing a quantitative picture of behavior on a piece of paper, and that the results were predictable and reliable. I was also swept up by the almost religious zeal of my teachers who insisted that this was the approach that would finally lead us to an objective understanding of the forces that control all human behavior. I wanted to learn more.

At the start of my junior year I supplemented my scientific education with a course in chemistry, a subject that I already loved since high school, and also signed up for several more psychology courses. The one in abnormal psychology taught by Ralph Hefferline really grabbed me. As the year progressed I began thinking more and more about a career in academic psychology.

Then Uncle Joe, my mother's older brother, intervened. He had, by then, made a small fortune in real estate and established himself as the senior member of our extended family. He had always taken a great interest in me since I was the first of the American-born generation, and he was eager to see me prosper. One afternoon, in the first semester of my junior year, he came to our house to talk to me about my future plans. I proudly informed him that I wanted to do research in psychology and hoped some day to be a professor.

His response, which is permanently etched in my memory, was not at all what I expected. He began by telling me he approved of my ambition, even thought it was a great idea. "But first," he said, "you have to go to medical school. That will broaden your horizon and provide you with some security if your research doesn't work out. When you've finished medical school you'll be in a great position to start doing exactly what you want to do—research in psychology. And you'll also be in a great position to do many other interesting things, should you decide to change your mind."

The amazing thing about my conversation with Joe—this down to earth man with no formal education—is that it immediately altered the course of my life. When I greeted him that day I was pretty clear that I was on my way to a Ph.D. in psychology. In a matter of minutes I was seriously—and for the first time—entertaining the possibility of becoming a medical doctor. As the idea sunk in, I arranged to take the additional science courses that were required for medical school.

Joe's intervention soon paid me a great intellectual dividend. In the second semester of my junior year I began a course in physics, a subject I knew nothing about and that, until then, I had no intention of studying. Fortunately Columbia was among the first to offer an introductory course that did not require much background in math, a forerunner of those now referred to as "physics for poets." For me it was transformative. Based on a new textbook—*Introduction to Concepts and Theories in Physical Science* by Gerald Holton—it opened my eyes to the way science uses quantitative methods of observation and experimentation to explain the world. I had already had a taste of this in looking at the graphs that rats generated in Skinner boxes. But that now seemed like child's play in comparison with the work of Galileo, Newton, Faraday, and Einstein. And even though I did not understand all the nuances I got the big picture, a picture of a world made a bit more comprehensible by the cumulative discoveries of generations of scientists.

A great benefit of my enthusiasm for so many classes was my election to Phi Beta Kappa in my junior year. This guaranteed my admission to most medical schools even though I had not taken the usual premedical program of studies. Urged by my parents to remain close to home, I decided to continue at Columbia by moving on to its medical campus further uptown.

In anticipation of this move I filled my senior year with sciences. To round out my understanding of psychology I also took a class called "The Biology of Behavior" that was not a mainstream listing of the behaviorist-dominated psychology department but was offered, instead, by Columbia's School of General Studies. Its instructor, Murray Jarvik, opened my eyes to the value of brain research in the study of behavior. Murray will also figure later in my story and became a lifelong friend.

Columbia Medical School

Columbia's College of Physicians and Surgeons is on 168th street in Manhattan, about 3 miles north of the main campus. When I started there in the Fall of 1954 I signed up for lodgings at Bard Hall, the student residence. Freed at last from the long daily subway rides to Brighton Beach, I had a comfortable room overlooking the Hudson River and the continuous company of stimulating classmates.

I approached all the medical school classes with high hopes. Some were taught by leading researchers such as Erwin Chargaff, whose discovery of the ratios of the four bases in DNA was crucial for the Watson-Crick model of the double helix. Elvin Kabat's lectures on immunology, which emphasized his own experimental work, were particularly inspiring. I even liked anatomy.

But the big disappointment for me was psychiatry. Having started medical school with the belief that academic psychiatrists would be engaged in

experimental studies of behavior, I was surprised to learn that my teachers cared only about psychoanalysis and were not interested in research. Even though I was intensely curious about psychopathology, and was fascinated by the concurrent brilliance and craziness of a manic-depressive patient I worked with, I was uncomfortable with the prospect of devoting myself to a field that seemed to rely so heavily on strongly held opinions rather than scientific evidence.

As I progressed into the clinical years of medical school I was drawn to endocrinology, a field that had already developed quantitative laboratory tests to aid in diagnosis and treatment. Endocrinology also appealed to me because the pituitary, which controls other glands, is itself controlled by secretions from nerve cells in the hypothalamus, and these, in turn, are influenced by emotions. Viewed in this way endocrinology was not only grounded in science but also relevant to aspects of human behavior that I found interesting.

I was also pleased to discover that I liked working in the clinics. This was particularly true in endocrinology, which offered excellent treatments for some prevalent disorders such as hypothyroidism, thus guaranteeing many satisfied patients. By the end of my third year in medical school I decided to get training in endocrinology and opted for a medical internship at the Peter Bent Brigham Hospital in Boston, just down the street from Harvard Medical School. A main attraction was its chief of medicine, George Thorn, a distinguished endocrinologist.

Becoming a Physician at the Brigham

My first day at the Brigham opened another exciting chapter in my long education. Arriving on the ward in one of the starched white cotton suits the hospital provided, but with little understanding of what I was supposed to do, I was surprised to find my fellow intern, Donald Harrison, already busily at work with the patients. Donald had gone to medical school at the University of Alabama, which offered a much more practical education than I had received. He had been a whiz student and I was immediately in awe of the way he combined exuberant enthusiasm, Southern charm, high intelligence, and hands-on medical knowledge. Fortunately he was also an enormously generous person who was eager to teach me the rudiments of patient care in exchange for a few bits of the book-learning I had accumulated at Columbia. A few months with him and I had picked up the tricks of the trade.

My 2 years at the Brigham, the first as an intern and the second as a medical resident, were filled with many such comradely experiences that come when a small group of young people keep working to exhaustion for a worthy cause. The only time off from our continuous duty was every other

night and weekend. But the work was exciting and this intense process of initiation had the desired effect of minting skilled physicians.

The Brigham was also an important site of medical innovation, which attracted some unusual patients. Being interested in endocrinology, I had the opportunity to work with people with adrenal diseases who were drawn there because of George Thorn. We were also encouraged to start thinking about doing research. Having decided that population control was the most important world problem, I submitted a pie-in-the-sky proposal to Dr. Somers Sturgis, a professor of gynecology, on male contraception which proposed to make antibodies to sperm cells and to use them for birth control. As I now reread the proposal I see how naive it was. But even though nothing came of it, I found that I enjoyed thinking about experiments.

The Brigham's interest in making us into medical scientists was not restricted to encouraging such armchair speculation. In order to be invited to complete the medical residency, it was necessary to leave after 2 years of clinical training, for at least 2 years in the lab. In those days, in which all medical doctors were subject to the draft, the most desirable way to do this research was as a member of the United States Public Health Service (USPHS)—one of the uniformed services—and to be assigned to a research unit at the National Institutes of Health (NIH). Located in Bethesda, MD, a suburb of Washington, the NIH was, at the time, establishing itself as the world leader in biomedical research. And every year they accepted a handful of young doctors for research training while concurrently serving as commissioned officers in the USPHS. For trainees like me at the Brigham, getting one of these plum positions was the perfect way to learn to do research while fulfilling the requirement for 2 years of uniformed service as a medical doctor.

Of the units at the NIH that offered these positions which interested me most was in the Clinical Endocrinology Branch of the National Institute of Arthritis and Metabolic Diseases. Competition for this position was intense, and applications and interviews had to be arranged more than a year advance, in the midst of my hectic internship. Of all the jobs I ever applied for this was the one that I was most eager to get, and most worried would elude me. I was very relieved to learn, in April 1959, that I would be appointed as a Senior Assistant Surgeon in the USPHS and was assigned to the Clinical Endocrinology Branch under the supervision of J. Edward Rall, beginning July 1, 1960.

Becoming a Scientist at NIH

The 3 years I spent at the NIH were, in my mind, the time of transition from being a student to being an adult. For the first time in my life I would be making a living, earning about $6,000 dollars a year, a princely sum 20 times as much as the $300 dollars per year I had earned as an intern.

This meant I could have a real residence; first, a house I shared with two friends; and then, a little apartment of my own at 2700 Q Street in Georgetown, a 20-minute drive to NIH. And I had a serious girlfriend, Ellen Slater, whom I had known since medical school and would eventually marry.

Yet, in many ways I was still a student. Even though I had become a competent physician, I would need a lot of guidance to get started in research. This need was particularly pressing because Ed Rall, who hired me, had just decided to turn his attention to administration and encouraged me to figure out my own path.

Fortunately there was Ira Pastan. Ira had arrived as a trainee in the Clinical Endocrinology Branch a year before I did and had settled into the lab of Jim Fields, one of the labs that was open to me. Warm, insightful, and already a productive young scientist, Ira took me under his wing and taught me the essentials of biochemical experimentation. He was doing metabolic studies on slices of thyroid gland and, after some brief discussion, I decided that I would do similar experiments with slices of the pituitary gland, that master gland seated beneath the hypothalamus that had first attracted me in medical school. Having learned that the hypothalamus contained serotonin and norepinephrine, two neurotransmitters that might regulate pituitary functions, I decided to study their effects on the metabolism of pituitary slices using the same techniques that Ira was using in the thyroid.

The results were dramatic. Both serotonin and norepinephrine increased glucose oxidation by pituitary slices by way of the hexose monophosphate pathway, and the increases were impressive—up to fivefold. Within months of arriving at NIH I submitted a paper to *Endocrinology,* a top journal, which soon accepted it. But the micromolar concentrations of the neurotransmitters needed to produce these effects suggested that they might not be acting as ligands for receptors but in some other way. I soon found evidence for an alternative mechanism by blocking the action of the amines with monoamine oxidase inhibitors, drugs already in use by psychiatrists to treat depression. The effect of the drugs indicated that metabolites of norepinephrine and serotonin were the active agents, rather than the neurotransmitters themselves, raising questions about the physiological significance of this *in vitro* effect. My paper about this was promptly accepted by the *Journal of Biological Chemistry*, then the top journal in the field.

These early experiences at NIH influenced me greatly by showing me—and others—that I was a competent experimentalist. They also brought me into contact with several outstanding NIH scientists to whom I turned for help. Among them was Julie Axelrod who was then doing his Nobel Prize-winning work on norepinephrine metabolism and who gave me reagents, encouragement, and advice. Julie and I became friends and remained in touch for the rest of his life.

But my career in the laboratory was almost aborted by an unexpected event. Shortly after I arrived at NIH as a commissioned officer

in the USPHS, John F. Kennedy was elected President. As is now well known, but was then top secret, Kennedy had Addison's disease—adrenal insufficiency—with very low levels of corticosteroids that required daily replacement therapy. Because symptoms of Addison's disease can be exacerbated by stress, Kennedy's doctors wanted to have someone around who could immediately deal with any signs of deterioration in his condition. From what I have been able to piece together they decided to assign this duty to a young endocrinologist in the uniformed services who had worked with patients with Addison's disease. Because of my experience at the Brigham I was a reasonable candidate and, after being sworn to secrecy, was asked if I would like to be considered. I said yes, and assuming they would never pick me, thought no more of it.

A few days later my mother called me in a panic. Government agents, she told me, were asking questions about me all over Brighton Beach, and she was worried that I was in some kind of trouble. She was greatly relieved by my explanation that they must be checking out my security clearance for an important assignment but still worried because one of the people they interviewed was an artist who had a studio in our basement.

To understand why she continued to be worried I need to tell you more about the ideologies of the people of Brighton Beach. As I described my childhood you might have the picture of a community filled with orthodox rabbis on the lookout for violators of the laws governing the Sabbath. But the fact of the matter is that the most prominent belief system in the Brighton Beach of my youth was not Judaism but Socialism, and many residents were even members of the Communist party. My mother had reason to believe that this might include the man with the studio in our basement who was interviewed by the government agents.

Whether or not her belief was correct, I was soon politely informed that my services at the White House would not be needed after all. The explanation I was given was that they had chosen someone from the Navy because this had been Kennedy's branch of the service. I never found out what really happened, and my FBI file, which I later obtained, makes no mention of this episode. Whatever the reasons, I was free to continue with my research at NIH.

Gordon Tomkins and Marshall Nirenberg: From Endocrinology to Molecular Biology

My research was about to take a major turn because of a conversation with Gordon Tomkins, a brilliant and charismatic scientist who would soon become my mentor (Fig. 1). About 7 years older than me, Gordon was a Californian who had gone to medical school at Harvard and also interned at the Brigham. Interested in hormones he had thought about doing some clinical work but decided he belonged in the lab and got a Ph.D. in biochemistry from UC Berkeley. When I met him he was settling into a position as

Fig. 1. Gordon Mayer Tomkins (1926–1975) in 1974.

head of a newly formed Laboratory of Molecular Biology, which was located just around the corner from the Clinical Endocrinology Branch in NIH's massive Building 10.

My first conversation with Gordon is as memorable to me as the one I described with my uncle Joe. When he asked me what I was interested in I answered "endocrinology," and he offered a startling response: "You know what endocrinology is? Endocrinology is just molecular biology." To which I replied, "What exactly is molecular biology?"

To justify my ignorance you must understand that this conversation happened early in 1961, when molecular biology was not exactly a household word. But Gordon had already realized that hormones work by regulating gene expression, and he decided, on the spot, to tell me why. In the course of the next 2 hours he explained the central dogma of molecular biology: that regions of DNA act as templates for the synthesis of specific messenger RNAs that, in turn, encode the structures of specific proteins. In Gordon's view hormones work by changing the synthesis of certain messenger RNAs and the proteins they encode, thereby influencing biological functions. His explanations were so convincing and his personality so warm and inspiring that, by the end of the conversation, I asked him if I could join his lab.

He told me he had a better idea. Instead of immediately working with him—which was especially problematic because he would soon be going to Paris for a sabbatical—I should first work with a young biochemist whom he had recently hired as a member of his unit. In Gordon's view this young man, whose tiny lab was just a few doors away, was a brilliant experimentalist who could teach me a lot. Furthermore he had only one post-doc in

his lab, and Gordon thought he could also use another pair of hands. This was how I came to work with Marshall Nirenberg.

Moving into Marshall's lab turned out to be a very lucky break, because the following month he and his post-doc, Heinrich Matthaei, made an extraordinary discovery. They had developed a system for studying *in vitro* protein synthesis by extracts of *Escherichia coli,* and they were adding various types of RNAs to the extracts to see if they could direct the incorporation of radioactive amino acids into proteins. Among those they tested was a synthetic RNA, polyuridylic acid (poly-U). This simple experiment had two amazing results: poly-U did, indeed, direct the synthesis of radioactive protein; and the protein product contained only a single amino acid, phenylalanine. Because there was already reason to believe that sequences of three nucleotides in RNA directed the incorporation of a particular amino acid into protein—the so-called triplet code—these results raised the possibility that the code for phenylalanine was a sequence of three uridines, a possibility that was soon confirmed.

Amazing as that result was in itself, it quickly became clear that Marshall and Heinrich had not only found the first component of the genetic code but also a way of finding the nucleotide triplets that encoded all 20 of the amino acids found in proteins. As they set out to follow this lead, I was given the assignment of finding out what happens to poly-U when it is added to the *E. coli* extract. Over the next year I discovered that poly-U associates with clusters of ribosomes that were just being implicated in the translation of messenger RNA into protein. This was not only interesting in itself but also was further evidence that the synthetic polynucleotide was, indeed, acting like a real messenger RNA. I also discovered that a single molecule of poly-U could direct the synthesis of multiple copies of the artificial protein called polyphenylalanine, providing direct evidence that messenger RNA could be used over and over again, and was not used up in the synthesis of a single protein molecule. These findings were considered to be of such great importance that when Marshall and I submitted them to *Science* they were promptly published as back-to-back papers.

Even more exciting than these successful experiments was my immersion in a lab that was engaged in one of molecular biology's greatest adventures, the race to decipher the genetic code. Marshall had become the frontrunner with the initial finding with poly-U. But as soon as that became known, others began using the same approach. Most notable among them was Severo Ochoa, who had already won a Nobel prize for work with polynucleotide phosphorylase, the enzyme used to make poly-U. Over the next few years Marshall would earn his own Nobel prize. But despite my association with this groundbreaking research and the thrill of being pictured in the newspapers as a member of NIH's "code of life team" I decided to follow a plan I had made with Gordon to join him in Paris for the last

3 months of his sabbatical. In July of 1962, with Marshall's blessing, I set sail for France.

Those 3 months were a welcome respite from years of hard work. Although Gordon had a lab at the CNRS laboratory in Gif-sur-Yvette, in the outskirts of Paris, he had wound down his experiments because of the summer vacation season, and there was a lot of free time for conversations, visits with scientists at the Institut Pasteur, and exploration of Paris. It was also a great opportunity for me to travel through the French countryside with Gordon and his wife Millicent, a gifted artist and singer, who gave solo performances at churches along the way. In the course of these excursions Gordon and I frequently talked about our future plans.

Mine were once again in flux. The exciting discoveries in Marshall's lab, the inspiring mentorship of Gordon, and my considerable personal success at the lab bench had, together, hooked me on a career in science. But instead of simply cruising in the wake of these two exceptional young men I wanted to find my own way, and this led me back to my college ambition to be an experimental psychologist and my short-lived interest in psychiatry. Having learned from Gordon that "endocrinology is molecular biology" it did not require much imagination to consider that the brain mechanisms that control behavior could also be thought of in terms of this exciting new field. And because I was also interested doing something that would be clinically relevant, it occurred to me that much of psychiatry is also molecular biology and that my new training might even qualify me for a career in psychiatric research.

I also had an idea about bridging the gap between molecular biology and behavior which came from Mike Sporn and Wes Dingman, two contemporaries of mine at NIH. Mike and Wes were interested in messenger RNA, which had then been identified in bacteria but not yet in mammals, and we collaborated on a study showing that RNA isolated from rat liver nuclei had potent messenger activity in *E. coli* extracts, a simple experiment then considered to be so significant that it was published in *Nature*. But even more important to me than this bit of work was that Mike and Wes got me interested in the idea that messenger RNA synthesis was involved in the storage of memories in the brain, which suggested a way of using molecular biology to study a mental mechanism.

Mike and Wes had already done a pioneering experiment that supported this idea by injecting 8-azaguanine, an analogue of a normal precursor of RNA, into the cerebrospinal fluid of rats just before training them in a swimming maze. They found that rats injected with this chemical did not show the same progressive improvement of performance as controls that were injected with saline. This raised the possibility that the drug-treated rats had difficulty learning because their brains were making dysfunctional 8-azaguanine-containing messenger RNA and that synthesis of functional brain messenger RNA was needed for normal learning. These findings,

and the alternative interpretations they considered, were published in 1961 in the first issue of *The Journal of Psychiatric Research,* but got little attention because of their appearance in this obscure new publication.

When I mentioned this line of research to Gordon he suggested that I discuss it with a psychologist friend whom he had met as an undergraduate at UCLA. The friend, who was studying memory in mice, turned out to be none other than Murray Jarvik, who taught me behavioral biology at Columbia. Murray happily agreed to come to NIH for some experiments, bringing with him a simple apparatus for measuring passive-shock-avoidance learning. To test the role of messenger RNA in learning we used a new drug, actinomycin-D, which inhibits RNA synthesis, and measured the effects of injecting different doses into mouse brains by studying incorporation of a radioactive precursor into RNA. We were disappointed to find that mice whose brain RNA synthesis was substantially inhibited learned the simple passive avoidance task as well as controls and had normal memory 3 hours later; and experiments with larger doses of actinomycin were abandoned because of the toxicity of the drug. Nevertheless, the approach was so exciting that it got me several invitations to present symposium papers, including one at the American Psychological Association in 1964. These presentations, which combined the tutelage of Gordon Tomkins with speculations about the molecular processes that control synaptic connections, were subsequently summarized in *Nature* as "Relationship of Biological Regulatory Mechanisms to Learning and Memory."

While the experiments with Murray Jarvik were ongoing I began getting tempting job offers. But I had already decided to satisfy my ambition to become a psychiatric researcher by signing up for a residency in psychiatry at McLean Hospital, a Harvard-affiliated mental hospital in a suburb of Boston. Gordon, who was skeptical, assured me that if I hated working with psychiatric patients NIH would take me back and give me a laboratory of my own. Comforted by his continuing friendship I put my three eventful years at NIH behind me and set out for three more at McLean.

Becoming a Psychiatrist and Neuroscientist at McLean

My life was also about to change in another way. Right after the move from NIH, Ellen Slater and I got married. Fortunately I had been awarded a special fellowship, which paid a living wage rather than the meager resident stipend of the time. This allowed us to live in a small apartment in Cambridge at 60 Brattle Street and to pay tuition for Ellen at the nearby Harvard School of Education, which she soon began attending. We could also afford an occasional babysitter when our first daughter, Elizabeth, was born the following year.

Both of us really needed that help. Ellen, who had majored in poetry and French literature at Vassar, was struggling to integrate graduate studies in a more practical subject—psychological counseling—with the mothering of a demanding infant; and I was working overtime learning psychiatry, setting up a lab, and doing my share of baby care. But it was also the best of times, building a family while each of us learned a new field. McLean proved to be a wonderful place for me to learn psychiatry, providing stimulating teachers such as Alan Stone and Alfred Stanton and fascinating patients, many drawn from the vast faculty and student populations in the Boston area.

I was also pleased with the laboratory facilities. Directed by Jordi Folch-Pi, a distinguished neurochemist, they were located in a brick building on the bucolic McLean campus, a short walk from the ward where I worked. The scientists, who all had appointments at Harvard, greeted me warmly as a young colleague. I was the first psychiatry resident to work in their midst and they were happy to forge this link with the clinical world that surrounded them.

But the biggest break of all was the appearance of Harry (Hersh) Cohen, a graduate psychology student from Tufts who sought me out shortly after I arrived at McLean. Hersh had heard about my interest in memory and received permission to do the research for his Ph.D. thesis with me. This stroke of good luck made it possible for me to keep working on the molecular basis of memory storage—a field that was heating up—while holding down my job as a full time psychiatry resident. It was also wonderful to feel that I was no longer simply a trainee, because I now had my first graduate student.

Early Studies of Protein Synthesis and Memory

Hersh did not waste much time in getting started. Because we had no behavioral equipment at McLean he went to the hardware store and got the materials to build it. In a matter of weeks he made two mazes with electrified floors, which we used to train mice to escape or avoid shock, a more complex task than Murray Jarvik and I had employed. With these mazes we reexamined the effects of actinomycin D and again were stymied by its toxicity. This led us to shift our attention from RNA synthesis to protein synthesis using a new drug, puromycin, that had already been used by others for this purpose.

Puromycin, whose general effects on mammalian protein synthesis were discovered around 1959, was first used in memory experiments by Josefa and Louis Flexner and colleagues at the University of Pennsylvania. In July 1963, just as I arrived at McLean, the Flexners published a paper in *Science* showing that injections of puromycin into mouse brains 1 day after maze-learning impaired memory tested 3 days later. In contrast, identical

injections 6 days after training had no effect on memory. In the next 2 years Bernie Agranoff and colleagues at the University of Michigan, who were studying learning in goldfish, also began reporting effects of puromycin on memory. But Agranoff's group found that injections of puromycin after learning impaired memory only if given within 30 minutes after completion of training, which was a much shorter interval than the Flexner group reported.

When Hersh and I examined the effects of puromycin injections before training—so that protein synthesis was already inhibited when the mice learned to solve a maze—our results fit better with those of the Agranoff group. In our first study we found that injections of puromycin into the mouse brain before training did not interfere with learning but that memory deteriorated in the 3-hour period after training and was virtually absent thereafter. These and other controlled experiments were interpreted to mean that memory during training and for minutes after training ("short term memory") is not dependent on brain protein synthesis, whereas memory thereafter ("long term memory") requires brain protein synthesis. In the paper we published in *Science* we also raised the possibility that the Flexners' finding of an amnesic effect of puromycin injections 1 day after training could mean that there is a third phase of memory storage that operates over this longer time frame.

Axoplasmic Transport of Brain Proteins

In the course of these behavioral experiments, I turned my attention to a distinctive feature of neurons that might have bearing on the role of protein synthesis in memory storage. It was known, from experiments with peripheral nerves by Paul Weiss and others, that neuronal proteins are slowly transported from a site of synthesis in nerve cell bodies down the axon to nerve terminals. If protein synthesis was, indeed, required for memory, and if this protein works by facilitating synaptic functions in nerve terminals (in addition to or instead of on the postsynaptic side), it became important to know how quickly new proteins are transported to the nerve terminals along the short axons in mouse brains. To study this I took advantage of the recent finding that homogenization of brains under appropriate conditions shears off nerve endings, which can be isolated on sucrose gradients as particles called synaptosomes. The method I invented was to inject radioactive leucine into mouse brain and to compare the rate of radioactive protein appearance in whole brain homogenates and in synaptosomes—including soluble and particulate fractions of synaptosomes that could be separated by further disruption and gradient centrifugation. Early in my psychiatric residency I worked out this method, which I described in a paper in *Science* in November 1964. In subsequent work I showed that radioactive protein begins to appear at nerve endings within 15 minutes after its synthesis,

during the same period that short term memory is being converted into protein-synthesis–dependent long term memory.

My work with axoplasmic transport of proteins proved particularly auspicious because it brought me to the attention of Frank Schmitt. Frank, a distinguished biophysicist at MIT, had founded the Neuroscience Research Program (NRP) in 1962 to help develop the nascent field of neuroscience. This was largely accomplished by organizing small work sessions at NRP headquarters in the Brandegee Estate in Brookline. While I was still a resident at McLean, Frank asked me if I would participate in a work session on axoplasmic transport, which would be held the following year, in April 1967. The conference would be an important one because it would bring together a rich mix of people including the great Paul Weiss, the acknowledged leader in the field. But Frank was very concerned that Paul, a senior scientist with a strong personality, would be too domineering to serve as chair of this work session, and he and his colleague, Fred Samson, asked me to take on that task—jokingly explaining that my psychiatric training might be helpful in chairing a meeting that was likely to become very stormy. I was particularly pleased by this request because it helped me realize that I was becoming recognized as a player in neuroscience despite my lowly position as a psychiatry resident. Fortunately the *Work Session on Axoplasmic Transport,* which was published as an NRP Bulletin, proved to be a great success, and Paul Weiss and I became friends.

First Job at Einstein

In my final year of residency I was actively recruited by the faculties of several venerable East Coast schools. But I was most attracted to a New York City newcomer, Albert Einstein College of Medicine, which offered me an assistant professorship of psychiatry with a joint appointment in molecular biology. The Department of Molecular Biology, which had been founded by Bernie Horecker, a distinguished biochemist, was probably the first of its kind in a medical school, reflecting the innovativeness that was typical of the Einstein of that time. My startup package consisted of a brand new laboratory in the Department of Psychiatry built to my design by remodeling a large tile-walled space that was originally used as a lavatory—an indication of the lack of research space in psychiatry departments of that period. My only duties as a psychiatrist were to meet with and supervise residents and to spend a few hours a week seeing patients. The rest of my time could be devoted to research, which was soon supported by a research grant and a Career Development Award from the National Institute of Mental Health (NIMH).

Coming back to New York, our home town, was exhilarating for Ellen and me. It became even more so with the birth of our second daughter Jessica less than a month after we arrived. We rented an apartment with a

view of the Hudson on Palisades Avenue in Riverdale and settled into our wonderful new life.

Protein Synthesis and Long Term Memory

Work in the laboratory had also gotten off to a fast start because Hersh Cohen, now a newly minted Ph.D., joined me at Einstein as a post-doc to continue our work on protein synthesis and memory. That work had been greatly advanced by the Agranoff group's experiments with acetoxycycloheximide, a protein synthesis inhibitor that worked by a different mechanism than puromycin. In 1966 they published a paper in the first volume of a new journal, *Brain Research,* which reported that acetoxycycloheximide injections into goldfish brain immediately after learning blocked memory measured 3 days later, confirming their results with puromycin. But the picture was clouded by the Flexners' 1966 report that, in striking contrast with their pioneering study with puromycin, acetoxycycloheximide injections into mouse brain 1 day after training did not interfere with memory—which raised the possibility that the amnesic effect of injections of puromycin so long after training was due to some other effect of the drug.

Fortunately Hersh and I quickly discovered the reasons for this discrepancy. We found that puromycin produces abnormalities in brain electrical activity, including occult seizures, suggesting that this action—which is not shared by cycloheximide or acetoxycycloheximide—contributes to puromycin's amnesic effect. This interpretation was supported by the finding that diphenylhydantoin, an anticonvulsant, attenuated the amnesic effect of puromycin but not that of the other drugs. The upshot of these studies was that puromycin, which had played such an important role in sparking this line of research, was not really useful in studying the relationship of brain protein synthesis to memory because of the drug's powerful side effect on brain function, and that its amnesic effect when injected 1 day after training appeared to be due to occult seizures (like the retrograde amnesic effect of electroconvulsive shock) rather than to inhibition of brain protein synthesis.

Having cleared up the confusion generated by puromycin's side effects, Hersh and I went on to a long series of experiments that showed that intracerebral or subcutaneous injections of cycloheximide or acetoxycycloheximide before training have no effects on initial learning but do indeed interfere with memory measured a few hours after training and thereafter, and that the critical protein synthesis is initiated within minutes after training under our experimental conditions. These results were consistently obtained in carefully controlled studies with mice that studied maze learning motivated by either shock avoidance or a water reward. When taken together they strongly supported our conclusion, and that of the Agranoff group, that learning and "short term" memory are not

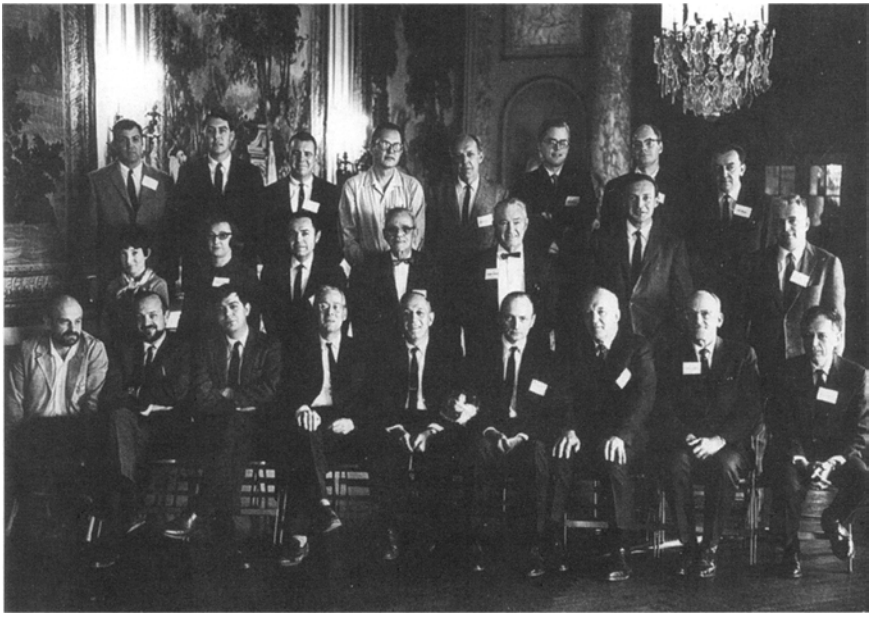

Fig. 2. Participants at Consolidation of the Memory Trace Work Session, Neuroscience Research Program, Brookline, MA, November 1967. Left to right. *Back row*: Hersh Cohen, David Quartermain, Joe Parks, Ted Melnechuk, Richard Roberts, Bruce McEwen, Adrian Rake, Jan Bures. *Middle row*: Patricia Dimond, Catherine LeBlanc, George Adelman, Wardwell Holman, Everett Johnson, Tony Deutsch, Bernie Agranoff. *Front row*: Roy John, Steve Chorover, Samuel Barondes, George Koelle, Seymour Kety, Gardner Quarton, Neal Miller (Work Session Chair), Frank Schmitt, Murray Jarvik.

dependent on brain protein synthesis, whereas "long term" memory, which is being established in the few hours after training, is, indeed, dependent on brain protein synthesis. The implication of these results was that the newly synthesized proteins play a role in the alteration of the functional synaptic connections that store the memory, which became the topic of a historic work session at NRP in 1967 (Fig. 2).

Brain Protein and Glycoprotein Metabolism

While this work on memory was going on I continued to study the rapid transport of newly synthesized brain proteins to nerve endings. Further proof came from autoradiographic studies of synaptosomes with the electron microscope, in collaboration with Bernard Droz. We found that labeled protein could be directly visualized in synaptosomes within 15 minutes after injections of radioactive amino acids, and the significance of the finding coupled with the novelty of the technique led to its publication

in *Science.* I also became interested in the possibility that not all proteins at synapses originated in the neuronal cell bodies and that some could be made by mitochondria in nerve terminals.

Further work in this general area was done with Gary Dutton, a new post-doc and with Howard Feit, an M.D.-Ph.D. student. With them I began studying the metabolism and axoplasmic transport of microtubule protein (tubulin), a specific brain protein known to be a major component of axons. Tubulin was a particularly attractive subject because it was easy to purify from brain homogenates by precipitation with vinblastine followed by electrophoresis on polyacrylamide gels. A major result of these studies was that this structural protein, a major component of axons, turns over with a half life of several days. This finding helped change the picture of the brain, which had been viewed as structurally very stable. The true picture was that the neuron was constantly changing, a theme elaborated in *Cellular Dynamics of the Neuron,* the 1969 book I edited, which was based on a Paris meeting on the subject.

Included in that book was a report of our findings in a new field, the modification of brain proteins by glycosylation, which I had begun studying with my post-doc, Gary Dutton, and with Marty Zatz, an M.D.-Ph.D. student. I had become interested in glycosylation for two reasons. First it seemed to me that this posttranslational modification might be an important way to modulate the function of brain proteins and could even play a role in short term memory in ways already envisioned for posttranslational phosphorylation. Second I had already become interested in the possibility that the glycoproteins on cell surfaces and in the extracellular matrix might play a role in cell adhesion and recognition, an interest that I would pursue for many years.

Life Changes

In the midst of this scientific excitement, disaster struck. Little more than a year after we arrived in New York Ellen found a lump in her breast. Although she was only 29, and the experts we consulted assured us that it was a benign fibroadenoma, it proved to be a cancer. Nevertheless, after radical surgery and extensive radiation, we were convinced that she was cured. As we gradually went back to our normal lives we began thinking about schools for the children and buying a house, which raised questions about where to settle down.

I had, by then, come to the attention of other universities, which prompted Einstein to quickly promote me to tenure. I had also been appointed Director of Einstein's Interdepartmental Institute for Training in Research in the Behavioral and Neurological Sciences, a pioneering program organized by Saul Korey in 1957 with generous support from the NIH, and a program that fit with my personal goal of increasing the role of

biological science in psychiatry. But despite my professional satisfaction at Einstein, Ellen and I were reluctant to put down roots in New York. Instead we were increasingly drawn to California, which I had visited several times because of a generous offer from Stanford.

The turning point came when Salvador Luria invited me to give a lecture at the Salk Institute for their nonresident fellows. When I accepted this invitation I was contacted by Arnold Mandell, a young biological psychiatrist who had just been appointed as the founding Chair of Psychiatry at the brand new medical school at the University of California in San Diego. Arnie said he would come to my talk and would like to show me around.

It was a thrilling visit. I was stunned by the majestic appearance and intellectual vitality of the Salk Institute, the warm reception I received from Jonas Salk and the assembled scientists, and the grand vision for UCSD that was just beginning to rise on a vast campus across the road. When Arnie explained his dreams of a research-based Department of Psychiatry, and offered me a full professorship on the spot, the opportunity to participate in this new adventure seemed irresistible. On a return visit with Ellen she was as enthusiastic as I was.

Before making our final decision we had another treat in store for us. The whole family had been invited to spend three weeks in Boulder, Colorado at the Second Intensive Study Program of the Neurosciences Research Program—another of the contributions of NRP to my personal scientific development and that of the emerging field of neuroscience. It was a great experience for me because it led to lasting friendships with other participants, such as Gunter Stent. It was also a wonderful holiday for the children, their first time in the mountains and on horseback, and helped to convince us that we were ready to move west. Four months later, in December 1969, we all got in the car to move to La Jolla.

Building Psychiatry and Neuroscience at UCSD

Our departure came at a convenient time for my coworkers. Hersh Cohen, who was being recruited for faculty positions, made a surprise move to Wall Street and now holds a major position with Citigroup. My two M.D.-Ph.D. students got their degrees and moved on to clinical training, Marty Zatz in psychiatry and Howard Feit in neurology, and both went on to academic careers. Gary Dutton, a post-doc, decided to join me at UCSD with salary support from my NIH grant. So did Larry Squire, whom I had met at Einstein where he was a post-doc in Murray Jarvik's lab, and who welcomed the opportunity to check out California.

Having Gary and Larry join me in this move allowed me to get a research program going while I attended to my other duties at UCSD. These were quite numerous because our Department of Psychiatry was then made up of just two faculty members: Arnie Mandell and me. I had tried very hard to entice Sol Snyder to sign up with us, and UCSD was willing to offer

him a full professorship despite his young age, but Johns Hopkins had the good sense to make him the same offer—and to eventually make him the founding chair of their new Department of Neuroscience. Which left it up to Arnie and me to do all the teaching, clinical work, and administration, as well as to build up our labs. It was a great relief when Lew Judd arrived the following summer to share the enormous load.

As soon as I arrived at UCSD I also began working to help build an interdepartmental neuroscience program like that at Einstein. The nucleus of this program had already been established by Bob Livingston. Working with him and Jon Singer, a professor of biology, I submitted a proposal to the Alfred P. Sloan Foundation, which was, at the time, very interested in fostering neuroscience. They gave us a generous grant, which I administered, to support students, post-docs, and research. This grant provided funding for about 10 years and played an important role in the development of UCSD's neuroscience program, which is now a world leader.

Ellen also had a lot to do to get us settled. After months of searching she found us an affordable Frank Lloyd Wright-style house with an ocean view at 1642 Kearsarge Road, on the lower part of Mount Soledad. It was within walking distance of downtown La Jolla and the La Jolla Elementary School, which my daughters would attend, and a 5-minute drive to UCSD. We could not believe our good fortune.

But as soon as we moved in, disaster struck again. Ellen's cancer had spread to her liver; and this time we knew it was a death sentence. Seizing what time she had left we lived through grim treatments and exhilarating remissions for a year and a half. When it ended she was only 33, and I was alone with my two little girls, barely 5 and 7 years old.

What saved me during my darkest time was Ellen's parents. In the midst of her illness they retired and moved to La Jolla, just a few miles from our home; and when Ellen died they were there to help me with the responsibilities of a single parent. Their presence was also a godsend for Elizabeth and Jessica who knew that they could always rely on their beloved Grandma Fanny.

Molecules and Memory

While I was reeling from this tragedy, the work in the lab went on. Larry Squire began using cycloheximide to more clearly define the sequential phases of memory in mice, an interest he would maintain in his later research on human memory. Much of his work used the Deutsch Carousel, an automated machine designed by Tony Deutsch, a professor of psychology at UCSD, to study learning and memory of a discrimination task. With this apparatus Larry found evidence that a protein-synthesis dependent component of mouse memory can already be detected during the course of prolonged training, which helped refine our view of the stages of memory. He went on to show that anisomycin, a protein synthesis inhibitor that is structurally different from cycloheximide, is equally effective in blocking

long term memory, which greatly increased our confidence that the amnesic effect of these drugs is really due to inhibition of protein synthesis rather than to some unknown side effect. While completing these studies Larry established his own research program at UCSD where he is now Distinguished Professor of Psychiatry, Neurosciences, and Psychology (as well as editor of this series of volumes).

As we became convinced that newly synthesized brain proteins are needed to store long term memories, and that reversible modifications of existing proteins are probably essential for short term memory, the next problem was to identify the relevant proteins. In the early 1970s this seemed to be an impossible task, because the proteins involved in a particular memory were likely to be confined to a limited number of neurons in the vast mouse brain. Encouraged by conversations with Eric Kandel, who had already discovered electrophysiological correlates of learning in single cells of *Aplysia,* I decided to try to follow his lead in the hope of ultimately identifying the proteins involved in plasticity at identified synapses. Working with *Aplysia californica* also was attractive because these animals live along the coast of La Jolla and could be readily harvested from tide pools that were within a few miles of our lab. And even though I had no experience in cellular neurophysiology, I had recruited Werner Schlapfer, a post-doc, and Paul Woodson and Jacques Tremblay, two graduate students, who were eager to give it a try.

By 1974 we began describing various forms of synaptic plasticity measured in identified cells in the abdominal ganglion of *Aplysia* and the influence of exogenous neurotransmitters and drugs. To examine the molecular effects of these reagents we turned to Irwin Levitan, a post-doc with a background in biochemistry. He found that serotonin and octopamine increased levels of cyclic AMP in the abdominal ganglion as well as the phosphorylation of a prominent protein peak that could be resolved by electrophoresis on a polyacrylamide gel. The combined results of the electrophysiological and molecular studies was very encouraging because they raised the possibility that this phosphoprotein might be involved in a form of memory. But the amount of tissue in the abdominal ganglion was too small for detailed studies of such proteins with the molecular tools of the mid-1970s. To me this seemed like a decisive limitation of this line of research that made it less attractive than the other project I was concurrently engaged in, which was turning up abundant pure proteins with intriguing functional properties.

Slime Molds, Discoidins, and Vertebrate Lectins

The competing project in my lab grew out of my interest in glycosylation of brain proteins and their potential role in the formation of synaptic connections. The development of synaptic connections was of particular interest

to me because I believed that abnormalities in the molecules that control this process might be responsible for the variations in neuronal circuits that may lead to certain forms of mental illness; and my fascination with cell surface glycoconjugates had been kindled by Vic Ginsburg, another young member of Gordon's Laboratory of Molecular Biology, whose lab was across the hall from Marshall's. Vic was one of the early proponents of the now widely accepted idea that specific cellular associations may be controlled by the precise structures of the complex carbohydrates on and around cell surfaces. Just as Marshall was working on a nucleic acid code that determined the structure of proteins, Vic believed there is a sugar code that determines intercellular interactions. But unlike the nucleic acid code which is inscribed as a template made up of four nucleic acid building blocks, the sugar code was presumed to be based on progressive incorporation of six sugar building blocks (galactose, mannose, N-acetyl-glucosamine, N-acetyl-galactosamine, fucose, and sialic acid) into complex sugar chains under the direction of a particular combination of enzymes, the glycosyltransferases, that are expressed in particular cells. How these complex sugar structures on cell surfaces actually mediate cell-cell interactions was not something Vic worried about. But their potential role in this process was what excited him. It was Vic's idea, and its relevance to the formation of specific synaptic connections that stimulated my work with Marty Zatz and Gary Dutton, and that formed the basis of one of the papers—"Brain Glycomacromolecules and Interneuronal Recognition"—that I presented at the NRP meeting in Boulder in 1969.

The direction of my thinking about this problem took a big turn in 1972 with the arrival of Steve Rosen, a new post-doc. Steve had begun his graduate work at Cornell with an interest in memory but went on to do his thesis on cell adhesion in *Dictyostelium discoideum,* a cellular slime mold. This organism exists in two forms: as a unicellular ameba that lives on soil bacteria; and as a member of a colony of thousands of cells that stream together, adhere to each other, and differentiate into a multicellular organism called a fruiting body. The transformation from unicellular nonadhesive cells to aggregating adhesive cells is induced by starvation and occurs over the course of about 8 hours. As a graduate student Steve made the serendipitous discovery that, in the course of this transformation, the aggregating cells make a substance that agglutinates erythrocytes. This raised the possibility that the agglutinin is responsible for the developmentally regulated adhesion, and we agreed that when he came to my lab we would try to find out.

When Steve arrived he quickly confirmed his earlier observations. Working with David Simpson, another post doc, he set out to isolate the active component of the extract by a standard protein purification technique, gel filtration on a Sepharose column, which separates proteins on the basis of their molecular weight. To his great dismay none of the fractions

that came through the column had any agglutination activity. But because of our preconceived notion that the agglutinin might bind to carbohydrates, and knowing that Sepharose is a cross-linked polymer of galactose, he washed the column with a solution of galactose. This released the pure galactose-binding-protein, which we named discoidin, a new member of a class of proteins called lectins that had previously been found in plant extracts. Studies of the effects of simple sugars as inhibitors of hemagglution by purified discoidin showed that N-acetyl-galactosamine binds discoidin better than galactose, and that other simple sugars do not bind at all.

These encouraging results, which we began publishing in 1973, suggested that cell adhesion involves interactions between carbohydrate-binding-proteins and their ligands on cell surfaces or in the extracellular matrix. In the next few years Steve and Dave, working with Bill Frazier, Chen-Min Chang, and Dick Reitherman, accumulated evidence in support of this idea. In the course of this work they found that there are actually two discoidins, discoidin I and II, which are synthesized at different stages in the development of the multicellular organism, and that other species of slime molds also have their own distinct lectins.

Stimulated by this work Tom Nowak, a new graduate student, began looking for developmentally regulated lectins in embryonic chick tissues by making extracts and screening for substances that agglutinate erythrocytes. He found some agglutination activity, but none that was blocked by simple sugars. Then, in the midst of these discouraging results, a paper describing an animal lectin was published by Vivian Teichberg and colleagues in the April 1975 issue of *PNAS*. Using methods like those in our papers on discoidin, they had detected agglutination activity in extracts of the electric organ of an eel, purified the relevant protein on a Sepharose column by elution with lactose, a beta-galactoside, and named the pure protein electrolectin. The main difference between their method and ours is that they included dithiothreitol, a reducing agent, in all their solutions. If dithiothreitol was omitted the lectin was quickly inactivated by oxidation.

When Tom repeated his experiments using dithiothreitol or another reducing agent, beta-mercaptoethanol, he too found lactose-binding agglutinins in various tissue extracts. Concentrating on an agglutinin from embryonic chick muscle he discovered that its synthesis, like that of discoidin, was under striking developmental control, with an increase of 10- to 100-fold between 8 and 16 days of embryonic development and a decline thereafter. Tom went on to purify the lectin with the help of David Kobiler and Larry Roel and to show that it is present on the surface of differentiating muscle cells. We soon found that it is also expressed in other cell types of interest, including neurons.

These discoveries, following on the heels of our work with discoidin, led me to rethink my research priorities. Although I had worked for more than a decade on the molecular basis of memory storage, and Irwin Levitan had

some promising findings that might allow for identification of molecules involved in synaptic plasticity in *Aplysia,* the work on lectins seemed more attractive for several reasons. First, the developmentally regulated lectins we found in slime molds and chick tissues were abundant proteins that we could easily purify in milligram quantities, in striking contrast with the minute quantities of poorly characterized proteins that Irwin had identified as radioactive peaks on polyacrylamide gels. In the 1970s, before recombinant DNA techniques made possible the synthesis of limitless quantities of any protein by translation of its cDNA, having milligrams of pure protein was a very big deal. Furthermore, the lectins had intriguing properties: they bound specific sugar-containing molecules on and around cell surfaces, which made them reasonable candidates for roles in specific cellular interactions. If we were lucky, lectins might even influence the formation of specific synaptic connections, a hypothesis I put forth once again in *Neuronal Recognition,* a book I edited in 1976. These considerations led me to gradually phase out my work on learning and memory as well as the Ph.D. explorations of my other students—Steve Flanagan, Elaine Traynor, Susan Newlin, and Paula Shadle—and commit myself to studies of lectins.

The Impact of Genetic Technology

The focus on lectins led to several discoveries. The first was stimulated by work in the laboratory of Rick Firtel, a colleague at UCSD. In 1981, using newly developed recombinant DNA techniques, Rick and his colleagues discovered that there were actually three genes encoding discoidin I, and published the deduced amino acid sequences of the three proteins. When we inspected these sequences we found that all forms of discoidin I contain the sequence arg-gly-asp, a sequence also found in fibronectin, a human cell adhesion molecule. Because it was already known that synthetic peptides containing this sequence block attachment of fibroblasts to extracellular matrix, Wayne Springer, a post-doc, and Doug Cooper, a graduate student, tested the effects of similar peptides on the adhesion of slime mold cells to various coated surfaces, and on their streaming into aggregates. We found that the synthetic peptides blocked attachment and streaming, as did univalent antibodies to discoidin I. From these and other experiments we concluded that, as with fibronectin, this sequence of three amino acids in discoidin I is a critical element in its biological function and that this part of the protein, rather than its carbohydrate-binding site, is the one clearly involved in cell adhesion. So the role of discoidin I in adhesion was confirmed, but the biological significance of its interaction with sugars—the reason we were interested in it in the first place—is still not completely clear.

Exciting though these findings were, the path of their discovery, and the ambiguous role of the carbohydrate site of discoidin I made me reconsider

my commitment to continued work with slime molds. The main attraction of this experimentally favorable model system was as a potential source of discoveries that would guide research on humans. Indeed Wayne Springer and Andy Feinberg were busily developing methods to examine cell sorting in slime molds, which we hoped to apply to human cell recognition. But in our analysis of the action of discoidin I the guidance was clearly the other way around: our progress in understanding slime molds was based on discoveries already made with human fibronectin.

This conclusion was premature. Beginning in 1993, with extensive sequencing of human DNA, many investigators found human proteins that contain discoidin-domains, as well as evidence that these domains play important roles in cell signaling and adhesion. Among these human proteins are two that are now called discoidin-domain-receptor-1 and -2 (DDR1 and DDR2). These integral membrane proteins were first identified in a genetic screen for tyrosine kinases. Then, in comparing their sequences with those in the gene data base, the computer revealed the surprising finding that the tyrosine kinases each have an extracellular domain that resembles discoidin I. This resemblance raised the possibility that these proteins bind to extracellular matrix; and, because their ligands were not then known, they were named discoidin-domain proteins. The suspicion that they might bind to extracellular proteins soon led to the discovery that they bind specifically to collagen and that this interaction activates specific intracellular signaling pathways.

Of particular interest to neuroscientists, DDR1 is abundant in the brain, and has been directly implicated in synapse formation. So too are other discoidin-domain-containing proteins such as neuropilins and neurexins, which participate in brain cell adhesion and synapse formation by interactions with semaphorins and with neuroligin. Recently RS1, a cell adhesion protein that interacts with neuronal cells in the retina, has been shown to be an octamer of eight subunits each largely composed of a discoidin domain; and mutations in this domain cause retinoschisis, a common X-linked form of hereditary macular degeneration that affects males early in life. So the discovery of discoidin did contribute to studies of neuronal cell adhesion and synapse formation after all.

Although I did not then know how genetic technology would make our discovery of discoidin relevant to cellular interactions in the human brain, it was already clear in the mid 1980s that vertebrate genes and tissues had become experimentally accessible in ways that I did not anticipate when plunging into slime mold research. Meanwhile we kept turning up new galactose-binding lectins in a variety of animal tissues. First Eric Beyer, an M.D.-Ph.D. student, purified one from chicken intestine that had different properties than the one we had found in chick muscle. Then Howard Ceri, Robert Cerra, Hakon Leffler, and Carl Sparrow found several galactose-binding lectins in rat and human tissues, and Marie Roberson

found another lectin in *Xenopus*. When our immunohistochemical studies with fluorescence and electron microscopes localized these lectins on cell surfaces and in extracellular matrix, I drew attention to this new class of extracellular proteins with a review in *Science*. In other immunohistochemical studies with Tom Jessell, Jane Dodd, and their student, L.J. Regan, we found evidence for two different lectins in subsets of neurons of dorsal root ganglion and spinal cord, a step toward addressing their potential role in neuronal interactions that first attracted me to this field.

Further discovery of related lectins followed when Michael Gitt began supplementing our biochemical work with gene cloning in the mid-1980s. While screening human cDNA clones with an antibody raised against a purified mammalian lectin, Michael found a few that encoded a second related lectin. When he identified the human genes that encoded these two lectins in genomic DNA he named them *LGALS1* and *LGALS2* (which encode the lectins we now call galectin-1 and galectin-2).

As I became increasingly familiar with the new genetic technology I also began paying attention to its application to studies of heritable human diseases. Having served briefly as a consultant for the Hereditary Disease Foundation, I had been informed by Nancy Wexler of the search for the Huntington's disease gene; and, when the gene was mapped in 1983, I decided to explore the application of this technology to psychiatry. With the help of David Housman, who had played a key role in the Huntington's disease project, I organized a small conference—"Looking for Genes Related to Mental Illness"—at the Neurosciences Institute, the successor to the Neuroscience Research Program, which had been moved to Rockefeller University under the direction of Gerry Edelman. The highlight of this conference, held in October 1984, was the report by Housman and his post doc, Daniella Gerhard, of genetic studies of manic-depressive patients from Amish families identified by Janice Egeland. Using the same approach that had located the Huntington's disease gene, they had some evidence that a gene on chromosome 11 might influence the risk of developing manic-depression (bipolar disorder), a finding they would publish in *Nature* a few years later.

As I developed my interest in lectin genes, and in the gene variants that influence the risk of mental illness, my professional life was about to undergo another major change. In 1985 I received a letter from Zach Hall asking if I would be interested in moving to the University of California School of Medicine in San Francisco (UCSF) as Chair of the Department of Psychiatry. I was already a big fan of UCSF, which my mentor Gordon Tomkins had joined in 1968, and which I visited several times around 1974 when, shortly before his untimely death, Gordon tried to recruit me to help set up a new neuroscience program. Zach Hall was eventually hired to head that program which he developed into a world leader. Now Zach was asking if I would help build bridges between neuroscience and psychiatry.

Zach's inquiry came at a time when I was ready to consider such a move. Both my daughters were in college at UCLA, which greatly diminished my parenting responsibilities. With their departure I was eager to begin a new life, even find a wife, and it seemed to me that this might be easier if I moved to San Francisco. The city itself was yet another attraction. And UCSF was rich in colleagues and close friends, including Steve Rosen who was studying a lymphocyte lectin (L-selectin) like those we had been looking for in slime molds. Although I was not eager to take on the administration of a vast psychiatry department, the resources it could provide seemed an ample reward for these new responsibilities.

The hardest thing about leaving La Jolla was the many friends I had made. Most of them were the people I worked with every day, such as David Segal and Lew Judd. But I would also miss the members of the First Thursday Dinner Club, which I had joined at its inception in 1979 along with Gustav Arrhenius, Francis Crick, Sandy Lakoff, Richard Lerner, Walter Munk, Leslie Orgel, Roger Revelle, Ellie Schneour, and Charlie Thomas. Drawn from UCSD, the Salk Institute, and the Scripps Research Institute, we met every month in La Valencia Hotel for conversations that I always looked forward to. It was also hard to leave my home on the La Jolla hillside, where my children had grown up, and my mother-in-law Fanny. Nevertheless, I accepted Zach's challenge. In September 1986 I drove up to Los Angeles to visit my daughters and continued north to San Francisco to begin yet another new life.

Building Psychiatric Science at UCSF

The challenge proved to be even greater than I had imagined. The psychiatry department I inherited was still steeped in the psychoanalytic traditions that I had found so limiting when I was a medical student, and many of its faculty members were not happy with Dean Rudi Schmidt's decision to bring me in to steer it in a more scientific direction. Furthermore, the Langley Porter Psychiatric Institute, in which the department is headquartered, had just a few tiny labs, so space and resources would have to be diverted to build facilities for research. Such changes were bound to meet with the resistance I continuously struggled with during my 7 years as Psychiatry Chair.

Fortunately there were some young people at UCSF who helped me move the department in this new direction. The first one I hired was David Cox, a medical geneticist. Along with Victor Reus, a biological psychiatrist, we set out to build an NIMH-sponsored program to hunt for gene variants in patients with bipolar disorder, following the lead of Housman and others. To flesh out this program I hired Nelson Freimer, a recent Langley Porter graduate, and enlisted the participation of Rick Meyers, a young geneticist in the physiology department. They soon joined forces in a new

Neurogenetics Laboratory we built on the site of an abandoned kitchen in Langley Porter.

Stanford, which is just a short drive from UCSF, was another source of talent. Among its psychiatry residents was Rob Malenka, a cellular neurophysiologist, and John Rubenstein, a molecular biologist with training in child psychiatry, both of whom I recruited as assistant professors. They were soon joined by three more young psychiatrist-scientists: Larry Tecott, a behavioral geneticist from our own residency program; Mark Von Zastrow, a cellular neurobiologist from Stanford; and Allison Doupe, who had done a psychiatry residency at UCLA and a post doctoral fellowship in systems neuroscience at Caltech. This group formed the core of UCSF's Center for Neurobiology and Psychiatry, which I have led since concluding my term as Chair of Psychiatry at the start of 1994.

While these recruitments were going on I continued my research on lectins with the help of Hakon Leffler, Doug Cooper, and Michael Gitt, in a new lab built on the site of a former suite for occupational therapy—a more elegant shell for remodeling than the lavatory I had converted when moving to Einstein 30 years earlier. I also continued a collaboration with Tom Jessell on lectin expression in the nervous system, along with two of his Columbia trainees, Mary Hynes and Linda Buck—before her Nobel Prize-winning discovery of olfactory receptors. But my main aim during that period was to find all the vertebrate lectins we could, instead of concentrating on their biological functions. With the help of Steve Massa, Yuko Oda, Phillipe Marschal, and Margaret Huflejt, we discovered and characterized a number of new human, rodent, and frog galactose-binding-lectins. Hakon Leffler was particularly interested in discovering the specificity of each lectin by examining its affinity for various galactose-containing saccharides, a project he now continues as Professor of Laboratory Medicine at Lund University in his native Sweden.

We did, however, devote a lot of attention to an unusual feature of these lectins. Like discoidin, none of them has a signal peptide characteristic of secreted proteins. Yet we knew that they become concentrated on the surface of cells and in the extracellular matrix. Working with a cell line of mouse myoblasts, Doug Cooper found that its lectin is initially confined to the cytoplasm and then accumulates in membrane evaginations which pinch off, releasing it outside the cell. The details of this novel secretory mechanism have still not been worked out.

As it became clear that all the lectins we found share a carbohydrate-recognition domain of about 130 amino acids, and that members of this family were also being discovered in other laboratories, and given a variety of names, I contacted the main investigators to reach a consensus about nomenclature. We agreed on the name galectin, with each of the known mammalian galectins receiving a number, and new ones to be numbered in the order in which they were found. This name has caught on: PubMed

citations of galectin continue to grow exponentially, and galectins were recently the subject of a special issue of *Glycoconjugate Journal,* which the editors kindly dedicated to me.

Other Activities

Throughout my career I have been an eager participant in communities outside of my home institution. In recent years this has included membership in the scientific boards of biotechnology companies such as Dupont-Merck Pharmaceuticals, Guilford Pharmaceuticals, and Renovis Inc. The repeated meetings of these groups have taught me a lot about the practical applications of biomedical research and have fostered friendships with other members such as Sidney Brenner, David Martin, Sol Snyder, and Corey Goodman. Sidney also invited me to serve with him on Singapore's International Advisory Committee for Biomedical Research, and it has been fascinating to see how this small nation has positioned itself as a significant player in this field.

But my most enduring and gratifying extramural association has been with the McKnight Endowment Fund for Neuroscience. An offshoot of the Minneapolis-based McKnight Foundation, its support of neuroscience began with consultations in the mid-1970s with Fred Plum and Julius Axelrod. They convened a founding committee that I was asked to join along with Edward Evarts, Seymour Kety, and James McGaugh. At our initial meeting in July 1976, chaired by Julie, we created a Scholars Awards program to help young faculty establish an independent career. This remains an influential program that supports about six new Scholars each year, many of whom have become leaders in the field. I served on the initial selection committee for these awards and have been associated with the development of new McKnight awards ever since.

In 1986 Russ Ewald, the Executive Director, persuaded the Board of Directors of the McKnight Foundation to provide long term support for this program by spinning it off as an independent nonprofit organization—the McKnight Endowment Fund for Neuroscience. Fred Plum was the founding President, and I succeeded him 3 years later, serving for almost a decade. I was succeeded by Torsten Wiesel and then Corey Goodman (Fig. 3) but continue to participate in various McKnight activities. I am very gratified by my long association with the McKnight Foundation and believe that its sustained commitment to neurosciences has had an impact that rivals that of the Neuroscience Research Program, which helped me so much in my youth.

My involvement with the McKnight Foundation also changed my life in another way, by bringing me together with my wife, Louann Brizendine. Already on the UCSF faculty, Louann was acquainted with Larry Ellison, the billionaire founder of Oracle, and had interested him in the possibility

Fig. 3. Presidents of the McKnight Endowment Fund for Neuroscience at the McKnight Conference on Neuroscience, Aspen CO, May 2000. Left to right: Torsten Wiesel, Samuel Barondes, Fred Plum, Corey Goodman. (Photo kindly provided by Peter Mombaerts.)

of establishing a foundation to support biomedical research. Knowing little about such activities she was advised by Eugene Roberts, a mutual friend, to consult me because of my work with McKnight. Early in 1996 Louann came to see me about this, and we soon developed a personal relationship, marrying in 2002. The foundation she worked to establish, with the help of Joshua Lederberg became the Ellison Medical Foundation, which Josh continues to lead.

Aside from the McKnight Foundation, my most important extramural affiliation had been with the National Institutes of Health, a beloved alma mater which I have served almost continuously since I left in 1963 and which I returned to for several brief sabbaticals as a Fogarty Scholar, beginning in 1979. One of my favorite assignments was as Chair of the NIMH Genetics Workgroup whose members were Aravinda Chakravarti, Mary Claire King, Eric Lander, Bob Nussbaum, Ted Reich, Joe Takahashi, and Steve Warren. In 1997 we prepared a report that continues to shape NIMH policy on psychiatric genetics and that established the principle of sharing clinical data and DNA samples. I most recently served on NIMH's Board of Scientific Counselors, which I chaired from 2001 to 2003.

I have also developed a new career as a writer of books for a general audience. My interest in publishing goes back to *Cellular Dynamics of the Neuron* in 1969 and continued with my editorship of Current Topics in Neurobiology, a series that included my 1976 book *Neuronal Recognition.*

Over the years I served as Chair of the Publications Committee of the Society for Neuroscience and was on the founding editorial boards of *The Journal of Neurobiology, The Journal of Neuroscience, Glycobiology,* and *Molecular Psychiatry.*

But I really got the writing bug when I was commissioned to write *Molecules and Mental Illness,* a volume on biological psychiatry in the Scientific American Library, which was published in 1993. It was followed in 1998 by *Mood Genes,* about the hunt for the gene variants that predispose people to mania and depression, and, 5 years later, by *Better Than Prozac,* about psychiatric drugs. Another one is in the works.

Looking Ahead

In reviewing my life in science it is hard to avoid the temptation to speculate about the future. I do this with trepidation because my past record of prognostication is a mixed one. On the one hand the prediction that molecular biology would transform neuroscience, which came to me via Gordon Tomkins, has been fulfilled so convincingly that students find it hard to believe that it was not always self-evident. On the other hand the impact of molecular research in psychiatry has not yet been as great as I expected.

This is not to say that psychiatry has remained the same. During my training the intellectual core of the field was mainly Freudian, psychiatric residents were taught that psychopathology was the result of the traumas of early childhood, and the standard treatment was a form of wide-ranging psychoanalytic psychotherapy designed to undo this damage. Now the field has incorporated a great deal of brain science; residents are well aware that genetic susceptibility to mental disorders has an etiological role on a par with life events, and the more focused psychotherapies that have largely replaced psychoanalysis are heavily supplemented with drugs that influence molecular targets in the brain.

But, impressive though these changes have been, progress has been slower than I anticipated. Geneticists who have been searching for relevant gene variants in patients with mental disorders have been frustrated by the complexity of the problem, because so many genes appear to be involved that it is hard to implicate any one with certainty. And despite the identification of a series of intriguing molecular targets for new psychiatric drugs, creating them has proved to be extremely difficult. As scientists at pharmaceutical companies know only too well, many promising compounds have been abandoned because of undesirable side effects, whereas others simply do not work or are no better than those already available.

Nevertheless, I remain optimistic. We keep finding more affordable ways to identify variants in individual genomes, so the massive screens this makes possible are bound to identify many of the genes that influence the risk of mental illness. We also keep learning so much about the proteins

and small molecules in the brain, and about ways to manipulate them, that new treatments will certainly follow. So it seems to me that it is just a matter of time until we successfully translate this growing knowledge and technology into new ways to alleviate mental suffering.

In the end, what has been most rewarding to me about my activities in neuroscience and psychiatry is that it has allowed me to combine my interests in elegant science with my enduring fascination with the moral and psychological issues that I was introduced to in my childhood. This rich mixture was the allure that drew me to these fields. The allure remains.

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