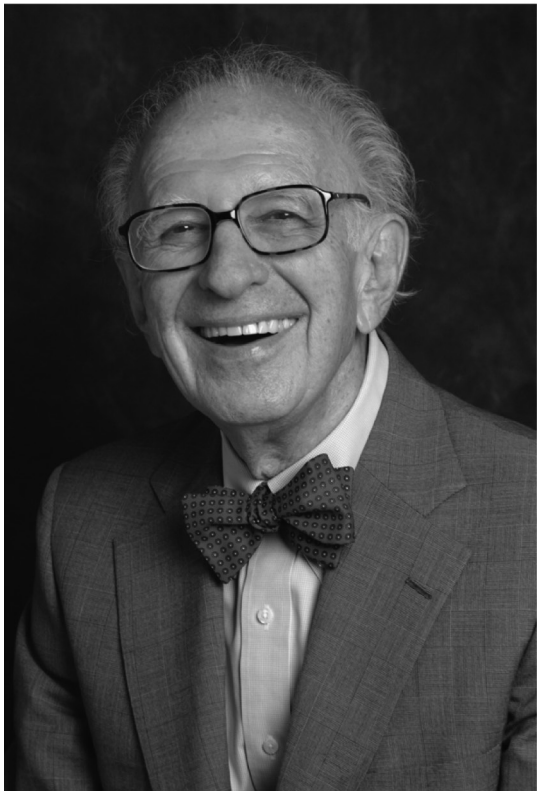

Eric Kandel

Born:

Vienna, Austria
November 7, 1929

Education:

Harvard College, Cambridge, MA, BA (1952)
NYU School of Medicine, New York, NY, MD (1956)

Appointments:

Intern, Montefiore Hospital, New York (1956–1957)
Associate in Research, Laboratory of Neurophysiology, NIMH, Bethesda (1957–1960)
Psychiatry Resident, Mass Mental Health Center, Psychiatry Instructor, Harvard Medical School (1960–1964)
Special Fellow, U.S. Public Health Service, College de France (Lab of Ladislav Tauc) (1962–1963)
Associate Professor to Professor, Depts. of Physiology and Psychiatry, NYU School of Medicine (1965–1974)
Professor, Depts. of Physiology, Biochemistry and Molecular Biophysics, Columbia U (1974–present)
Director, Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia U (1974–1983)
University Professor, Columbia U (1983–present)
Senior Investigator, Howard Hughes Medical Institute (1984–present)
Kavli Professor and Director, Kavli Institute for Brain Science Columbia U (2004–present)
Co-Director, Mortimer B. Zuckerman Mind Brain Behavior Institute, Columbia U (2009–present)

Honors and Awards (Selected):

National Academy of Sciences, 1974
National Institute of Medicine, 1988
Corresponding Member, German Academy of Science, Leopoldina, 1989
Orden Pour le Mèrite für Wissenschaften und Künste, Member, 1997
Athenian Academy, Foreign Associate, 2001
Austrian Academy of Sciences, Foreign Member, 2002
The Royal Society of London for Improving Natural Knowledge, Foreign Member, 2013
Twenty-three honorary degrees
Honorary Citizenship of the City of Vienna, Austria, 2009

Scientific Awards (Selected):

Karl Spencer Lashley Prize in Neurobiology (Awarded by the American Philosophical Society), 1981
The Dickson Prize in Biology and Medicine (Awarded by the University of Pittsburgh), 1982
Albert Lasker Basic Medical Research Award (Shared with Vernon B. Mountcastle), 1983
Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research (Awarded by Brandeis University), 1984
Gairdner International Award for Outstanding Achievement in Medical Science, 1987
Harvey Prize (Awarded by the Technion, Israel Institute of Technology, Haifa, Israel), 1993
Wolf Prize in Biology and Medicine, Israel, 1999
Dr. A.H. Heineken Prize for Medicine (Awarded by the Royal Netherlands Academy), 2000
Nobel Prize in Physiology or Medicine (shared with Paul Greengard and Arvid Carlsson), 2000
Austrian Medal of Honour for Science and Art, 2005
Benjamin Franklin Medal for Distinguished Achievement in the Sciences, American Philosophical Society, 2006

Most of Kandel's work has been devoted to the cellular and molecular mechanisms of learning and memory, first in the snail Aplysia *and later also in mice.*

Eric Kandel

Prologue: Life in Vienna in the 1930s

There was little in my early life to indicate that biology would become the passion of my academic career. In fact, there was little to suggest that I would have an academic career at all. Rather, my early life was importantly shaped by my childhood experiences in Vienna, and I spent many later years coming to grips with the circumstances in Austria at the time of my birth.

I was born in Vienna on November 7, 1929, 11 years after the multiethnic Austro-Hungarian Empire fell apart following its defeat in World War I. Although Austria had been radically reduced in size (from 54 million inhabitants to only 7 million) and in political significance, its capital, the Vienna of my youth, was still one of the great cultural centers of the world. A city of one and a half million people, it was home to Sigmund Freud, Karl Kraus, Robert Musil, Arthur Schnitzler, and for a while, Arnold Schoenberg. The music of Gustav Mahler and of the earlier 19th-century Vienna School resonated throughout the city, as did the bold expressionist images of Gustav Klimt, Oskar Kokoschka, and Egon Schiele. Despite its cultural and intellectual vibrancy, however, Vienna in the 1930s was the capital city of an oppressive, authoritarian political system. I was too young to appreciate its cultural richness, but I sensed later, from the perspective of a more carefree adolescence in the United States, the oppressive conditions in Vienna that affected my childhood.

Even before the Anschluss, in 1938, anti-Semitism was endemic in Viennese life. Jews, who made up nearly 20 percent of the city's population, were discriminated against in the civil service and in many aspects of social life. They were nonetheless fascinated by the city in which they had lived for over a thousand years. My parents genuinely loved Vienna, and in later years, I came to understand why the city exerted such a powerful hold on them. My parents loved the dialect of Vienna, its cultural sophistication, and its artistic values. "The greatest grim irony of all was the fierce attachment of so many Jews to a city that through the years demonstrated its deep-rooted hate for them," wrote George Berkley (1988), the American historian of Vienna and its Jews. This fierce attachment was considered by the historian Harvey Zohn to be the most tragically unrequited love in world history.

In spite of the hostile climate, Austrian Jews continued to make remarkable contributions to theater, music, literature, science, and medicine in the period between the two World Wars. The Salzburg Festival was directed by Max Reinhardt; the Vienna Opera was conducted by Bruno Walter. Stefan

Zweig and Franz Werfel were two of the most popular writers in the German language, and Elias Canetti, who later won the Nobel Prize in Literature for his books describing his youth in Vienna, began writing in the 1930s. Two of the three Austrians awarded the Nobel Prize in Physiology or Medicine in the 1930s were of Jewish origin: Karl Landsteiner was honored in 1930 for his discovery of blood groups and Otto Loewi in 1936 for discovering acetylcholine, a chemical transmitter that slows the heart. Of the 52 Olympic medals earned by Austrians from the beginning of the modern Olympics to 1936, 18 were won by Jewish athletes. Fully half of the practicing physicians and medical faculty at the University of Vienna were Jewish. This was the last period during which Viennese medicine attracted students and patients from all over the world. They came to study with, or to be treated by, pioneers in diagnostics and therapeutic medicine, such as the pediatrician Béla Schick, the ear specialist Heinrich von Neumann, and the psychoanalyst Sigmund Freud. As this listing makes clear, the period of my early youth was "the final flowering of the Austrian Jewish intellectual activity."

My parents were not born in Vienna, but they had spent much of their lives there, having each come to the city at the beginning of World War I, when they were very young. My mother, Charlotte Zimels, was born in 1897 in Kolomea, a town of about 43,000 inhabitants in Galicia, a region of the Austro-Hungarian Empire. (Kolomea is now part of the Ukraine and has been renamed Kolomyya.) Almost half the population of Kolomea was Jewish, and the Jewish community had a very active culture. My mother came from a well-educated middle-class family, and although she had spent only one year at the University of Vienna, she spoke and wrote English as well as German and Polish.

My father, Herman, was born into a poor family in 1898 in Olesko, a small town of about 3,500 people near Lvov (Lemberg), now also part of the Ukraine. He was drafted into the Austro-Hungarian Army directly from high school. After the war, he worked to support himself; he never went back to school.

My parents met in Vienna and married in 1923, shortly after my father had established himself as the owner of a small toy store. My older brother, Lewis, was born on November 14, 1924. We lived in a small apartment at Severingasse 8 in the Ninth district, a middle-class neighborhood near the medical school and not too far from Freud's apartment, although we had no association with either. Both of my parents worked in the store, and we had a full-time housekeeper to help out at home.

I went to a school near our house. Like most elementary schools in Vienna, it was very traditional and very good, and I followed the path blazed by my exceptionally gifted brother in the same school with the very same teachers. Throughout my years in Vienna I felt that his was an intellectual virtuosity that I would never match. By the time I began reading and writing, he was already starting to master Greek and to play the piano.

My fondest early memories are of family get-togethers and vacations. On Sunday afternoons my Aunt Minna (my mother's sister) and Uncle Srul would come for tea. This was an occasion for my father and uncle to play cards, games at which my father excelled and which brought out great animation and humor in him. We celebrated Passover in a festive way at the home of my grandparents Hersch and Dora Zimels, and we invariably went on vacation in August to Monichkirchen, a small farming village in the southeast portion of Lower Austria, not far from Vienna.

Just as we were about to depart for Monichkirchen in July 1934, the Austrian Chancellor, Engelbert Dollfuss, who had outlawed the Nazi Party, was assassinated by a band of Austrian Nazis disguised as policemen—the first storm to register on my newly developing political awareness. During the early years of Dollfuss's successor, Kurt von Schuschnigg, the Austrian Nazi Party went further underground, but it continued to gain new adherents, especially among teachers and other civil servants. Paradoxically, the Austrian drive toward authoritarianism was abetted by Dollfuss's political attitudes and actions. Modeling himself on Mussolini and Hitler, Dollfuss had renamed his Christian Socialist Party the Fatherland Front and took to wearing a modified swastika. To assure his control of the government, he abolished Austria's constitution and outlawed not only the Nazi Party but *all* opposition parties. Thus, although Dollfuss opposed the efforts of the Austrian National Socialist movement to form a Pan-German state with Germany, his abolition of the constitution and of other political parties helped open the door for Hitler to march in.

And march in he did, as I well remember. Since his youth, Hitler had dreamed of a unified Austria and Germany. Not surprisingly, a key point in the Nazi program, from its very beginnings in the 1920s, was the merger of all German-speaking people into a Greater Germany. Hitler began to put this program into action in the fall of 1937 by increasing his rhetoric and threatening to move against Austria. Schuschnigg, eager to assert Austria's independence, met with Hitler on February 12, 1938, in Berchtesgaden. Hitler showed up with two of his generals in tow and threatened to invade Austria unless Schuschnigg lifted the legal restrictions on the Austrian Nazi Party and appointed three Austrian Nazis to key positions in his Cabinet. Schuschnigg refused, but as Hitler continued to intimidate him, he compromised and agreed to legalizing the Nazi party and granting it two cabinet positions.

The agreement between Schuschnigg and Hitler so emboldened the Austrian Nazis that they began to challenge the Austrian government in a series of incidents that the police had difficulty controlling. Faced with Hitler's aggression from without and the Austrian Nazi rebellion from within, Schuschnigg took the offensive on March 9 and boldly called for a plebiscite on Austria's autonomy to be held four days later, on March 13.

This courageous move caught Hitler completely by surprise—an awkward surprise, since it seemed almost certain that the vote would favor

an independent Austria. Hitler responded by mobilizing troops and threatening to invade Austria unless Schuschnigg postponed the plebiscite, resigned as chancellor, and formed a new government with an Austrian Nazi, Arthur Seyss-Inquart, as chancellor. Schuschnigg turned for help to England and Italy, two countries that had formerly supported Austrian independence. But on this occasion both countries failed to respond. Abandoned by his potential allies and concerned about needless bloodshed, Schuschnigg resigned on the evening of March 11. "Austria is yielding to force," he announced in an emotional farewell radio address to the nation. "God protect Austria." Even though Schuschnigg had resigned and the new President Miklos gave in to all the German conditions, Hitler nonetheless invaded Austria.

Hitler's triumphal march into Vienna and his ecstatic reception by the Viennese public made an indelible impression on me. My brother had just finished building his first short-wave radio receiver, and on the evening of March 13, we both listened with earphones as the broadcaster described the crossing of the Austrian border by German troops on the morning of March 12. Hitler followed later that day, crossing the border first at Braunnau am Inn, his native village, and then moving into Linz, the capitol of Upper Austria, where people welcomed him in the marketplace as a native son, screaming "Heil Hitler." Of the 120,000 people of Linz, almost 100,000 came out to greet Hitler. In the background we could hear the Horst Wessel song, a hypnotic Nazi marching song that even I found captivating. On the afternoon of March 14, Hitler's entourage reached Vienna, where a wildly enthusiastic crowd welcomed him as the hero who had unified the German-speaking people.

The extraordinary reception Hitler met with in Linz and Vienna caused him to realize that Austria would not demand to be a relatively independent protectorate of Germany, as he had assumed. Instead, Austrians would readily accept—indeed, would welcome—annexation. It seemed as if everyone, from the modest shopkeepers to the most elevated members of the academic community, now embraced Hitler. In a shocking move, even Theodor Cardinal Innitzer, the influential Archbishop of Vienna, welcomed Hitler and ordered all the Catholic churches in the city to fly the Nazi flag and to ring their bells in honor of Hitler's arrival. As the Cardinal personally greeted Hitler, he assured him of his own loyalty and that of all Austrian Catholics—which is to say, most of the population of Austria. The Cardinal promised Hitler that Austria's Catholics would become "the truest sons of the great Reich into whose arms they had been brought back on this momentous day," provided that the liberties of the Church were respected and its role in the education of the young guaranteed (Berkley 1988 p 323).

That night, and for days on end, all hell broke loose. Viennese mobs erupted in a nationalistic fervor, which they expressed by beating up Jews and destroying their property. Foreign commentators, long accustomed to Nazi tactics in Germany, were astonished by the wanton brutality of the

Austrian Nazis; even German Nazis were amazed and emboldened by the viciousness of the attacks in Vienna. In his autobiography, the German playwright Carl Zuckmayer, who had moved to Austria in 1936 to escape Hitler, described Vienna during the days following the annexation as a city transformed "into a nightmare painting of Hieronymus Bosch." It was as if

> Hades had opened its gates and vomited forth the basest, most despicable, most horrible demons. In the course of my life I had seen something of untrammeled human insights of horror or panic. I had taken part in a dozen battles in the First World War, had experienced barrages, gassings, going over the top. I had witnessed the turmoil of the post-war era, the crushing uprisings, street battles, meeting hall brawls. I was present among the bystanders during the Hitler Putsch in 1923 in Munich. I saw the early period of Nazi rule in Berlin. But none of this was comparable to those days in Vienna. What was unleashed upon Vienna had nothing to do with [the] seizure of power in Germany. . . . What was unleashed upon Vienna was a torrent of envy, jealousy, bitterness, blind, malignant craving for revenge. All better instincts were silenced . . . only the torpid masses had been unchained. . . . It was the witch's Sabbath of the mob. All that makes for human dignity was buried (Zuckmayer 1966).

Having watched the build-up of anti-Jewish laws in Germany following Hitler's rise to power in 1933, my parents needed no convincing that the violence in Austria was not likely to fade away. We knew that we had to leave—and as soon as possible. My mother's brother, Berman Zimels, had emigrated a decade earlier to New York and established himself as an accountant. He quickly provided us with affidavits stating that he would support us upon our arrival in the United States, but even with the affidavits, it took about a year for my parents' Polish quota number to be called. When the number finally was called, we had to emigrate in stages because of U.S. immigration laws. My mother's parents left first, in February 1939, my brother and I next, in April 1939, and finally my parents, in September 1939, only days before World War II broke out.

During the year that we lived under Nazi rule, we experienced directly Vienna's humiliating form of anti-Semitism. The day after Hitler marched into Vienna, every one of my non-Jewish classmates—the entire class, with the exception of one girl—stopped talking and interacting with me. In the park where I played, I was taunted and roughed up. This viciousness toward Jews, of which my treatment was a mild example, culminated in the horrors of Kristallnacht on November 8, 1938. On the morning of November 7, 1938, a 17-year-old Jewish youth, distraught over his parents' tragic fate at the hands of the Nazis, shot a third secretary in the German Embassy

in Paris, mistaking him for the German Ambassador. In retaliation for this act, almost every synagogue in Germany and Austria was set on fire. Of all the cities under Nazi control, Vienna saw the most wanton destructiveness on Kristallnacht. Jews were taunted and brutally beaten. They were expelled from their businesses and temporarily evicted from their homes so that their neighbors could loot them. My father, together with hundreds of other Jewish men, was rounded up by the police. He was released a few days later only because he had fought in the Austro-Hungarian army as a soldier in World War I.

I remember Kristallnacht, more than 75 years later, almost as if it were yesterday. It fell two days after my ninth birthday, on which I had been showered with toys from my father's shop. When we returned to our apartment a week or so after having been evicted, everything of value was gone, including my toys.

My last year in Vienna fostered in me a profound sense of gratitude for the life I have led in the United States. It is probably futile, even for someone trained in psychoanalytic thinking, as I am, to attempt to trace the complex interests and actions of my later life to a few selected experiences of my youth. Nevertheless, I cannot help but think that the experiences of my last year in Vienna helped to determine my later interests in mind, in how people behave, the unpredictability of motivation, and the persistence of memory. Over the years, my professional interests evolved from a youthful exploration of European intellectual history at Harvard, where I studied the motivation of German intellectuals during the Nazi era, to the allure of psychoanalysis and its more systematic approach to mental processes, and finally to my fascination with the biology of conscious and unconscious memory.

My early experiences in Vienna almost certainly contributed to my curiosity about the contradictions and complexities of human behavior. How are we to understand the sudden eruption of such great viciousness in so many people? How could a highly educated and cultured society that at one moment nourished the music of Haydn, Mozart, and Beethoven descend in the next moment into barbarism?

The answer to this question is complex, and many scholars have attempted partial answers. One conclusion, troubling to an academic like myself, is that a society's culture is not a reliable indicator of its respect for human life. This rather simplistic conclusion raises the question: How can values within a society become so radically dissociated? As far as I can tell, the Viennese achieved it by shifting their frame of reference. By defining Jews in racial rather than religious terms, they were able to exclude Jews from the more highly evolved European Aryan race, the race they believed to be responsible for the rise of Western civilization.

My last year in Vienna was likely also an important factor in my later interest in the mechanisms of memory. I am struck, as others have been, with how deeply the traumatic events of childhood are burned into memory—and

I would again emphasize that my experiences were trivial compared to those of so many who were seriously harmed or killed. For me, the frightening experiences of my last year in Vienna are certainly the most powerful of my "flashbulb memories," the emotionally charged and vivid memories of significant events in our lives.

Resettlement in the United States

Needless to say, arriving in the United States in April of 1939 was like a breath of fresh air. I never actually said, "Free at last," but I felt it then and have felt it ever since. We settled in Brooklyn and lived at first with my mother's parents. My grandfather was a religious and scholarly man who was somewhat unworldly. My brother said that my grandfather was the only man he knew who could speak seven languages but could not make himself understood in any of them. My grandfather and I liked each other a great deal, and he readily convinced me that he should tutor me in Hebrew during the summer of 1939 so that I might be eligible for a scholarship at the Yeshiva of Flatbush, an excellent parochial school that offered both secular and religious studies at a very high level. Under his tutelage, I succeeded in gaining a scholarship and entered the Yeshiva in the fall of 1939. By the time I graduated, in 1944, I spoke Hebrew almost as well as English, had read through the five books of Moses, the books of Kings, the Prophets, and the Judges in Hebrew, and also learned a smattering of the Talmud.

After my parents arrived, my father worked in a toothbrush factory. Even though he was not fond of his job, he threw himself into the work with his usual energy and was soon reprimanded by the union steward for producing toothbrushes too quickly and making the other workers appear slow. My father was undeterred. He simply loved America—he often referred to it as the "golden Medina," the golden state. Even while still in Vienna he had read avidly the novels of Karl May, an author whose books celebrated the conquest of the American West and the bravery of the American Indians.

In time, my father managed to save enough money to rent and outfit a modest clothing store at 411 Church Avenue in Brooklyn. We lived in an apartment above the store. My father and mother worked together and sold simple women's dresses and aprons, as well as men's shirts, ties, underwear, and pajamas. They earned enough not only to support us all, but also to send me to college and medical school. My father worked in that store until the week before he died, at age 78, in 1976. My mother sold the store soon thereafter and died in 1991 at age 94.

Erasmus Hall High School and Harvard College

In 1944, when I graduated from elementary school, the Yeshiva of Flatbush did not as yet have a high school, so I went to Erasmus Hall High School,

a local public school in Brooklyn that was academically very strong. There I became interested in history, in writing, and in girls. I worked on the school newspaper and became sports editor. I also played soccer and was co-captain of the track team. At the urging of one of my history teachers, John Campagna, a Harvard alumnus, I applied to Harvard College and was one of two students out of my class of about 1,400 to be admitted, both of us on scholarships! Fair Harvard indeed!

Even though I was thrilled by my good fortune, I was apprehensive about leaving Erasmus, convinced that I would never again feel the sheer joy I had experienced there. It was at Erasmus that I first sensed myself emerging from behind the shadow of my brother. I now had distinct interests of my own—jazz, sports, American constitutional history—things that did not interest Lewis. At Harvard I majored in 19th- and 20th-century European history and literature and wrote my honors dissertation on *The Attitude Toward National Socialism of Three German Writers: Carl Zuckmayer, Hans Carossa, and Ernst Junger*. Each of those writers was still alive, and each represented a different position on the political spectrum of fascism: uncompromising liberal opposition and emigration (Zuckmayer), resigned acceptance and internal (spiritual) emigration (Carossa), and intellectual support (Junger). I came to the rather depressing conclusion that many German artists, intellectuals, and academics had succumbed all too eagerly and opportunistically to the nationalistic fervor and racist propaganda of National Socialism. Later studies have found that Hitler did not have widespread popular support in his first year in office. Had intellectuals mobilized effectively and brought along segments of the general population, Hitler's government might well have been toppled.

I originally thought of doing graduate work in European intellectual history, along the lines of my undergraduate dissertation. However, in the course of my studies at Harvard I became friends with a fellow student, Anna Kris, who had also emigrated from Vienna with her parents. Anna's parents, Ernst and Marianne Kris, were both prominent psychoanalysts from Freud's circle. Anna and her parents were very influential in getting me interested in psychoanalysis.

It is difficult to recapture now the extraordinary fascination that psychoanalysis held for young people in 1950. During the first half of the 20th century, psychoanalysis provided a remarkable set of insights into the human mind—insights about unconscious mental processes, psychic determinism, and perhaps most interesting, the irrationality of human motivation. As a result, psychoanalysis outlined a far more coherent, interesting, and nuanced view of the human mind than any other school of psychology. In addition, Anna's parents, who represented academic psychoanalysis in its most intellectual and interesting form, were extraordinary people—intelligent, cultured, and filled with enthusiasm. Ernst Kris, a former curator of

applied art at the Kunsthistorisches Museum in Vienna, had been a world-class art historian before becoming a psychoanalyst. After taking up psychoanalysis, he focused on the psychology of art, an area in which he helped train, among others, the great art historian Ernst Gombrich. Marianne Kris, a wonderful therapist, was the daughter of Oskar Rie, a well-known Viennese pediatrician and Freud's best friend. Marianne, in turn, was a close friend of Freud's distinguished daughter, Anna.

Both Ernst and Marianne Kris were extremely generous and encouraging to me, as they were to Anna's other friends. As a result of my frequent interactions with them and their colleagues, I was converted to their view that psychoanalysis offered a fascinating new approach, perhaps the only approach, to understanding the human mind, including the irrational nature of motivation and unconscious and conscious memory. Eventually, psychoanalysis began to seem much more exciting and interesting to me than European literature and intellectual history.

Medical School at New York University

To become a practicing psychoanalyst, it was best to go to medical school, become a physician, and train as a psychiatrist—a course of study I had not previously considered. So in 1951, almost on impulse, I went to summer school at Harvard and took the required course in introductory chemistry. That summer I shared a house with Robert Goldberger, Henry Nunberg, James Schwartz, and Robert Spitzer, and we all became lifelong friends. A few months later, based on this one chemistry course and my overall college record, I was accepted at NYU Medical School, with the proviso that I complete the remaining course requirements before I entered medical school in the fall of 1952.

I entered NYU Medical School dedicated to studying psychiatry and becoming a psychoanalyst. Although I stayed with this career plan through my internship and psychiatric residency, by my senior year in medical school, I had become so interested in the biological basis of medical practice (as had everyone else in my class) that I decided to learn something about the biology of the mind. At the time, most psychoanalysts thought of the mind in nonbiological terms; however, some of them had begun to discuss the potential importance of the biology of the brain for the future of psychoanalysis. Two of these psychoanalysts, whom I got to know personally, were Lawrence Kubie and Mortimer Ostow; both had a background in neurology. After considerable discussion with them and with another biologically oriented psychoanalyst, Sydney Margolin, I decided to take an elective period at Columbia University with Harry Grundfest. In 1955 NYU had no one on the faculty who was doing basic neural science, and Grundfest was the most intellectually interesting neurobiologist in the New York area.

Harry Grundfest's Laboratory at Columbia University

Grundfest had obtained his PhD in zoology and physiology at Columbia in 1930 and went on to a postdoctoral fellowship there, studying with Selig Hecht, an outstanding psychophysicist who was interested in phototransduction, the transformation of light into neural signals. (Hecht also was the teacher of George Wald, who won the Nobel Prize in 1967 for his discovery of the chemical structure of the visual pigments.) Grundfest joined the Rockefeller Institute in 1935, where he remained for a decade, collaborating with Herbert Gasser. In 1944, while Grundfest was in his lab, Gasser shared the Nobel Prize in Physiology or Medicine with Joseph Erlanger for their introduction of the oscilloscope to neurophysiological studies. The oscilloscope made possible accurate temporal resolution of the waveform and conduction velocities of a propagated action potential. In collaboration with Grundfest, Gasser elaborated on his discovery that the conduction velocity of the action potential is a function of the diameter of the axon. Grundfest also carried out reconstructions of the compound action potential from cross-sectional measurements of axonal diameters in mixed nerves, work that formed much of Gasser's Nobel Prize Lecture.

In deciding to work with Grundfest, I was strongly encouraged by Denise Bystryn, an extremely attractive and interesting Frenchwoman whom I had just met and would later marry. Denise is also Jewish. Her mother helped her father escape from a French concentration camp, and her parents survived the war by hiding from the Nazis in the southwest of France. During a good part of that time Denise was separated from her parents, hidden in a Catholic convent near Cahors. Denise's experiences, although more difficult, paralleled mine in a number of ways that seemed significant to her but did not seem at all important to me when we first met. Over the years, however, our shared childhood experiences in Europe have proved to be defining in both our lives.

Denise, her brother Jean-Claude, and her parents emigrated to the United States in 1949. Denise attended the Lycée Français de New York for a year and was admitted at age 17 to Bryn Mawr College as a junior. On graduating from Bryn Mawr at age 19, she enrolled at Columbia University as a graduate student in sociology. When we met, she had just started research for her PhD thesis in medical sociology with Robert Merton. Denise's father, a gifted mechanical engineer who unfortunately died a year before I met Denise, had advised her to marry a poor intellectual because he would probably be sufficiently ambitious to do interesting scholarship. Denise believed she was following that advice (she certainly married someone who was poor) and always encouraged me to make decisions that favored my doing science.

I spent the first several months in Grundfest's lab working on a number of projects with Dominick Purpura, an independent young scientist just starting out on his own career of cortical physiology. To my surprise, I found

my first experience in a laboratory really interesting, and very different from the classroom. The research questions we were asking fascinated me, and the discussions were penetrating and enjoyable. Dominick was very bright and very entertaining. (I have referred to him as the Woody Allen of neurobiology.) But the actual performance of the experiments was also pleasurable and, when successful, very satisfying. Nevertheless, I began to worry about the methods we were using to address rather sophisticated questions about the electrical properties of dendrites. We were using evoked responses that were initiated by stimulating small areas of the cortex, thereby activating thousands of neurons; I thought these methods too indirect to give easily interpretable results. Grundfest and Purpura, of course, were also concerned and talked repeatedly about doing direct, intracellular recordings from cortical neurons, but neither thought this was likely to succeed.

An Introduction to Stephen Kuffler

It was in this frame of mind that I was introduced to Stephen Kuffler, a Viennese-trained physician-turned-physiologist who, together with Bernard Katz and Grundfest, was to become one of my great neurobiological heroes. One evening Grundfest threw into my lap the September 20, 1955, issue of the *Journal of General Physiology*, with three of Kuffler's papers on excitation and inhibition in the dendrites and soma of isolated sensory nerve cells of the lobster and crayfish. Grundfest said something about Kuffler's being very good and that these papers provided direct evidence of the graded properties of dendrites, evidence that was consistent with what he and Purpura were seeing in cortical neurons. I took the issue home and read the papers as best I could. Although I understood relatively little, one thing stood out immediately: Kuffler was studying dendrites that he could actually see, and he was recording from them directly. He used an invertebrate sensory neuron that sent its dendrites into skeletal muscle that is much like the muscle spindles of vertebrates. In the introduction to the three papers Kuffler wrote:

> The greatest advantage of the present preparation lies in its accessibility, since all cellular components can be isolated and visually observed. Further, the state of excitability of the structures could be controlled and graded by utilizing the physiological mechanisms given by the stretch receptor nature of the preparation. . . . It seems of special interest that the sensory cell of crustacea possessed numerous anatomical features, which bear a striking resemblance to many central nervous system cells of vertebrates (Kuffler and Eyzaguirre 1955).

I learned from Kuffler's papers a new criterion for good science—the importance of having a preparation suitable for testing the questions

to be answered. Kuffler taught me to respect the power of invertebrate neurobiology.

On my graduation from medical school in June 1956, Denise and I married. After a brief honeymoon in Tanglewood, I started an internship at Montefiore Hospital while she continued her thesis research at Columbia. I returned to Grundfest's lab, spending six weeks with Stanley Crain, who had pioneered the electrophysiological study of nerve cells in tissue culture. Crain taught me how to make microelectrodes and how to obtain and interpret intracellular recordings from the giant axon of the crayfish. These experiments confirmed the insights I had gained from reading Kuffler's paper. Crain also gave me my first insights into the universality of cellular processes.

Based on my two brief stints in his laboratory, Grundfest offered to nominate me for a position at the National Institutes of Health, an alternative to serving in the physician's draft, which provided medical personnel for the military during the years following the Korean War. On the basis of Grundfest's recommendation, I was accepted by Wade Marshall, chief of the Laboratory of Neurophysiology at the National Institute of Mental Health/National Institute of Neurological and Communicative Disorders and Stroke (NIMH/NINCDS).

The Neurophysiology Laboratory at the National Institutes of Health

By the time I arrived in Bethesda, Marshall had passed the peak of what had been a remarkable career. In the 1930s he was arguably the most promising and accomplished young scientist working on the brain in the United States. As a graduate student at the University of Chicago in Ralph Gerard's lab in 1936, he discovered that he could record electrical deflections in the somatosensory processing area of the cerebral cortex by moving the hairs of a cat's limb. He appreciated that one might use this electrical signal (the evoked response) to map the brain's representation of the surface of the body.

To study this further, Marshall joined Phillip Bard, chairman of the department of physiology at the Johns Hopkins Medical School, as a postdoctoral fellow in 1937. Bard was a major presence in American neurophysiology. Together with his student Clinton Woolsey, he had surgically removed the somatosensory cortex of the monkey and studied its effect on the "placing reaction," a form of tactile behavior. Marshall joined Woolsey and Bard, and together they carried out a classic series of studies in which they mapped sensory inputs from the body surface in the somatosensory cortex and showed that a topographical representation of the entire body is wired into the brain. Today, this map is still shown in every textbook of neural science. Marshall next collaborated with John Talbott and mapped retinal inputs in the striate cortex. Finally, with Harlow W. Ades, he mapped cochlear inputs in the auditory cortex.

These marvelous scientific achievements came at a price, however. Marshall was so psychologically fatigued that he collapsed and left science altogether for a number of years. When he returned, in about 1945, he moved on to a completely new problem: spreading cortical depression, a propagating, reversible silencing of cortical electrical activity. Marshall enjoyed doing occasional experiments, but he had lost his scientific drive and now focused much of his energy and interests on administrative matters, which he did well. Although eccentric, moody, and somewhat unpredictable, he was a wonderful lab chief. In particular, he was supportive and generous to young scientists and gave us a great deal of freedom.

Just before I arrived at the NIH in 1957, the neurosurgeon William Scoville and the cognitive psychologist Brenda Milner had described the now-famous patient H.M. In order to treat H.M.'s intractable bilateral temporal lobe epilepsy, Scoville had removed the medial temporal lobe on both sides of H.M.'s brain, including the hippocampus, a structure located deep within the temporal lobe. The procedure largely eliminated H.M.'s seizures; however, while retaining all his cognitive functions, he lost the ability to put new information into long-term memory. These findings pinpointed the medial temporal lobe, and especially the hippocampus, as sites specialized for memory storage.

Until the Scoville and Milner paper, the person most closely identified with attempts to localize memory had been Karl Lashley, professor of psychology at Harvard and perhaps the dominant figure in American neuropsychology in the first half of the 20th century. Lashley explored the surface of the cerebral cortex in the rat and systematically removed different areas. In the process, he failed to identify any particular region of the brain that was special to or necessary for the storage of memory. Based on these experiments, he formulated the law of mass action, according to which memory is not localized to any specific region of the cortex but is a distributed property of the cortex as a whole. The extent of any memory defect, Lashley argued, was correlated with the size of the cortical area removed, not with its specific location.

Since I had already begun to think about problems in psychiatry and psychoanalysis in biological terms, the cellular and molecular mechanisms of learning and memory struck me as a wonderful problem to study. I had first become interested in the study of learning at Harvard, where B.F. Skinner, the great behaviorist, was a dominant force in the 1950s. It was clear to me even then that learning and memory are central to behavior, and thus to psychopathology and to psychotherapy. Nothing was known about the cellular mechanisms of learning and memory, and the techniques for studying them, some of which I had learned from Stanley Crain in Grundfest's lab, were just becoming available.

My initial ideas about how to tackle the biology of memory were confused and vague. Because intracellular recordings seemed such a powerful analytic

tool for studying nerve cells, and because the hippocampus seemed particularly important for memory, I wanted to explore the hippocampus in cellular terms. The prospect was even more attractive because, as the great anatomists Santiago Ramón y Cajal and Rafael Lorente de Nó had pointed out, the cellular architecture of the hippocampus is remarkably conserved among mammals, and the main cell type, the pyramidal cell, is found in a discrete layer that is easy to target with microelectrodes. In addition, because the pyramidal cells send their axons into a large fiber tract (the fornix), one could identify individual cells electrophysiologically by stimulating the axons in the fornix, which would then fire signals back to the cell bodies. I thought it would be interesting to compare pyramidal neurons to the only other mammalian neurons that had been well studied at that time, the motor neurons of the spinal cord. I had the idea that the properties of the pyramidal cells themselves might reveal something about memory storage. I was emboldened to try this technically demanding study because Karl Frank was in the laboratory next to ours, pioneering the examination of spinal motor neurons with intracellular recordings in parallel with John Eccles. Although Frank himself thought that studying the hippocampus was chancy, he was not discouraging.

Almost as soon as I began, my research took an extremely fortunate turn in the person of Alden Spencer, who arrived in Marshall's lab having just graduated from the University of Oregon Medical School. Like me, Alden was becoming interested in the biology of learning and memory. It therefore took little effort to convince him that we should join forces on the hippocampus. Although Alden had no experience with intracellular recordings, he had done electrophysiological research on the brain at the University of Oregon, where he worked with John Brookhardt. Among Alden's many remarkable talents, he had good surgical skills and a fine knowledge of the anatomical organization of the mammalian brain.

Being both naïve and brash, we were not reluctant to tackle what appeared to Frank and others to be the technically difficult problem of obtaining intracellular recordings from cortical neurons in a pulsating brain. Alden and I developed a simple way of reducing pulsations in the hippocampus that allowed us to obtain, on occasion, high-quality recordings for a long enough period (up to one hour) to carry out an initial analysis of the electrical properties of pyramidal cells. By applying to the hippocampus the powerful methodologies we had learned from Frank, we easily picked some low-hanging intellectual fruit.

First, we found that action potentials in hippocampal neurons are initiated not only at the axon hillock, as they are in motor neurons, but also at a second site, which we inferred to be the apical dendrites. These putative dendritic action potentials, which we called fast prepotentials, appeared to trigger the firing at the axon hillock. Second, we found that hippocampal neurons, unlike motor neurons, are not silent in the absence of synaptic

activity; they tend to fire spontaneously, and this firing often takes the form of bursts, or spikes, that are maintained by the summation of depolarizing afterpotentials. Third, we found that hippocampal neurons engage a powerful, recurrent inhibitory system that gives rise to a prolonged inhibitory synaptic action that is several orders of magnitude longer than the recurrent inhibition in the spinal cord.

The mere technical success of obtaining intracellular recordings from hippocampal neurons and the few interesting questions we were able to address caught the enthusiastic attention of, and drew encouragement and help from, our senior colleagues at the NIH: Marshall, Frank, Frank's gifted colleague Michael Fuortes, and the great biophysicist Ichiji Tasaki. When John Eccles visited the NIH he, too, was generous in his comments. But even in our brashest moments, we both realized that ours was a typical NIH story: in the Intramural Program young, inexperienced people were given the opportunity to try things on their own, knowing that wherever they turned, experienced people were available to help out.

As Alden and I reviewed our work, we realized that the properties of hippocampal neurons are not sufficiently different from those of spinal neurons to explain the ability of the hippocampus to store memory. Thus, it dawned on us what in retrospect is quite obvious: the neuronal mechanisms of learning and memory reside in how neurons are functionally connected. Learning results when connections among neurons are modified by appropriate sensory signals. This conclusion, so clear in retrospect, emerged only gradually as we learned, mostly through reading and discussions with one another, to think more effectively about the biology of learning and memory.

This realization led us to reappraise our strategy. Even though we were now quite familiar with the hippocampus, it was not the place to begin. The hippocampus has a large number of neurons and an immense number of interconnections. We would have great difficulty working out how sensory information specific to learning reaches the hippocampus and how learned information processed by the hippocampus might influence motor output.

Alden and I therefore became convinced that to make headway with the study of learning at the cellular level, we would have to take a very different approach. Alden, a committed mammalian neurophysiologist, turned to the study of the spinal cord, particularly the modifiability of spinal reflexes, and went on to make important contributions in collaboration with Richard Thompson. However, even the spinal cord proved too difficult for a detailed cellular analysis, and both Alden and Thompson ended up abandoning it.

The Search for a Tractable System for Studying Learning

Influenced by Kuffler, Grundfest, and Crain, I yearned for a more radically reductionist approach to the biology of learning and memory. I wanted a system that would serve the cellular study of learning as well as the giant

axon of the squid had served the study of the action potential or the nerve-muscle synapse of the frog had served the study of synaptic transmission. I wanted to find an experimental animal in which a simple behavior could be modified by learning. Ideally, that behavior should be controlled by only a small number of large, accessible nerve cells; in that way, I could relate the animal's overt behavior to events occurring in the cells that control that behavior.

Such a reductionist approach is traditional in biology. In neurobiology it is exemplified by the work on the squid's giant axon by Hodgkin and Huxley, the nerve-muscle synapse of the frog by Bernard Katz, and the eye of *Limulus* by Keefer Hartline. When it came to the study of behavior, however, most investigators were reluctant to apply a strict reductionist strategy. In the 1950s and 1960s it was often said that behavior was the area of biology in which simple animal models, particularly invertebrate ones, were least likely to produce fruitful results. The brain that really learns—the mammalian brain, especially the human brain—is so complex that inferences from studies of invertebrates would not stand up. It was thought that the human brain, with its higher-order capabilities, must have neuronal organizations that are qualitatively different from those found in invertebrates.

These arguments held some truth, but they overlooked certain critical issues. Work by students of comparative behavior, such as Konrad Lorenz, Niko Tinbergen, and Karl von Frisch, had already shown that certain behavior patterns, including elementary forms of learning, are common to both humans and simple animals. I therefore believed from the outset that the mechanisms of memory storage are likely to be conserved in phylogeny and that a cellular analysis of learning in a simple animal would reveal universal mechanisms that extend to more complex organisms as well.

Not surprisingly, I was strongly discouraged from pursuing this strategy by some senior researchers in neurobiology, particularly Eccles. His concern reflected, in part, the existing hierarchy of acceptable research questions in neurobiology. Few self-respecting neurophysiologists, I was told, would leave the study of learning in mammals to work on an invertebrate. Was I compromising my career? Of even greater concern to me were the doubts expressed by some very knowledgeable psychologists, who were skeptical that anything interesting about learning and memory could be found in a simple invertebrate animal.

I had made up my mind, however. Since we knew nothing about the cell biology of learning and memory, I believed that any insight into the modification of behavior by experience, no matter how simple the animal or the task, would prove to be highly informative.

After an extensive search that included crayfish, lobster, flies, and the nematode worm *Ascaris*, I settled on *Aplysia*, the giant marine snail. *Aplysia* offered three major technical advantages: its nervous system has a small number of cells, the cells are unusually large, and, as I came to realize, many

of the cells are invariant and identifiable as unique individuals. The only two people in the world working on *Aplysia* at this time were French: Ladislav Tauc, in Paris, and Angelique Arvanitaki-Chalazonitis, in Marseilles. So far so good! But Denise's advice in the matter was decisive: ever the Parisian chauvinist, she thought that living in Marseilles instead of Paris would be like living in Albany instead of New York City. So before leaving the NIH in 1960, I arranged a postdoctoral fellowship with Ladislav Tauc: I was to join him in Paris in September 1962, as soon as I had completed my residency training. It proved an excellent choice.

Residency Training in Psychiatry at Harvard Medical School

I began my psychiatric residency at the Massachusetts Mental Health Center of the Harvard Medical School in the spring of 1960. When I arrived at Harvard, I found an unanticipated bonus. Stephen Kuffler, whose thinking had so influenced my own, had been recruited a year earlier from Johns Hopkins to build up the neurophysiology unit at Harvard. Kuffler brought with him several young postdoctoral fellows—David Hubel, Torsten Wiesel, Ed Furshpan, and David Potter—each of whom was extraordinarily gifted. In this way Kuffler succeeded, in one fell swoop, in setting up at Harvard the premier group of neural scientists in the country. I now had my first opportunity to interact with Kuffler and with the remarkable people he had assembled around him. Even though I was in full-time residency training, Kuffler and his group were extremely accessible, and their generosity allowed me to remain intellectually engaged in neurobiology. Moreover, Jack Ewalt, professor of psychiatry at the Massachusetts Mental Health Center, provided me with funds and space so that I even managed to do some research in my spare time. I obtained the first intracellular recording from hypothalamic neuroendocrine cells and found that these hormone-releasing cells had all the electrical properties of normal nerve cells.

During my residency I began to think about simple forms of learning in preparation for work on *Aplysia*. I read Kimble's wonderful revision of Hilgard and Marquis's classical text *Conditioning and Learning*, and I reread Skinner's great book *The Behavior of Organisms*. This reading made me realize that the paradigms of simple learning articulated by Ivan Pavlov and Edward Thorndyke, describing changes in behavior in response to controlled stimulation, included precise protocols for stimulating experimental animals. It occurred to me that the paradigms they described—habituation, sensitization, classical conditioning, and operant conditioning—could readily be adapted to experiments with an isolated *Aplysia* ganglion using artificial electrical stimuli rather than natural sensory stimuli. While recording the behavior of a single cell in a ganglion, one nerve axon pathway to the ganglion could be stimulated weakly as a conditioned stimulus while another pathway was stimulated as an unconditioned stimulus, following

the exact protocol used for classical conditioning with natural stimuli in intact animals. One could then see whether synapses changed systematically in response to these patterns of stimulation, and if so, whether the synaptic changes in any way paralleled changes in the overt behavior of intact animals that classical psychologists had described.

I soon began to call these patterns of stimulation derived from learning experiments in intact, behaving organisms *analogs of learning*. It dawned on me that by applying analogs of learning directly to a neuronal system and analyzing the results, I could take an initial step toward the study of learning in the intact animal.

Paris, *Aplysia,* and Neural Analogs of Learning

Based on this idea, I was awarded an NINCDS postdoctoral fellowship for work to be done in Tauc's laboratory. In September 1962, about a year after our son, Paul, was born, Denise and I took off for Paris with him. Tauc proved an excellent person to work with; both our interests and our areas of competence complemented each other. He was, of course, completely at home with *Aplysia*, but he also had a strong background in physics and biophysics, which I lacked. Born in Czechoslovakia, Tauc had originally studied the electrical properties of plant cells. As a result, he had no experience with behavior and had up to this point thought little about the problems of neuronal integration that dominated thinking about the mammalian brain, problems that Alden and I had discussed incessantly. Tauc was quite enthusiastic about my approach, which proved even more effective than I had anticipated. In my cellular studies of analogs of habituation, sensitization, and classical conditioning in *Aplysia*, I found synaptic changes that parallel the behavioral changes seen in experiments on intact animals. This encouraged Tauc and me to write in our 1965 paper in the *British Journal of Physiology*:

> The fact that the EPSPs (excitatory postsynaptic potentials) can be facilitated for over half-an-hour with an input pattern scheme designed to simulate a behavioral conditioning paradigm also suggests that the concomitant changes in the efficacy of synaptic transmission may underlie certain simple forms of information storage in the intact animal (Kandel alnd Tauc 1965).

A Brief Return to Harvard Medical School

Upon completing a very productive 16-month stay in Tauc's laboratory, I returned to Harvard in November 1963. In July 1965 our daughter, Minouche, was born, completing our family: one boy, one girl, exactly what we had hoped for.

During this period at Harvard I struggled with three choices that were to have a profound effect on my subsequent career. First, I realized that to do effective science I could not combine basic research and a clinical practice in psychoanalysis, as I had earlier hoped. I therefore decided not to apply to the Boston Psychoanalytic Institute, a decision which meant that I would not attempt to become a psychoanalyst, but would instead devote myself full time to science. It was my strong sense that one of the problems within academic psychiatry, a problem that has only become worse with time, is that young people take on much more than they can handle effectively. I concluded that I could not and would not do that.

The second choice arose a few months later, when Ewalt and Howard Hiatt, then chairman of the department of medicine at Beth Israel Hospital at Harvard, suggested that I take on the newly vacated chairmanship of the department of psychiatry at the hospital. For a moment I was forced to rethink my decision to focus full time on science. The person who had just left that position, Grete Bibring, was a leading psychoanalyst and a colleague of Marianne and Ernst Kris in Vienna. Earlier in my life this position would have represented my highest aspiration. But by 1965 my thinking had moved in a very different direction, and I decided against it, with Denise's strong encouragement. (Denise summarized it simply: "What?" she asked, "throw your scientific career away?") Instead, I made my third choice. I decided to leave Harvard and accept an invitation to start a small neurophysiology group focused specifically on the neurobiology of behavior in the departments of physiology and psychiatry at the NYU Medical School.

Harvard was quite wonderful, and it was not easy to leave that intellectually heady neurobiology environment. My interaction with Kuffler had increased after my return from Paris, and until his death in 1980, he proved a marvelous friend and counselor. Moreover, my interactions during this period with members of Kuffler's group—Hubel, Wiesel, Furshpan, Potter, and Ed Kravitz, a biochemist who joined them later—were extensive, and I learned much from them. Many years later, at a small meeting at the Marine Biological Laboratory at Woods Hole in honor of Steve Kuffler, I was surrounded by Steve's Harvard entourage, some of whom were struggling with the decision of whether to leave Harvard for attractive positions elsewhere. I could not resist beginning my lecture with the remark, "I am here as living proof that there is life after Harvard."

New York University and a Focus on the Behavior of *Aplysia*

The position at NYU had several great attractions that, in the long run, proved critical. First, it brought us back to New York and closer to my parents and to Denise's mother, all of whom were having medical problems and benefited from our being nearby. Second, NYU gave me the opportunity

to recruit an additional senior neurophysiologist, and Alden Spencer agreed to move to NYU from the University of Oregon Medical School, where he had returned after his stay at the NIH. Alden occupied the laboratory next to mine, and although he and I never collaborated experimentally again, we talked daily not only about our science—the neurobiology of behavior—but about almost everything else. He died in 1977, at age 46, from amyotrophic lateral sclerosis, after we had both moved to Columbia University. While he was alive, no one influenced my thinking on matters of science as much as Alden. I still think about him frequently.

Alden and I arrived at NYU together in the winter of 1965. Within a year we were joined by Jimmy Schwartz, whom I had first met in the summer of 1951 at Harvard summer school and who was now a member of the department of microbiology at NYU and was becoming interested in behavior. The three of us formed the nucleus of the Division of Neurobiology and Behavior at NYU.

With several important decisions behind me, I made a strong effort to focus on whole-animal behavior. In France I had found that chemical synapses are remarkably plastic—they readily undergo long-lasting changes in strength—but I had no evidence that the changes were in fact behaviorally meaningful, that they occur when an animal learns something. During my last few weeks in France I had begun to replicate my results by substituting natural stimuli for electrical stimulation of nerves, but I still had not shown that synaptic plasticity occurs during behavioral learning. As a first step I thought it essential to show that *Aplysia* is capable of learning. With this in mind, I set about recruiting a postdoctoral fellow with a specific interest in behavioral learning. I was fortunate to recruit, first to Harvard and then to NYU, Irving Kupfermann, an extremely critical and thoughtful student of behavior. We were later joined by another learning psychologist, Harold Pinsker, and together we set about delineating a very simple behavior that we could study: the gill-withdrawal reflex. We quickly found that this simple reflex could readily be modified by two forms of learning: habituation and sensitization.

In exploring these two forms of learning, we focused on short-term memory. In 1971 we were joined by another experienced behavioral psychologist, Tom Carew, who brought a new level of energy and insight to our behavioral studies. He arrived as Pinsker was leaving, and soon afterward we shifted from working on short-term memory and started on long-term memory. Tom found that spaced repetition of stimuli converts the memory underlying short-term habituation and sensitization to longer-lasting memories. In 1981, after several unsuccessful attempts, Carew, Terry Walters, Tom Abrams, and Robert Hawkins were able to define the conditions for reliably producing classical conditioning in *Aplysia*. This was a particularly exciting period; Carew, Walters, Hawkins, and I met regularly to discuss how to explore whether a simple reflex, in a simple invertebrate, could show

the higher-order cognitive features of classical conditioning recently demonstrated in mammals by Leo Kamin and somewhat later by Robert Rescorla and Alan Wagner. Soon, Hawkins was indeed able to demonstrate that the gill-withdrawal reflex can undergo second-order conditioning, blocking, overshadowing, and other cognitive aspects of associative learning, features that were surprising to uncover in such a simple behavior.

We thus were able to describe a rather rich repertory of learning in *Aplysia*. But long before this inventory of the animal's behavior was complete, we returned to our initial concerns. What happens in the brain of an animal when it learns a task? How does it remember? We proceeded, first with Kupfermann and Vincent Castellucci and then with Jack Byrne and Hawkins, to work out most of the neural circuitry of the gill-withdrawal reflex. We identified the specific sensory neurons and motor cells that produce movements of the gill. Next, we found that the sensory neurons make direct connections to the motor neurons as well as indirect connections through interneurons, both excitatory and inhibitory. The aversive shocks to the tail that produce sensitization of the gill-withdrawal reflex also activate modulatory interneurons that act on terminals of the sensory neurons. We now could turn to thinking about how learning might occur in this reflex.

Cellular Mechanisms of Learning

At the end of the 19th century Ramón y Cajal introduced the principle of connection specificity, which states that during development, a neuron will form connections only with certain neurons and not with others. Kupfermann, Castellucci, and I saw this remarkable regularity of connections in the circuitry of the gill-withdrawal reflex of *Aplysia.* We also saw, in exquisite detail, that specific, identifiable cells make invariant connections to one another. This invariant organization of neurons presented serious questions: How could we reconcile hardwired circuits in the nervous system and the specificity of connections with an animal's ability to learn? Once acquired, where or how is learned information retained in the nervous system?

One solution was proposed by Ramón y Cajal in his Croonian Lecture to the Royal Society of London in 1894, when he suggested that "mental exercise facilitates a greater development of the protoplasmic apparatus and of the nervous collaterals in the part of the brain in use. In this way, preexisting connections between groups of cells could be reinforced by multiplication of the terminal branches of protoplasmic appendices and nervous collaterals" (Cajal 1894).

This remarkably prescient idea was by no means generally accepted. On the contrary, different theories of learning held the attention of neural scientists at various times. Two decades after Ramón y Cajal's proposal, the physiologist Alexander Forbes suggested that memory is sustained not by changes in synaptic strength of the sort suggested by Ramón y Cajal, but by dynamic

changes resulting from reverberating activity within a closed loop of self-exciting neurons. This idea was elaborated by Ramón y Cajal's student Lorente de Nó, who found in his own and in Ramón y Cajal's analyses of neural circuitry neurons that were interconnected in closed pathways; these neurons could therefore sustain reverberatory activity, thus providing a dynamic mechanism for information storage. In his influential book *The Organization of Behavior* (1949), D.O. Hebb proposed that a "coincident activity" initiated the growth of new synaptic connections as part of long-term memory storage, but for short-term memory, Hebb invoked a reverberatory circuit:

> To account for permanence, some structural change seems necessary, but structural growth presumably would require an appreciable time. If some way can be found of supposing that a reverberatory trace might cooperate with the structural change, and carry the memory until the growth change is made, we should be able to recognize the theoretical value of the trace, which is an activity only without having to ascribe all memory to it. The conception of a transient, unstable reverberatory trace is therefore useful. It is possible to suppose also some more permanent structural change reinforces it.

Similarly, in *The Mammalian Cerebral Cortex*, an influential book of 1958, B. Deslisle Burns challenged the relevance of synaptic plasticity to memory.

> The mechanisms of synaptic facilitation which have been offered as candidates for an explanation of memory . . . have proven disappointing. Before any of them can be accepted as the cellular changes accompanying conditioned reflex formation, one would have to extend considerably the scale of time on which they have been observed to operate. The persistent failure of synaptic facilitation to explain memory makes one wonder whether neurophysiologists have not been looking for the wrong kind of mechanisms.

Indeed, some scholars even minimized the importance of specific neuronal connections in the brain, advocating instead mechanisms of learning that were partially or even totally independent of "pre-established" conduction pathways. This view was held by Wolfgang Kohler, the famous Gestalt psychologists, and subsequently by the neurophysiologists Ross Adey and Frank Morrell. Adey wrote in 1965:

> No neuron in natural or artificial isolation from other neurons has been shown capable of storing information in the usual notion of memory. . . . In particular, the possibility exists that

> extraneuronal compartments may participate importantly in the modulation of the wave processes that characterize the intracellular records, and that these wave processes may rank at least equivalently with neuronal firing in the transaction of information and even more importantly in its deposition and recall.

Finally, a macromolecular notion of memory was advocated by Holger Hyden, based upon his finding of changes in the nucleotide composition of RNA. He proposed that learning gives rise to a specific pattern of neural activity, which alters the stability of RNA molecules, enabling the exchange of one base pair for another. In this way, he held, new RNA molecules are formed with new base sequences that are specific to the instructing pattern of neural activity induced by learning. Hyden's hypothesis implied that the patterns of stimulation activated by learning could introduce changes in RNA.

We were in a position to test experimentally, which, if any, of these ideas had merit. Using the gill-withdrawal reflex we quickly established that memory in the *Aplysia* nervous system is not represented in self-exciting loops of neurons but in changes in synaptic strength. We found that all three simple forms of learning—habituation, sensitization, and classical conditioning—lead to changes in the synaptic strength of specific sensory pathways and that these changes parallel the time course of the memory process. Our findings, which were fully in line with our earlier studies of analogs of learning, gave rise to one of the major themes in our thinking about the molecular mechanisms of memory storage: although the anatomical connections between neurons develop according to a definite plan, the strength and effectiveness of those connections are not fully determined during development and can be altered by experience.

We therefore concluded the third in a series of papers on the cellular mechanisms of learning, published in *Science* in 1970, with the following comments:

> [T]he data indicate that habituation and dishabituation (sensitization) both involve a change in the functional effectiveness of previously existing excitatory connections. Thus, at least in the simple cases, it seems unnecessary to explain the behavioral modifications by invoking electrical and chemical fields or a unique statistical distribution in a neural aggregate. The capability for behavioral modification seems to be built directly into the neural architecture of the behavioral reflex.
>
> Finally, these studies strengthen the assumption . . . that a prerequisite for studying behavioral modification is the analysis of the wiring diagram underlying the behavior. We have, indeed, found that once the wiring diagram of the behavior is known, the analysis of its modification becomes greatly simplified.

> Thus, although this analysis pertains to only relatively simple and short-term behavioral modifications, a similar approach may perhaps also be applied to more complex as well as longer lasting learning processes (Castellucci et al. 1970).

A Beginning Molecular Analysis of Memory Storage

Having defined a critical site of plasticity, we were ready to begin a molecular analysis. Here again I could not have been more fortunate. As I mentioned earlier, soon after I arrived at NYU I ran into Jimmy Schwartz, who had attended NYU Medical School two years behind me. After medical school he obtained a PhD with Fritz Lipmann at the Rockefeller University, studying enzyme mechanisms and protein translation in cell-free bacteria extracts. As Schwartz and I began to talk again, he mentioned that he was thinking of moving from *E. coli* to the brain. *Aplysia* seemed ideal for the biochemical study of individual nerve cells, so in 1966, we joined forces to carry out biochemical studies on specific nerve cells of *Aplysia*.

Schwartz soon found that different kinds of nerve cells in *Aplysia* have different transmitter biochemistry. Cells that we had presumed on pharmacological grounds to be cholinergic did in fact synthesize and release acetylcholine. With time, he became interested in the molecular mechanisms of synaptic plasticity, and together we began to examine the role of protein synthesis in memory storage. We knew from the work of Louis Flexner and Bernard Agranoff in the mid-1960s that long-term memory in vertebrates requires protein synthesis, whereas short-term memory does not. In our first study together, in 1971, we found that blocking protein synthesis for 24 hours does not prevent the short-term synaptic changes associated with habituation and sensitization. That finding made us think that short-term changes representing memory storage might involve activation of a second-messenger pathway—for example, the cyclic AMP (cAMP) cascade, whose actions might persist longer than the millisecond of conventional synaptic actions.

In the discussion of our 1971 paper on the role of protein synthesis and synaptic plasticity we wrote:

> Alterations in molecular configuration would not be expected to persist for long periods of time, although molecular changes lasting for several minutes have been observed. . . . Most likely, the biochemical mechanisms underlying these short-term plastic changes are composed of a series of sequential reactions which result in a new distribution of transmitter substance. Mechanisms involving cyclic 3',5' AMP might serve as one example of a series of reactions which result in transient enhancement in the activity of a critical enzyme system. A pathway of

> this kind might trigger the mobilization of transmitter from one component (a long-term store) to another (an immediately releasable store). . . .
>
> If our conclusion is correct . . . rapidly synthesized RNA cannot immediately play a role in neuronal functions; it might, however, be important for long-term neuronal processes (Schwartz et al. 1971).

Earl Wilbur Sutherland and Ted Rall had shown in brain slices that several neurotransmitters known to exist in the brain can increase concentrations of cAMP by activating the enzyme adenylyl cyclase, which converts ATP to cAMP. We appreciated that we had a particularly good experimental preparation for examining, on the cellular level, the role of second-messenger pathways in synaptic transmission, synaptic plasticity, and memory storage. In 1972 Schwartz, Howard Cedar, and I found that stimulation of the pathway involved in sensitization increases the concentration of cAMP in the entire abdominal ganglion. Schwartz and Cedar next found that the transmitter serotonin can also increase cAMP, providing the initial evidence that serotonin might activate an adenylyl cyclase in *Aplysia*.

Columbia University and the Molecular Analysis of Short-Term Memory

It was at this time that I was invited to move from NYU to Columbia University's College of Physicians and Surgeons to become the founding director of the Center for Neurobiology and Behavior. I was able to persuade Schwartz, Spencer, and Kupfermann (who had established an independent research program concerned with feeding and motivational state in *Aplysia*) to join me. This move was attractive for several reasons. Historically, Columbia has had a strong tradition in neurology and psychiatry, and a friend and former clinical teacher, Lewis Rowland, was about to assume the chairmanship of the department of neurology. In addition, I had my first experience in neurobiology at Columbia with Harry Grundfest, who was now retiring and whom I was being recruited to replace. Finally, Denise was on the Columbia faculty and our house in Riverdale was near the College of Physicians and Surgeons, so the move would greatly simplify our lives.

In 1974, just after arriving at Columbia, Castellucci and I went back to the elementary circuit of the gill-withdrawal reflex to determine the exact site of the synaptic change produced by short-term sensitization. We wanted to know which component of the synapse changes. Is it, as we suspected on the basis of indirect evidence, the presynaptic cell, which releases a chemical transmitter, or is it the postsynaptic cell, which contains the receptors that bind and respond to the transmitter? Using a quantal analysis, we found that the synaptic facilitation characteristic of sensitization is presynaptic and that inhibitors of serotonin block this presynaptic facilitation.

Later, Hawkins and I found that shocks to *Aplysia*'s tail, which initiate sensitization, activate a set of modulatory interneurons, the most important of which release serotonin. The serotonergic and other modulatory interneurons all act on the sensory neurons and on their presynaptic terminals to enhance the release of the transmitter glutamate. We could now ask for the first time: Is cAMP directly involved in synaptic facilitation? In 1976 Marcello Brunelli took advantage of the size of the *Aplysia* neurons and injected cAMP directly into the presynaptic sensory cell; he found clear enhancement of synaptic transmission. This cAMP-induced enhancement parallels the enhancement produced by serotonin and by shocks to *Aplysia*'s tail.

I now began to interact with Paul Greengard, who was demonstrating that cAMP produces its actions in the brain through the cAMP-dependent protein kinase, or PKA. In 1980 Schwartz, Castellucci, Greengard, and I injected a purified catalytic subunit of bovine PKA into presynaptic sensory neurons and found that it simulates the actions of cAMP and of serotonin. Moreover, we could block the actions of serotonin by injecting into the sensory neuron a specific peptide (PKI) that inhibits PKA. With Steven Siegelbaum we next began to define some of the targets of PKA, focusing on one in particular, a novel potassium channel. Siegelbaum showed that this channel is closed by serotonin and by PKA and that the action is consistent with the channel's being phosphorylated directly by PKA.

The Howard Hughes Medical Institute and the Molecular Analysis of Long-Term Memory

Just before I arrived at Columbia, Arnold Kriegstein, an MD-PhD student, succeeded in culturing embryonic *Aplysia* in the laboratory, a quest that had intrigued and eluded biologists for almost a century. Most of us who were there will not readily forget Kriegstein's extraordinary in-house seminar in December 1973, when he first described his discovery that the red seaweed *Laurencia pacifica* is required to trigger metamorphosis from a free-swimming veliger larva to a small crawling snail. When he showed the first pictures of the tiny, postmetamorphic juvenile *Aplysia* I remember saying to myself, "Babies are always so beautiful!" Kriegstein's work opened up the study of development and cell culture in *Aplysia*.

Because we now had young animals at all stages of development, we at last had the essential requirements for the generation of dissociated cell culture. This was taken on by Sam Schacher and Eric Proshansky. With the help of Steven Rayport (another MD-PhD student at Columbia), the three soon succeeded in culturing the individual sensory neurons, motor neurons, and serotonergic modulatory interneurons of the gill-withdrawal reflex. The development of the culture system coincided with two other events that enabled me to begin studying the molecular mechanisms of long-term

memory storage. The first was my encounter with Richard Axel and my collaboration, in 1979, with him and with Richard Scheller, who became a joint postdoctoral fellow. The second was my being recruited to become a senior investigator at the Howard Hughes Medical Institute.

Axel and Scheller's success in 1982 in cloning the gene that encodes the egg-laying hormone in *Aplysia* seeded Axel's long-term interest in neurobiology and gave me not only a wonderful friend but also an exposure to the methods of recombinant DNA and modern molecular biology. The very next year, Donald Fredrickson, the newly appointed president of the Howard Hughes Medical Institute, asked Schwartz, Axel, and me to form the nucleus of a research institute at Columbia devoted to molecular neural science. This gave us the opportunity to recruit from Harvard both Tom Jessell and Gary Struhl, as well as to keep Siegelbaum at Columbia.

My first goal on becoming a Hughes investigator was to examine the molecular mechanisms underlying the synaptic changes that parallel long-term memory storage. In 1885, Herman Ebbinghaus transformed speculation about memory into a laboratory science by having subjects memorize lists of nonsense syllables. In this way Ebbinghaus generated two basic principles about memory storage. First, the transition from short-term memory to long-term memory is graded: practice makes perfect. Second, there is a fundamental distinction between short-term and long-term memory.

What was the molecular basis of this distinction? Flexner and Agranoff had found that inhibitors of protein synthesis disrupt long-term memory without adversely affecting learning or short-term memory. We found that long-term sensitization in *Aplysia* is similarly dependent on protein synthesis, whereas short-term sensitization is not. These findings illustrated the generality of the distinction between short-term and long-term memory processes for both invertebrates and vertebrates. In each case, spaced repetition of the learning stimulus transforms a transient memory into a more stable (long-term) memory through a process that depends on the synthesis of new protein. But how this occurred remained a mystery.

We had found earlier in *Aplysia* that long-term sensitization involves a persistent increase in the strength of the same synaptic connection that is altered by the short-term process—that is, the connection between the sensory and motor neurons of the gill-withdrawal reflex. To study this process more effectively, we turned to dissociated cell culture and found that we could reconstitute both short- and long-term synaptic facilitation in a culture consisting of only a single sensory neuron and a single motor neuron. We did this, together with Sam Schacher, Philip Goelet, and Pier Giorgio Montarolo, by applying either one or five brief, evenly spaced pulses of serotonin to the sensory neuron and motor neuron in the culture dish.

Much as we had seen in behavioral long-term memory, long-term synaptic change requires the synthesis of new protein, whereas short-term change does not. We had succeeded in tracking the protein synthesis–dependent component of memory storage in the elementary synaptic connection between two identified cells. We could now address directly several important questions: Why is protein synthesis required for long-term but not short-term facilitation? What are the molecular steps that switch on long-term facilitation? Once switched on, how is it maintained?

We next found that new protein synthesis begins with a flurry of gene activity initiated by PKA. With repeated applications of serotonin, PKA moves to the nucleus of the cell and in so doing activates the mitogen-activated protein (MAP) kinase, another kinase often recruited for growth. Thus, one of the functions of repeated stimulation is to cause both kinases to move into the nucleus. Pramod Dash and Binyamin Hochner, and later Cristina Alberini, Mirella Ghirardi, and Dusan Bartsch, provided the first evidence that in the nucleus, these kinases act on a gene regulator called CREB-1 (the cAMP response element binding protein) to initiate a cascade of gene transcription. With David Glanzman and Craig Bailey, we found that CREB-mediated transcription, which triggers the synthesis of new proteins, is also required for the growth of new synaptic connections—and it is the formation of these new synapses that sustains the long-term change.

This finding explained why long-term memory requires the synthesis of new proteins. It also showed us that since long-term synaptic change relies on the activation of genes in the nucleus, there is ready communication between the synapse and the nucleus. But the finding posed a new problem. Since long-lasting synaptic change requires gene transcription, a process that takes place in the nucleus, and the nucleus is shared by all the synapses of a neuron, is long-term memory storage a cell-wide process? Or can long-term synaptic changes be restricted to individual synapses?

Is Long-Term Facilitation Synapse Specific?

Experiments by Kelsey Martin, based on a beautiful new cell culture system that she developed, revealed that individual synapses or groups of synapses within a cell can be modified independently. Martin cultured one sensory cell with a bifurcating axon that connected with two motor neurons, thus forming two widely separated synapses. A single puff of serotonin applied to one synapse produced transient facilitation at that synapse only, as expected (Bacskai et al. 1993; Casadio et al. 1999). Similarly, five puffs of serotonin produced long-lasting facilitation (more than 72 hours) at the stimulated synapse only. These findings indicated that despite their recruitment of nuclear processes, long-term changes in synaptic function and structure occur only at synapses that have been stimulated by serotonin.

How does this come about? Martin, Andrea Casadio, Bailey, and I found that five puffs of serotonin send a signal to the nucleus to activate CREB-1, which then appears to send proteins to all terminals; however, only those terminals that have been marked by serotonin can use the proteins for synaptic growth. Indeed, we found that marking a previously unstimulated synapse with just one puff of serotonin, which normally produces facilitation lasting a few minutes, was sufficient to produce a weaker version of the long-term facilitation induced by five puffs of serotonin at the other synapse.

These results gave us a new and surprising insight into short-term facilitation. The stimulus that produces the short-term process has two functions. When acting alone, it enhances the strength of a particular synapse, thus contributing to short-term memory. When acting in conjunction with the activation of CREB initiated by a long-term process in either that synapse or any other synapse formed by the neuron, the stimulus marks those particular synapses. Marked synapses can then utilize the proteins activated by CREB for synaptic growth, thus producing a persistent change in synaptic strength.

The finding of long-range signaling between the synapse and the nucleus and between the nucleus and the synapse introduced a new dimension into our understanding of the integrative action of neurons. Long-term facilitation is indeed synapse specific and restricted, but once gene transcription has been activated, the potential for change at *all* of the synapses of a neuron is altered. As a result, the action of any given synapse is no longer determined simply by the history of that synapse; it is also determined by the history of the transcriptional machinery in the nucleus. Thus, the logic of the long-term process is quite different from that of the short-term process.

The Nature of the Local Marking Signal

How does one puff of serotonin mark a synapse for long-term change? We found that the synapse is marked both for long-term synaptic facilitation and for growth of new synaptic connections by covalent modifications of existing proteins, modifications that are mediated by PKA. For that structural change to persist, however, protein must be synthesized locally (Casadio et al. 1999). Oswald Steward's important work in the early 1980s had shown that dendrites contain ribosomes and that specific mRNA molecules, or transcripts, are transported to the dendrites and translated into proteins there (Steward 1997). But the function of those locally translated mRNA transcripts was unknown. Our experiments showed that one function of the local mRNAs is to stabilize synapse-specific, long-term functional and structural changes.

What proteins might be important for stabilizing these changes? To answer this question we needed a preparation in which we could study the

local mRNA transcripts and proteins in isolation—that is, in the processes (the axon and dendrites) of neurons, with no possible contamination by the cell body or surrounding glial cells. Martin cultured several hundred sensory neurons in a dish and then cut off their cell bodies, thus allowing us to study the mRNA transcripts and how they are regulated (Martin et al. 1998). We found that serotonin stimulates the translation of mRNA into new proteins in these isolated processes. Moreover, the mRNA transcripts in these processes contain regulatory sequences that are consistent with at least two mechanisms for regulating local translation of proteins.

These local mechanisms of translation serve different functions. One mRNA transcript, the elongation factor EF-1α, has an oligopyrimidine tract in the 5' untranslated region. This same tract is found in a small group of mRNA transcripts that are preferentially translated in response to stimulation by growth factors, or mitogens. The ability of growth factors to recruit these mRNA transcripts is blocked selectively by the drug rapamycin (reviewed in Schuman 1997; Steward 1997; Martin et al. 2000). Indeed, we found that rapamycin inhibits both the stabilization of long-term facilitation and the growth of new connections (Casadio et al. 1999). Other mRNA transcripts, which are necessary for initiating long-term facilitation, are not blocked by rapamycin; they are blocked by emetine, a general inhibitor of protein synthesis. These studies thus revealed a new, fourth type of synaptic action that is mediated by neurotransmitter signaling (see Figure 1).

Our understanding of three of the four types of neurotransmitter action emerged, at least in part, from the study of learning and memory. First, in 1951, Fatt and Katz opened up the modern study of chemical transmission with their discovery of ionotropic receptors that regulate ion flux through transmitter-gated channels to produce fast synaptic actions lasting for milliseconds (Fatt and Katz 1951). Second, in the 1970s metabotropic receptors were found to activate second-messenger pathways, such as the cAMP-PKA pathway, to produce slow synaptic activity lasting minutes (Greengard 1976). As we have seen in *Aplysia*, this slow synaptic action can regulate transmitter release, thereby contributing to short-term memory for sensitization. Third, an even more persistent synaptic action, lasting days, results from the repeated action of a modulatory transmitter such as serotonin. With repeated applications of serotonin, second-messenger kinases move to the nucleus, where they induce a cascade of gene transcription leading to the growth of new synaptic connections. This raises the problem of synapse specificity that we considered earlier. Our experiments in the bifurcated culture system revealed the fourth action of neurotransmitters: the marking of the synapse and the regulation of local protein synthesis, which establishes synapse-specific long-term facilitation and thus contributes to the solution of the specificity problem.

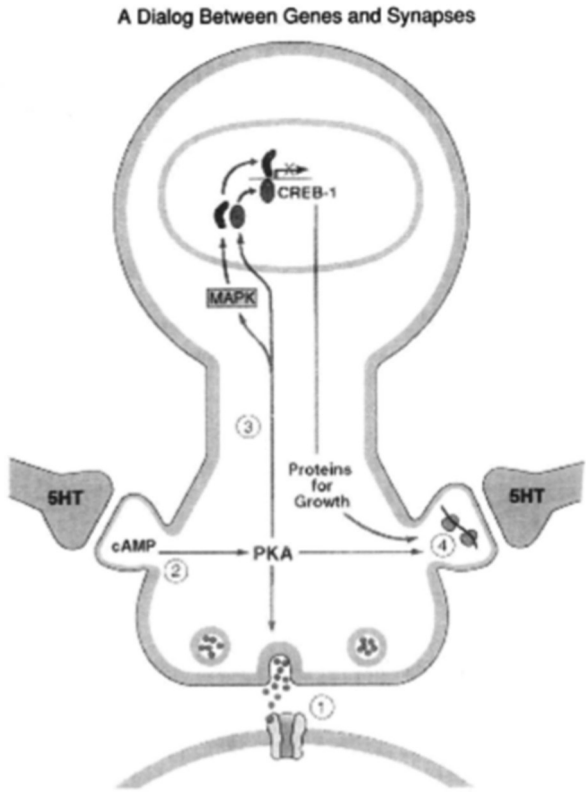

Fig. 1. Four different consequences of the action of neurotransmitters, showing that the synapses and the nucleus interact readily. **1.** Transmitter activation of a ligand-gated ion channel leads to a rapid synaptic action. **2.** Transmitter activation of a seven-transmembrane receptor and a second-messenger kinase leads to a more enduring synaptic action. **3.** Repeated transmitter activation of a seven-transmembrane receptor leads to the translocation of the kinase to the nucleus and the activation of mRNA transcription, producing a persistent synaptic action. **4.** Transmitter can also activate local protein synthesis to stabilize the synapse-specific facilitation.

A Return to the Hippocampus: Genetically Modified Mice and Complex Spatial Memory

In our studies in *Aplysia*, we focused on the simplest form of memory: implicit (or procedural) memory. These memories are concerned with the unconscious recall of perceptual and motor skills and do not require a hippocampus. The hippocampus is involved in explicit (or declarative) memory, the memory for people, objects, or places; these memories require conscious recall.

For years I tried to encourage people who left my lab to turn their attention to the hippocampus, but to no avail. Finally in 1990, when I reached my sixtieth birthday, I returned to the study of the hippocampus myself. I was emboldened to do so in great part because of the development of methods for inserting and for knocking out individual genes in mice. This work made it clear to me that mice offer a superb system for examining the role of individual genes in synaptic modification, on the one hand, and intact behavior—explicit memory storage—on the other. Mice have a well-developed medial temporal lobe and hippocampus, and these structures are necessary for explicit memory of objects and space. Moreover, in 1972, Tim Bliss and Terje Lømo, in Per Andersen's laboratory in Oslo, had discovered that electrically stimulating any one of the three major pathways in the hippocampus gives rise to a synaptic facilitation called long-term potentiation, or LTP. We were interested in two questions: What molecular signaling pathways are important for LTP? Is LTP important for explicit memory storage?

The contributions of Seth Grant and Mark Mayford were particularly influential in these new studies in genetically modified mice. Grant was the driving force in our first studies, in which we showed a role for nonreceptor tyrosine kinases in long-term potentiation and in spatial memory in the hippocampus. Mayford's critical thinking became important somewhat later, as we began to realize the limitations in the first generation of genetically modified mice. These limitations stimulated Mayford to develop promoters that limit the expression of genes to certain regions of the brain and to devise methods for controlling the timing of gene expression. Those two technical advances proved important in allowing us (as well as Susumu Tonegawa, whose lab was now also studying memory in genetically modified mice) to generate mice with more specific phenotypes. Genetic defects could be more readily interpreted in these mice than in the first generation of mice because we could relate any given defect more directly to specific synaptic changes and to behavior.

Over the next few years Mayford, Ted Abel, Mark Barad, Isabelle Mansuy, Chris Pittenger, Amy Chen, and Angel Barco created a number of regionally restricted and regulated transgenic animals that allowed us to examine the role of the PKA, CREB-1 and CREB-2, and protein synthesis–dependent transcriptional switch within the hippocampus and to determine that it is quite similar in principle to what we had encountered in *Aplysia*. Our lab and those of Alcino Silva and Dan Storm found that the cAMP, PKA, and CREB switch required for long-term forms of synaptic plasticity in the hippocampus was also required for spatial memory.

The Cognitive Map of Space: Steps toward a Molecular Biology of Attention

With this background information about genes, long-term potentiation, and spatial memory, we now could ask deeper questions: How does an animal

learn about extrapersonal space? Why does spatial memory go awry with defects in PKA signaling? What is the function of the transcriptional switch? To address those questions, we began to study how space is represented in the hippocampus.

One of the key insights to emerge from the study of higher cognitive functions is that each perceptual or motor act has an internal representation in the brain. These representations can be simple or complex. The simplest internal representations are those of the sensory systems, whose afferent fibers are arranged as topographic maps of the receptor surface. These are the representations that Wade Marshall, my former mentor at the NIH, had discovered in the 1930s and early 1940s. Marshall showed that this map is most clearly evident in the neural representation of *personal space*, the representation of touch. The neural representation of *extrapersonal space*, the space surrounding the body, is far more complex. Here, the representation is encoded in the pattern of firing of neurons that have no topographic relation to one another. This representation was discovered in 1971 by John O'Keefe at University College London, who made the brilliant observation that the hippocampus contains a complete representation of extrapersonal space—a cognitive map.

O'Keefe discovered that all of the pyramidal cells in the hippocampus, the very same cells we had used to study long-term potentiation, form an internal neural representation of the space surrounding an animal (O'Keefe and Nadel 1978). In a familiar environment, different pyramidal cells in the hippocampus fire as the animal traverses from one region to the next. This tendency is so marked that O'Keefe referred to the pyramidal cells as *place cells*.

Some place cells fire only when an animal's head enters one position in a given space. Others fire when the animal's head enters another position in the same space. Thus, a mouse's brain breaks up the space in which it walks into many small, overlapping fields; each field is assigned to specific cells in the hippocampus, forming a spatial map of the animal's surroundings. This holistic neural representation is thought to permit the animal to solve spatial problems efficiently. When the animal enters a new environment, a new place map is formed within minutes, in part from some of the pyramidal cells that made up the map of the first environment and in part from pyramidal cells that had been silent previously (reviewed in O'Keefe and Nadel 1978). Each cell will have the same firing field whenever the animal is reintroduced to that environment. Place fields are formed in minutes, and once formed, the map to which they contribute can remain stable for weeks.

The spatial map is the best-understood example of a complex representation in the brain. This true cognitive map differs in several ways from the sensory maps for touch, vision, or hearing. As we have seen, the map of space is not topographic: neighboring cells in the hippocampus do not

represent neighboring regions in the environment. Furthermore, a place cell will fire whenever an animal is in a given place, regardless of what the animal is looking at. Finally, the firing of place cells can persist after pertinent sensory cues are removed, even in the dark. Thus, although the activity of a place cell can be modulated by sensory input, it is not determined by sensory input, as the activity of a sensory neuron is. Place cells do not map current sensory input, but the location where the animal *thinks* it is.

Although place cells had been studied since 1971, nothing was known about the cellular or molecular mechanisms whereby new place fields are formed; specifically, no one had attempted to relate the biology of place cells to the molecular mechanisms of long-term potentiation or hippocampal-based memory. In 1995 it struck me that the formation of a new spatial map is a learning process. The map develops with time as the animal walks around, and once learned, the map is retained for days or weeks. I therefore wondered whether protein synthesis and the synaptic plasticity related to LTP might play a role in the long-term stabilization of the map.

To explore this problem, I was fortunate to start a collaboration with Robert Muller at Downstate Medical Center in Brooklyn, who had pioneered the systematic study of place cells. This problem was taken on by Cliff Kentros, a postdoctoral fellow in my lab; by Naveen Agnihotri, a graduate student; and by Alex Rotenberg, a joint student with Muller and myself. Using a combination of pharmacological and genetic approaches, we demonstrated that recruitment of PKA and protein synthesis is linked to the long-term (but *not* the short-term) stability of the representation of space in the hippocampus. Thus, PKA and protein synthesis are required for long-term memories of extrapersonal space because such memories are based on a *learned* representation of space whose long-term stability requires PKA and new protein synthesis (Rotenberg et al. 1996; Kentros et al. 1998; Rotenberg et al. 2000; Agnihotri et al. 2001; Muller 1996).

This raised a final problem. In people, explicit memory differs from implicit memory in requiring conscious attention for recall. How does conscious attention come to bear on explicit memory? Indeed, how can one study consciousness in the mouse? In the course of our work on place fields, Kentros, Agnihotri, Hawkins, and I found that the long-term stability of a spatial map correlates strongly with the degree to which a mouse is required to attend to its environment. Thus the long-term recall of a spatial map is not an implicit, automatic process; rather, it requires that a mouse pay attention to its environment, just as explicit memory in human beings requires conscious attention. The finding that attention, the recruitment of PKA, and new protein synthesis are required for a mouse to form and recall a stable cognitive map of space has opened up a molecular biological approach to attention.

The Late Phase of LTP and Long-Term Memory of Extrapersonal Space

To explore the role of PKA in the late phase of long-term potentiation and to determine its role in memory, Ted Abel, Mark Barad, Rusiko Bourtchouladze, Peter Nguyen, and I generated transgenic mice that express R(AB), a mutant form of the regulatory subunit of PKA that inhibits enzyme activity (Abel et al. 1997). To restrict expression of R(AB) to the postnatal hippocampus and other forebrain regions, we used the promoter from the Ca^{2+}/calmodulin protein kinase IIα (CaMKIIα) gene that Mayford had isolated and characterized. In these R(AB) transgenic mice, the reduction in hippocampal PKA activity is paralleled by a significant decrease in late LTP, whereas basal synaptic transmission and early LTP remain unchanged (see Figure 2). Most interesting, the decrease in late LTP is paralleled by behavioral deficits in hippocampus-dependent long-term memory of context and of extrapersonal space, whereas learning and short-term memory are unimpaired (Figures 3 and 4). Thus, PKA plays a critical role in the transformation of short-term memory of extrapersonal space into long-term memory in the mammalian hippocampus, much as it does in the storage of implicit memory in *Aplysia* and *Drosophila*.

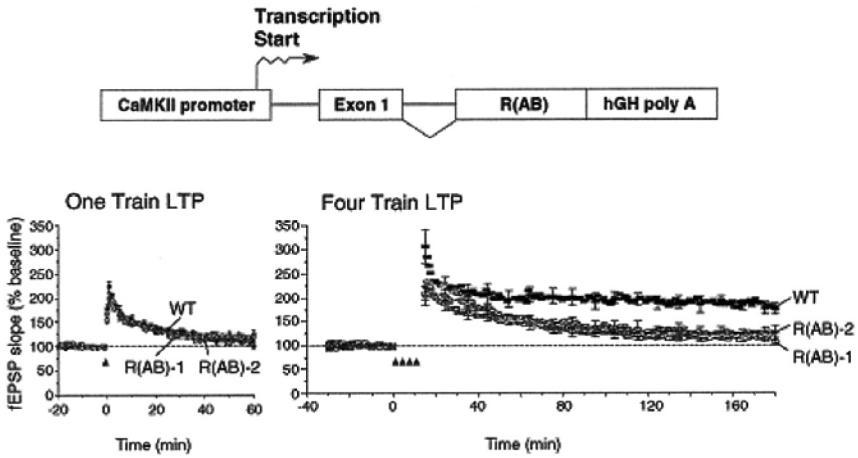

Fig. 2. A comparison of LTP in wild-type mice (WT) and two lines of mutant mice [R(AB)-1 and R(AB)-2] in which PKA has been compromised by the expression in the hippocampus of a transgene, a dominant negative inhibitor of PKA. This inhibitor, R(AB), is a mutated form of the regulatory subunit of PKA that inhibits the catalytic subunit but does not recognize cAMP. Early LTP is comparable in mutant and wild-type mice, but mutations that block PKA or CREB reduce or eliminate late LTP in the mutant mice. From Abel et al. 1997.

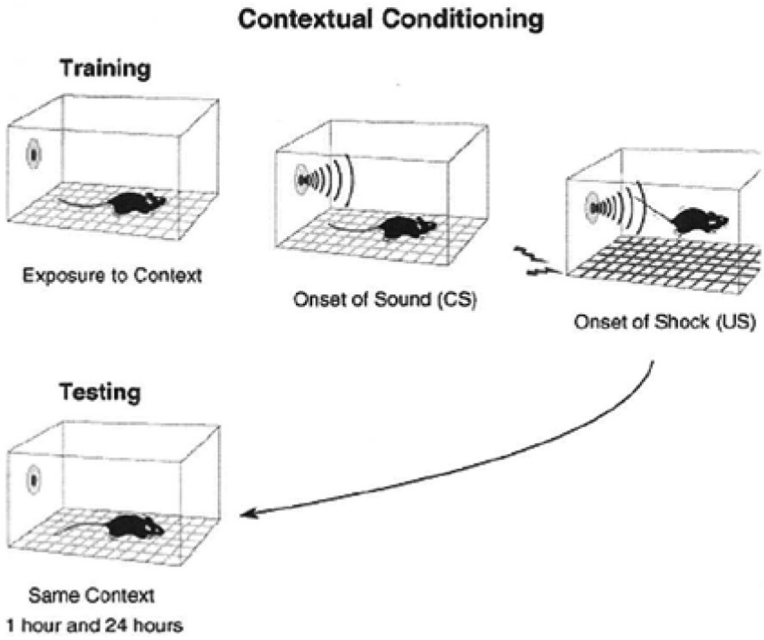

Fig. 3. Mice that express R(AB) were conditioned to freeze in the context of a box. They first walked around the box for a brief period and became familiar with the context. They then heard a sound (CS, conditioned stimulus) followed by a shock (US, unconditioned stimulus) delivered through the electrified grid in the floor. As a result, the animals learned to associate being in the box with the shock, and they froze when put in the box. The mice were then tested 1 hour and 24 hours after training. From Abel et al. 1997.

PKA and the Internal Representation of Extrapersonal Space: Toward a Molecular Biology of Cognition

Using R(AB) mice we could now ask, What are the specific functions of PKA and the late phase of LTP in spatial memory? Why do animals with compromised PKA signaling have difficulty with space (Abel et al. 1997)?

When an animal moves within an enclosed space, a particular subset of pyramidal cells becomes active (Muller 1996). When the animal is in a different space, a different set of pyramidal cells becomes active (see Figure 5). In one of our initial experiments, Kentros, Muller, Hawkins, and I simply blocked LTP pharmacologically, using an NMDA receptor antagonist (Kentros et al. 1998). We found that when placed in a new environment, animals with blocked NMDA receptors formed a good spatial map that was stable an hour later. However, after 24 hours the map had become completely unstable: most pyramidal cells no longer retained the initial representation of their place field. This suggested that activation of NMDA receptors—

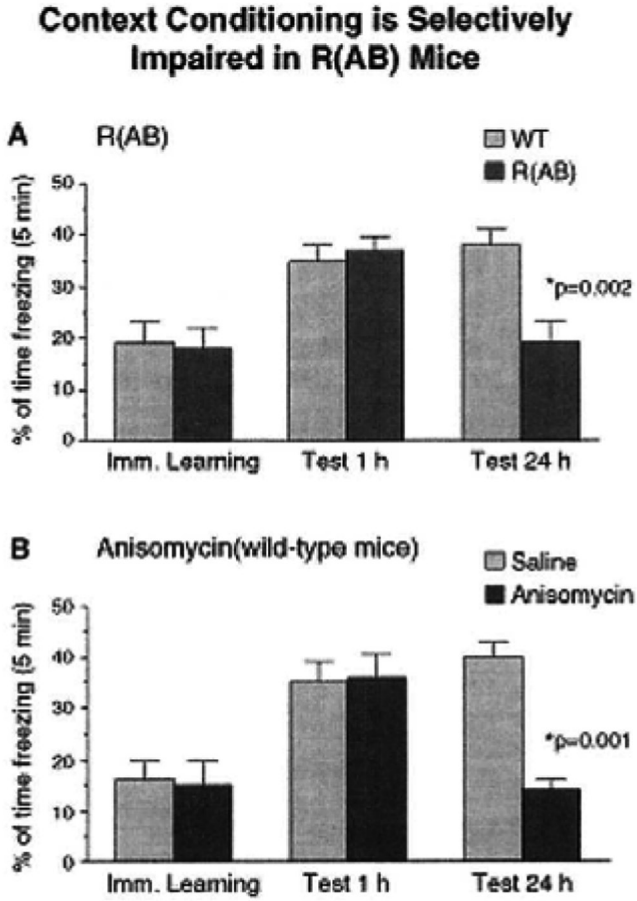

Fig. 4. Mutant mice that express the R(AB) gene in the hippocampus, blocking the action of PKA, underwent contextual conditioning and were tested after 1 hour and 24 hours (see Fig. 3). The mice learned well and froze when put in the box an hour after conditioning. However, they no longer froze when put in the box 24 hours after conditioning, indicating a defect in long-term explicit memory, which requires the hippocampus (**A**). Wild-type mice exposed to anisomycin, an inhibitor of protein synthesis, during training show a similar defect in long-term memory 24 hours after conditioning (**B**), also indicating a defect in long-term memory that requires the hippocampus. From Abel et al. 1997.

perhaps a step in modifying the strength of the synapse—is required for the long-term stabilization of a spatial map, a result consistent with the role of the late phase of LTP in the stabilization of such maps.

We next asked: Does a selective deficit—one that affects only the late phase of LTP and leaves the early phase intact—cause a selective abnormality

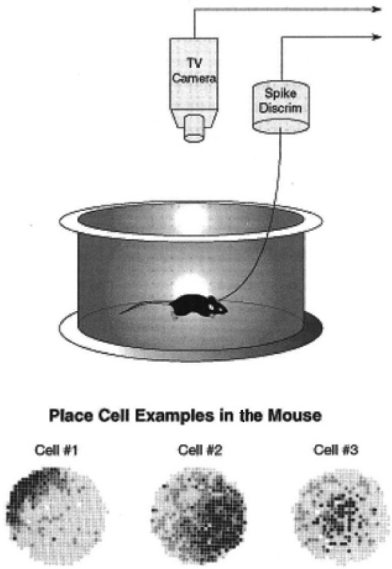

Fig. 5. Spatial memory can be studied in the mouse by recording from individual pyramidal cells in the hippocampus. The firing pattern of these place cells creates an internal representation of the animal's location in its surroundings. A mouse is attached to a recording cable and placed inside a cylinder (49 cm in diameter by 34 cm high). The other end of the cable goes to a 235-channel commutator attached to a computer-based spike-discrimination system. The cable is also used to supply power to a light-emitting diode mounted on the headstage the mouse carries. The entire apparatus is viewed with an overhead TV camera whose output goes to a tracking device that detects the position of the mouse. The output of the tracker is sent to the same computer used to detect spikes, so that parallel time series of positions and spikes are recorded. The occurrence of spikes as a function of positions is extracted from the basic data and is used to form two-dimensional firing-rate patterns that can be analyzed numerically or visualized as color-coded firing-rate maps. Dark areas indicate regions in the circular enclosure in which a given pyramidal cell fires at high rates. Based on Kandel 2000.

in the long-term stability of place cells? Since only the late phase of LTP requires PKA, Alex Rotenberg, Muller, Abel, Hawkins, and I returned to the R(AB) transgenic mice, which have diminished PKA activity and a diminished form of late LTP (Rotenberg et al. 2000). If reduced activity of PKA affects the stability of place cells, R(AB) mice should be able to form a stable map of space in a novel environment, as normal animals do, and the map should remain stable for at least an hour. However, the map should be unstable 24 hours later. This is precisely what we found (see Figure 6).

The fact that long-term instability in the spatial map and the deficit in long-term memory parallel the deficit in the late phase of LTP suggested that PKA-mediated gene activation and the synthesis of new protein might

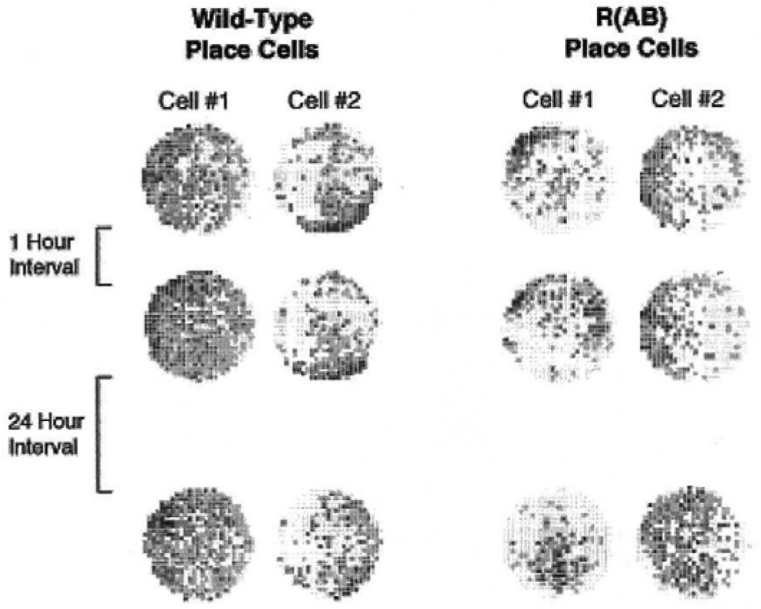

Fig. 6. The long-term stability of the place field of a pyramidal cell, as shown in two simultaneous recordings from pyramidal cells in the hippocampus of a wild-type mouse and a mutant mouse. In the wild-type mouse, the spatial fields form and are stable when the mouse is taken out of the test environment and put back one hour later. When the wild-type mouse is taken out and put back 24 hours later, the fields of the pyramidal cells are still quite stable. By contrast, pyramidal cells in the R(AB) mice, in which PKA has been compromised, form good fields that are stable an hour later, but do not remain stable after 24 hours.

be essential for the stabilization of the spatial map. Naveen Agnihotri, Kentros, Hawkins, and I tested this idea and found that inhibiting protein synthesis destabilizes place fields in the long term, much as inhibiting PKA does (see Figure 7; Rotenberg et al. 2000; Agnihotri et al. 2001).

In the course of this work we discovered, as mentioned earlier, that attention is a key feature in the formation of a stable place map in mice (Kentros et al. 2001). When a mouse does not attend to the space it walks through, the map forms but is unstable after three to six hours. When the mouse is forced to pay attention to the space, however, the map is invariably stable for days. How does this attentional mechanism work? Our recent work suggests that one necessary component is mediated by the dopaminergic modulatory system, acting through a D1/D5 receptor that activates adenylyl cyclase, cAMP, and PKA. The actions of dopamine and other modulatory transmitters might, among other things, trigger the protein synthesis–dependent steps that stabilize the map.

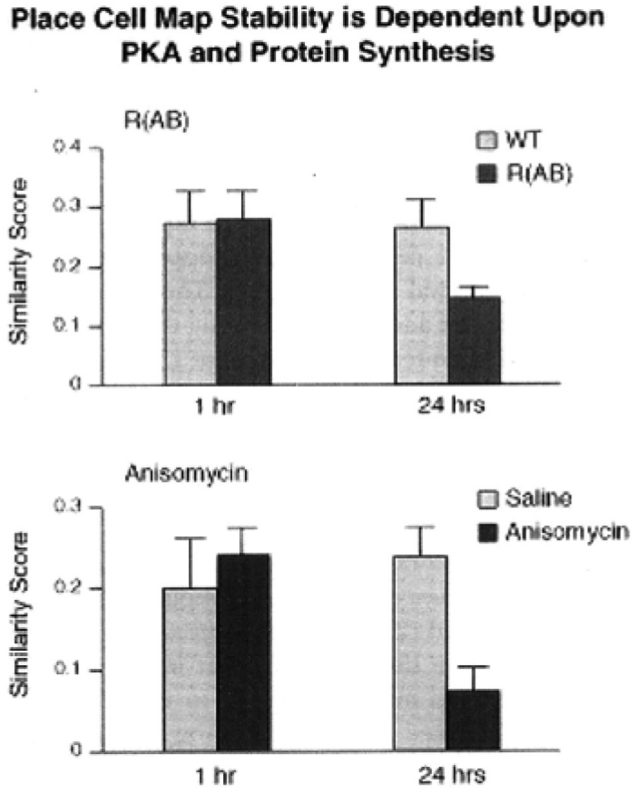

Fig. 7. Group data for R(AB) mice, with compromised PKA, and wild-type mice in which protein synthesis is inhibited. The top graph shows the group data for R(AB) and wild-type mice; the bottom graph shows that similar effects can be obtained by inhibiting protein synthesis with anisomycin. From Rotenberg et al. 2000; Agnihotri et al. 2001.

Constraints on LTP and Explicit Memory Storage

My colleagues and I (Mallaret et al. 2001) and Emmanuel Landau (Blitzer et al. 1998) and his colleagues found that the threshold for hippocampal synaptic plasticity and memory storage is determined by the balance between protein phosphorylation and dephosphorylation. This balance involves PKA and the Ca^{2+}-sensitive phosphatase calcineurin, the initial step in a phosphatase cascade (Mansuy et al. 1998; Mallaret et al. 2001). To determine whether endogenous calcineurin acts as a constraint in this balance, we inhibited calcineurin and examined the effects on synaptic plasticity and memory storage. Using the CaM kinase promoter and the doxycycline-dependent rtTA system that Mayford had first successfully applied to the brain, Isabelle Mansuy, Gael Malleret, Danny Winder, Tim Bliss, and I found that a transient reduction of calcineurin activity facilitates LTP both *in vitro*

and *in vivo* (see Figure 8) (Mallaret et al. 2001). This facilitation persists for several days in the intact animal, and it is accompanied by enhanced learning and strengthening of short- and long-term memory on several spatial and nonspatial tasks requiring the hippocampus. The LTP activity and memory improvements were reversed when we suppressed the expression of the transgene by withdrawing doxycycline. These results, together with previous findings by Winder and Mansuy showing that overexpression of calcineurin impairs PKA-dependent components of LTP and memory (Mansuy et al. 1998; Winder et al., 1998), demonstrate that endogenous calcineurin negatively affects synaptic plasticity, learning, and memory (Figure 8).

There Is Life after the Nobel Prize

Since my residency in psychiatry at Harvard in the early 1960s, Denise and I have spent much of each August in the town of Wellfleet on Cape Cod, and since 1972, in our summer home in South Wellfleet. The house has a beautiful view of Wellfleet Bay and is a lovely place for boating and swimming. There are also superb clay tennis courts at Oliver's, a five-minute drive away, where I enjoy playing. Most important, this is an opportunity for Denise and me to have a peaceful vacation and to get together with our two children, Paul and Minouche, and their families, who come for at least a part of the month.

Outside the house Denise has strung some clotheslines; being French-born, she likes the smell of laundry dried in the fresh air and sunshine. One day

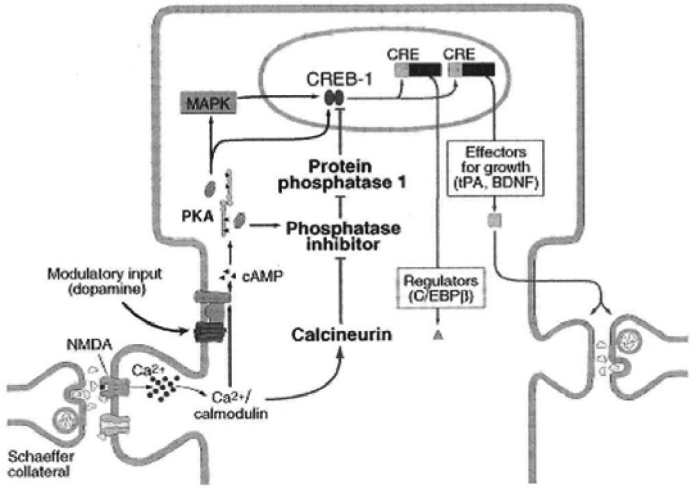

Fig. 8. Long-term potentiation requires regulation not only of kinases but also of phosphatases. The phosphatase cascade initiated by calcineurin shuts off a phosphatase inhibitor, thereby removing constraints on the protein phosphatase 1, which then proceeds to inhibit the kinase cascade. Based on Mallaret et al. 2001.

in August 1996 she and I were hanging the laundry when the phone rang inside the house. I went to answer it, and found Stephen Koslow, my project officer from the NIMH, on the line. He told me that the grant I applied for had been awarded and should be funded within a reasonable period of time. He then added that he and a number of people at NIMH thought I would get the Nobel Prize.

After I hung up the phone, I went outside and continued to hang the laundry. I told Denise that Koslow thought I was going to get the Nobel Prize. She responded, to my astonishment, "I hope not soon." I turned to her and said, "What do you mean 'not soon'? How could you, my wife, say that?" She answered, "As you know, I worked with Robert Merton and Harriet Zuckerman when I was a graduate student in sociology at Columbia, and they studied people who had won the Nobel Prize. They found that, by and large, after someone has won the Nobel Prize he or she did not contribute more to science. You still have a few ideas. Play them out. There is lots of time for the Nobel Prize later on."

So when I heard from the Nobel committee on Yom Kippur, October 9, 2000, that I was to be awarded the Nobel Prize in Physiology or Medicine, I realized that in addition to the pleasures and gratification of this remarkable award, I now had a challenge on my hands: I had to prove to Denise that I was not completely intellectually dead.

As a result of a number of fortunate circumstances, including sustained support from the Howard Hughes Medical Institute, I have continued to have a very enjoyable and productive scientific career. This was in important part made possible by several outstanding postdoctoral fellows and graduate students with whom it has been my privilege to work over the last 15 years.

A Functional Prion in the Maintenance of Long-Term Memory

Once we realized that there are separate processes for the initiation and maintenance of memory, we asked the question, How does the second mechanism work? Kausik Si, who joined my lab in 1999, addressed this question in a remarkably original and effective set of experiments.

Kausik argued that if the neuron sends mRNA transcripts to all of its terminals and only those terminals that are marked can use the transcripts productively, then presumably the transcripts must be dormant before being activated in some way. He thought that one way of activating protein synthesis at the synapse would be to recruit a regulator of gene translation that is capable of activating dormant mRNA. In *Xenopus* oocytes, there is an example of this. Here, the maternal RNA is silent until activated by a regulator of protein synthesis known as CPEB, the cytoplasmic polyadenylation element binding protein (Richter 1999). Kausik searched for a homolog in *Aplysia* and found, in addition to the developmental form of CPEB, a new form that had novel properties (Si et al. 2003a, 2003b, 2010). Blocking this form of CPEB at

a marked (active) synapse prevents the maintenance, but not the initiation, of long-term synaptic facilitation for a day or more after the memory is formed.

A remarkable feature of the *Aplysia* form of CPEB is that its N-terminus resembles the prion domain of yeast prion proteins and endows the *Aplysia* CPEB with self-sustaining properties. But unlike other prions that are pathogenic, the *Aplysia* CPEB appears to be functional: the active, self-perpetuating form of the protein does not kill cells, but rather controls synapse-specific translation. Notably, the persistence of long-term memory in *Drosophila* and in mice has also been found to involve CPEB (Keleman et al. 2007; Majumdar et al. 2012; Rajasethupathy et al. 2012; Pavlopoulos et al. 2013; Fioriti et al. 2014, 2015; Stephan et al. 2015; Drisaldi et al. 2015).

Based on the prion-like persistent properties of CPEB in *Aplysia* neurons, Kausik and I (Si et al. 2010) proposed a model for the persistence of memory storage in *Aplysia*. CPEB activates the translation of dormant mRNA transcripts by elongating their poly-A tail. *Aplysia* CPEB has two states: one is inactive and acts as a repressor, while the other is active. In an unmarked synapse, the basal level of CPEB expression is low, and the protein is inactive or repressive. According to the model, serotonin induces an increase in CPEB. When a given threshold is reached, CPEB is converted to the prion-like state, which is more active and lacks the inhibitory function of the basal state.

Once the prion state is established at an activated synapse, dormant mRNA transcripts, made in the cell body and distributed throughout the cell, are translated—but only at that activated synapse. Because the activated CPEB is self-perpetuating, it is capable of contributing to synapse-specific, long-term molecular change, thus providing a mechanism for the stabilization of learning-related synaptic growth and the persistence of memory storage in stable periods of normal growth, when very low levels of protein synthesis are required.

Animal Models of Drug Abuse: Molecular Mechanisms in the Gateway Effect

In a return to my clinical roots, I have begun to study disorders of memory in three contexts: drug abuse, age-related memory loss, and schizophrenia.

In 2010 Amir Levine and I collaborated with my wife, Denise, to explore the molecular mechanism for a gateway drug. Denise pioneered the epidemiology of the Gateway Effect in a paper she published in *Science* in 1975. She found that in human populations, cigarettes and alcohol generally serve as gateway drugs: people use them before progressing to marijuana, cocaine, or other illicit substances.

To understand the biological basis of the gateway sequence of drug use, we developed a mouse model and used it to study the effects of nicotine on subsequent responses to cocaine. We found that giving the mice nicotine increases their response to cocaine, as assessed by addiction-related behaviors

and reduced LTP-related synaptic plasticity in the striatum, a brain region critical for addiction-related reward. The responses to cocaine were enhanced only when we administered nicotine first, followed by nicotine and cocaine concurrently. Reversing the order of administration showed that cocaine has no effect on nicotine-induced behaviors or LTP in the striatum. We concluded that nicotine primes the response to cocaine by enhancing cocaine's ability to induce expression of the FosB gene. We found that this gene is activated through inhibition of histone deacetylase, which results in histone acetylation thereby enhancing gene expression throughout the striatum.

We tested this conclusion further and found that a histone deacetylase inhibitor simulates the actions of nicotine, priming the response to cocaine and enhancing FosB gene expression and depressed LTP in the nucleus accumbens. Conversely, in a genetically modified mouse model characterized by reduced histone acetylation, the effects of cocaine on LTP were diminished. We achieved a similar effect by infusing a low dose of theophylline, an activator of histone deacetylase, into the nucleus accumbens.

The epidemiological data—which indicate that most cocaine users start using the drug after having begun to smoke and while still smoking, and that initiating cocaine use after smoking increases the risk of becoming dependent on cocaine—are consistent with our findings in mice. If the findings in mice apply to humans, a decrease in smoking rates among young people would be expected to lead to a decrease in cocaine addiction.

Molecular Mechanism for Age-Related Memory Loss

To distinguish age-related memory loss more explicitly from Alzheimer's disease, Scott Small, Elias Pavlopoulos, and I explored its molecular underpinnings in the dentate gyrus, a subregion of the hippocampal formation found by Scott Small to be targeted by aging. We carried out a gene expression study in human tissue harvested postmortem from both the dentate gyrus and the entorhinal cortex, a neighboring subregion that is unaffected by aging and is known to be the site of onset of Alzheimer's disease. Using expression in the entorhinal cortex for normalization, we identified 17 genes that manifest reliable age-related changes in the dentate gyrus. The most significant change was an age-related decline in RbAp48, a protein that binds to CREB and to the CREB binding protein and acts to modify histone acetylation. To test whether the decline in this protein could be responsible for age-related memory loss, we turned to mice and found that, consistent with humans, the RbAp48 protein is less abundant in the dentate gyrus of old mice than in young mice.

We next generated a transgenic mouse that expressed a dominant-negative inhibitor of the RbAp48 protein in the adult forebrain. Inhibition of the protein in young mice caused hippocampus-dependent memory deficits similar to those associated with aging, as measured by novel object recognition and Morris water maze tests. fMRI showed that within the hippocampal formation, dysfunction

occurs only in the dentate gyrus and corresponds to a selective decrease in histone acetylation in this region of the brain. Upregulation of the RbAp48 protein in the dentate gyrus of old wild-type mice ameliorated age-related hippocampus-based memory loss and age-related abnormalities in histone acetylation.

Together, these findings show that the dentate gyrus is targeted by aging, and they identify a molecular mechanisms that contributes importantly to cognitive aging that could be useful therapeutically.

Animal Model of Schizophrenia: Transient and Selective Overexpression of Dopamine D2 Receptors in the Striatum Causes Persistent Abnormalities in Prefrontal Cortex Functioning

Eleanor Simpson and Christoph Kellendonk in my laboratory have developed a new animal model of the cognitive and negative symptoms of schizophrenia. Increased activity of D2 receptors in the striatum has been linked to the pathophysiology of schizophrenia. To determine directly the behavioral and physiological consequences of such increased receptor function, we generated mice with reversibly increased levels of D2 receptors only in the striatum. These mice exhibit cognitive impairments in working memory tasks and behavioral flexibility but not more general cognitive deficits. Moreover, the deficit in the working memory task persists even after the transgene has been switched off, indicating that it results not from continued overexpression of D2 receptors but from excess expression during development.

To determine what may mediate these cognitive deficits, we analyzed the prefrontal cortex, the brain structure importantly associated with working memory. We found that overexpression of D2 receptors in the striatum affects concentrations of dopamine, rates of dopamine turnover, and activation of D1 receptors in the prefrontal cortex, measures that are critical for working memory.

Life Is a Circle

But life is a circle. As I have continued to enjoy doing science, I have also, surprisingly, ended up where I began—as a would-be intellectual historian. In so doing I have essentially picked up where I left off on graduating from Harvard in 1952.

First in 2006 I published a scientific autobiography entitled *In Search of Memory*. This book went on to win both the *Los Angeles Times* and *The National Academy of Science* Book Awards in the Science category. Based on that book, the filmmaker Petra Seeger made a film also entitled "In Search of Memory" based on a sentimental journey that my family and I made to Europe on the occasion of our 50th wedding anniversary. Together with our children and grandchildren we traveled to the South of France and visited

the convent where Denise was in hiding during the war years. We then went on to Paris where she was born and to Vienna where I lived.

More recently, in 2012 I wrote a second book, this one about Science and Art entitled *The Age of Insight: The Quest to Understand the Unconscious in Art, Mind, and Brain from Vienna 1900 to the Present*. This book won the Bruno Keisky Prize, Austria's most important literary award.

In thinking of these endeavors in the context of my science, which I am continuing to do with great pleasure, I am reminded that in 1959, at the beginning of our career, my colleague Alden Spencer and I formulated a hierarchy of the four levels that define an academic life of a neural scientist. At that time, we saw this hierarchy as a series of *descending* degenerative steps in an intellectual carrier:

> First, the most important level, is the working *Neuroscientist*—the person who works at the bench, does everything with their own hands.
> One step down on the second rung is the *Neuroleader*—the scientist who runs a lab.
> Third is the *Neuropolitician*—the scientist who runs a department.
> Fourth is the *Neurohistorian*—the scientist who writes a textbook.

In the last several years I have had the privilege of working with Charlie Rose and we have so far put together 30 programs on Brain Science with 8 still to come—designed for the general viewer.

Thus in my return to intellectual history since the year 2000 I have gone on to define a new category, a fifth category of degeneracy, that of the *Neuroentertainer*.

I assure you: *je regret pas*: Indeed, I want to assure those of you who are in the running: There is life after the Nobel Prize. In fact a most enjoyable life.

My research has been generously supported by the Howard Hughes Medical Institute, the National Institutes of Health, the Mathers Foundation, FRAXA, and The Lieber Trust. I am particularly indebted to the Howard Hughes Medical Institute and its leaders, both former and current: Donald Fredrickson, George Cahill, Purnell Chopin, Tom Cech, Robert Tjian, and Gerry Rubin and Erin O'Shea. Their farsighted vision has encouraged Hughes investigators to take a long-term perspective and to tackle challenging problems. Research on learning and memory certainly meets both of these criteria!

References

The Nobel Prize Committee asks each awardee to prepare both an autobiographical essay and a scientific lecture (Kandel 2000). In this chapter, I have combined

parts of my essay and my lecture and added a brief summary of my scientific and extrascientific activities since the year 2000.

Abel, T., Nguyen, P.V., Barad, M., Deuel, T.A.S., Kandel, E.R., and Bourtchouladze, R. (1997) Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell 88:615–626.

Adey, W.R. (1965). Electrophysiological patterns and cerebral impedance characteristics in orienting and discriminative behavior. Symposium on Neural Mechanism of Conditioned Reflex and Behavior. Proc. Int. Union Physiol. Sci. XXIII Int. Congr. Tokyo, 4:324–329.

Agnihotri, N., Hawkins, R.D., Kandel, E.R., and Kentros, C. (2004) The long-term stability of new hippocampal place fields requires new protein synthesis. PNAS 101(10):3656–3661.

Bacskai, B.J., Hochner, B., Mahaut-Smith, M., Adams, S.R., Kaang, B.-K., Kandel, E.R., and Tsien, R.Y. (1993) Spatially resolved dynamics of cAMP and protein kinase A subunits in *Aplysia* sensory neurons. Science 260:222–226.

Barco, A., Alarcon, J.M., and Kandel, E.R. (2002) Expression of constitutively active CREB protein facilitates the late phase of long-term potentiation by enhancing synaptic capture. Cell 108:689–703.

Berkley, G.E., Vienna and Its Jews: The Tragedy of Success, 1880–1980s, Cambridge, Mass.

Bliss, T.V. and Lømo, T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J. Physiol. 232:331–356.

Blitzer, R.D., Conner, J.H., Brown, G.P., Wong, T., Shenolikar, S., Iyengar, R., and Landau, E.M. (1998) Gating of CaMKII by cAMP-regulated protein phosphatase activity during LTP. Science 280:1940–1942.

Bolshakov, V.Y. and Siegelbaum, S.A. (1995) Regulation of hippocampal transmitter release during development and long-term potentiation. Science 269:1730–1734.

Bolshakov, V.Y., Golan, H., Kandel, E.R., and Siegelbaum, S.A. (1997) Recruitment of new sites of synaptic transmission during the cAMP-dependent late phase of LTP at CA3-CA1 synapses in the hippocampus. Neuron 19:635–651.

Bourtchouladze, R., Franguelli, B., Blendy, J., Cioffi, D., Schutz, G., and Silva, A.J. (1994) Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. Cell 79:59–68.

Burns, B.D. (1958) The mammalian cerebral cortex. Monograph of the Physiological Society. Edward Arnold (Publisher) Ltd. London.

Cajal, S.R. (1894) La fine structure des centres nerveux. Proc R Soc Lond, 55:444–468.

Casadio, A., Martin, K.C., Giustetto, M., Zhu, H., Chen, M., Bartsch, D., Bailey, C.H., and Kandel, E.R. (1999) A transient, neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis. Cell 99:221–237.

Castellucci, V.F., Carew, T.J., and Kandel, E.R. (1978) Cellular analysis of long-term habituation of the gill-withdrawal reflex in *Aplysia*. Science 202:1306–1308.

Castellucci, V., Pinsker, H., Kupfermann, I., and Kandel, E.R. (1970) Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in *Aplysia*. Science 167:1745–1748.

Drisaldi B., Colnaghi L., Fioriti L., Rao N., Myers C., Snyder A.M., Metzger D.J., Tarasoff J., Konstantinov E., Fraser P., Manley J.L., and Kandel E.R. (2015) SUMOylation is an inhibitory constraint that regulates the prion-like aggregation and activity of CPEB3. Cell Reports 11:1694–1702.

Dudek, S.M. and Fields, R.D. (2002) Somatic action potentials are sufficient for late-phase LTP-related cell signaling. Proc. Natl. Acad. Sci. USA 99:3962–3967.

Engert, F. and Bonhoeffer, T. (1999) Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature 399:66–70.

English, J.D. and Sweat, J.D. (1996) Activation of p42 mitogen-activated protein kinase in hippocampal long term potentiation. J. Biol. Chem. 271:24329–24332.

Fatt, P. and Katz, B. (1951) An analysis of the end-plate potential recorded with an intracellular electrode. J. Physiol. (Lond.) 115:320–370.

Fioriti L., Myers C., Huang Y-Y, Li X., Stephan J., Trifilieff P., Kosmidis S., Drisaldi B., Pavlopoulos E., Kandel E.R. (2015) The persistence of hippocampal-based memory requires protein synthesis mediated by the prion-like protein CPEB3. Neuron 86:1433–1448.

Fioriti, L. Myers, C. Huang, Y-Y, Li, X., Stephan, J., Trifilieff, P., Kosmidis, S., Drisaldi, B., Pavlopoulos, E., Kandel, E.R. (2014) The persistence of memory and its reconsolidation require CPEB3-mediated protein synthesis in the hippocampus. Unpubl.

Frey, U. and Morris, R.G. (1997) Synaptic tagging and long-term potentiation. Nature 385:533–536.

Frey, U., Huang, Y.-Y., and Kandel, E.R. (1993) Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. Science 260:1661–1664.

Grant, S.G.N., O'Dell, T.J., Karl, K.A., Stein, P.L., Soriano, P., and Kandel, E.R. (1992) Impaired long-term potentiation, spatial learning, and hippocampal development in fyn mutant mice. Science 258:1903–1910.

Greengard, P. (1976) Possible role for cyclic nucleotides and phosphorylated membrane proteins in postsynaptic actions of neurotransmitters. Nature 260:101–108.

Hebb, D.O. (1949) The organization of behavior. John Wiley and Sons Inc: New York.

Hilgard E.R. and Marquis D.G. (1940) Conditioning and learning. Appleton-Century:New York.

Huang, Y.-Y. and Kandel, E.R. (1994) Recruitment of long-lasting and protein kinase A-dependent long-term potentiation in the CA1 region of hippocampus requires repeated tetanization. Learning & Memory 1:74–82.

Huang, Y.-Y. and Kandel, E.R. (1995) D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. Proc. Natl. Acad. Sci. USA 92:2446–2450.

Impey, S., Obrietan, K., Wong, S.T., Poser, S., Yano, S., Wayman, G., Deloulme, J.C., Chan, G., and Storm, D.R. (1998) Cross talk between ERK and PKA is required for Ca^{2+} stimulation of CEB-dependent transcription and ERK nuclear translocation. Neuron 21:869–883.

Kandel, E.R. (2000) The Molecular Biology of Memory Storage: A Dialog Between Genes and Synapses, Les Prix Nobel. Stockholm: Almquist & Wiskell International.

Kandel, E.R., and Kandel, D.B. (2014) Molecular basis for nicotine as a gateway drug. N. Engl. J. Med. 371:932–943.

Kandel, E.R. and Tauc, L. (1965) Heterosynaptic facilitation in neurones of the abdominal ganglion of *Aplysia depilans*. J. Physiol. (London) 181:1–27.

Keleman, K., Krüttner, S., Alenius, M., Dickson, B.J. (2007) Function of the *Drosophila* CPEB protein Orb2 in long-term courtship memory. Nat. Neurosci. 10:1587–1593.

Kellendonk, C., Simpson, E.H., Polan, H.J., Malleret, G., Vronskaya, S., Winiger, V., Moore, H., and Kandel, E.R. Transient and selective over-expression of dopamine D2 receptors in the striatum causes persistent abnormalities in the functioning of the prefrontal cortex. Neuron 49:603–615.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., and Muller, R.U. (1998) Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science 280:2121–2126.

Kentros, C.G., Agnihotri, N.T., Streater, S., Hawkins, R.D., and Kandel, E.R. (2004) Increased attention to spatial context increases both place field stability and spatial memory. Neuron 42:283–295.

Kimble, G.A. (1967) Foundations of conditioning and learning. Appleton-Century-Crofts: New York.

Kuffler, S.W. and Eyzaguirre, C. (1955) Synaptic inhibition in an isolated nerve cell. J. Gen. Physiol. 39:155–184.

Lee, S-H., Lim, C-S., Park, H., Lee, J-A., Han, J-H., Kim, H., Cheang, Y-H., Lee, S-H., Lee, Y-S., Ko, H-G., Jang, D-H., Kim, H., Miniaci, M.C., Bartsch, D., Kim, E., Bailey, C.H., Kandel, E.R., and Kaang B-K. (2007) Nuclear translocation of CAM-associated protein activates transcription for long-term facilitation in *Aplysia*. Cell 129:801–812.

Lee, S-H., Lim, C-S., Park, H., Lee, J-A., Han, J-H., Kim, H., Cheang, Y-H., Lee, S-H., Lee, Y-S., Ko, H-G., Jang, D-H., Kim, H., Miniaci, M.C., Bartsch, D., Kim, E., Bailey, C.H., Kandel, E.R., and Kaang, B-K. (2007) Nuclear translocation of CAM-associated protein activates transcription for long-term facilitation in *Aplysia*. Cell 129:801–812.

Majumdar, A., Cesario, W.C., White-Grindley, E., Jiang, H., Ren, F., Khan, M.R., Li, L., Choi, E.M.L., Kannan, K., Guo, F., Unruh, J., Slaughter, B., and Si, K. (2012) Critical role of amyloid-like oligomers of *Drosophila* Orb2 in the persistence of memory. Cell 148:515–529.

Ma, L., Zablow, L., Kandel, E.R., and Siegelbaum, S.A. (1999) Cyclic AMP induces functional presynaptic boutons in hippocampal CA3-CA1 neuronal cultures. Nature Neurosci. 2:24–3.

Malenka, R.C. and Nicoll, R.A. (1997) Silent synapses speak up. Neuron 19:473–476.

Mallaret, G., Haditsch, U., Genoux, D., Jones, M.W., Bliss, T.V.P., Vanhoose, A.M., Weitlauf, C., Kandel, E.R., Winder, D.G., and Mansuy, I.M. (2001) Inducible and reversible enhancement of learning, memory, and long-term potentiation by genetic inhibition of calcineurin. Cell 104:675–686.

Mansuy, I.M., Mayford, M., Jacob, B., Kandel, E.R., and Bach, M.E. (1998) Restricted and regulated overexpression reveals calcineurin as a key component in the transition from short-term to long-term memory. Cell 92:39–49.

Martin, K.C., Michael, D., Rose, J.C., Barad, M., Casadio, A., Zhu, H., Kandel, E.R. (1997a) MAP kinase translocates into the nucleus of the presynaptic cell and is required for long-term facilitation in *Aplysia*. Neuron 18:899–912.

Martin, K.C., Casadio, A., Zhu, H., Yaping, E., Rose, J.C., Chen, M., Bailey, C.H., Kandel, E.R. (1997b) Synapse-specific, long-term facilitation of *Aplysia* sensory to motor synapses: a function for local protein synthesis in memory storage. Cell 91:927–938.

Martin, K.C., Casadio, A., Zhu, H., Yaping, E., Rose, J., Bailey, C.H., Chen, M., and Kandel, E.R. (1998) Synapse-specific transcription-dependent long-term facilitation of the sensory to motor neuron connection in *Aplysia*: A function for local protein synthesis in memory storage. Cell 91:927–938.

Martin, K.C., Barad, M., and Kandel, E.R. (2000) Local protein synthesis and its role in synapse-specific plasticity. Curr. Opin. Neurobiol. 10:587–592.

Milner, B., Squire, L.R. and Kandel, E.R. (1998) Cognitive neuroscience and the study of memory. Neuron 20:445–468.

Morris, R.G.M., Anderson, E., Lynch, G.S., and Baudry, M. (1986) Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319:774–776.

Muller, R. (1996) A quarter of a century of place cells. Neuron 17:813–822.

Muller, D. (1997) Ultrastructural plasticity of excitatory synapses. Rev. Neurosci. 8:77–93.

Nguyen, P.V., Abel, T., and Kandel, E.R. (1994) Requirement of a critical period of transcription for induction of a late phase of LTP. Science 265:1104–1107.

O'Keefe, J. and Nadel, L. (1978) The Hippocampus as a Cognitive Map. Oxford: Clarendon Press.

Pavlopoulos, E., Jones, S., Kosmidis, S., Close, M., Kim, C., Kovalerchik, O., Small, S.A., Kandel, E.R. (2013) Molecular mechanism for age-related memory loss: the histone-binding protein RbAp48. Sci. Transl. Med. 5:200ra115.

Rajasethupathy, P., Antonov, I., Sheridan, R., Frey, S., Sander, C., Tuschl, T., Kandel, E.R. (2012) A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. Cell 149(3):693–707.

Richter, J.D. (1999) Cytoplasmic polyadenylation in development and beyond. Microbiol. Mol. Biol. Rev. 63:446–456.

Rotenberg, A., Mayford, M., Hawkins, R.D., Kandel, E.R., and Muller, R.U. (1996) Mice expressing activated CaMKII lack low frequency LTP and do not form stable place cells in the CA1 region of the hippocampus. Cell 87:1351–1361.

Rotenberg, A, Abel, T., Hawkins, R.D., Kandel, E.R., and Muller, R.U. (2000) Parallel instabilities of long-term potentiation, place cells, and learning causes by decreased protein kinase A activity. J. Neurosci. 20:8096–8102.

Schuman, E.M. (1997) Synapse specificity and long-term information storage. Neuron 18:339–342.

Schwartz, J.H., Castellucci, V.F., and Kandel, E.R. (1971) Functioning of identified neurons and synapses in abdominal ganglion of *Aplysia* in absence of protein synthesis. J. Neurophysiol. 34:939–953.

Si, K., Giustetto, M., Etkin, A., Hsu, R., Janisiewicz, A.M., Miniaci, M.C., Kim, J.H., Zhu, H., and Kandel, E.R. (2003a) A neuronal isoform of CPEB regulates

local protein synthesis and stabilizes synapse-specific long-term facilitation in *Aplysia*. Cell 115:893–904.

Si, K., Lindquist, S., and Kandel, E.R. (2003b) A neuronal isoform of the *Aplysia* CPEB has prion-like properties. Cell 115:879–891.

Si, K., Choi, Y-B., White-Grindley, E., Majumdar, A., and Kandel, E.R. (2010). *Aplysia* CPEB can form prion-like multimers in sensory neurons that contribute to long-term facilitation. Cell 140:421–435.

Skinner B.F. (1938) The Behavior of Organisms. Appleton-Century: New York.

Squire, L.R. and Kandel, E.R. (1999) Memory: Mind to Molecules. New York: Scientific American Books.

Stephan J.S., Fioriti L., Lamba N., Derkatch I.L., and Kandel E.R. (2015) The CPEB3 protein important in memory persistence is a functional prion that interacts with the actin cytoskeleton. Cell Reports 11:1772–1785.

Stevens, C.F. and Wang, Y. (1994) Changes in reliability of synaptic function as a mechanism for plasticity. Nature 371:704–707.

Steward, O. (1997) mRNA localization in neurons: A multipurpose mechanism? Neuron 18:9–12.

Tompa, P. and Friedrich, P. 1998. Prion proteins as memory molecules: an hypothesis. Neuroscience 86:1037–1043.

Ward, R.D., Simpson, E.H., Kandel, E.R., and Balsam, P.D. (2011) Modeling motivational deficits in mouse models of schizophrenia: behavior analysis as a guide for neuroscience. Behav. Processes 87:149–156.

Weiner, J. (1999) Time, Love, Memory: A Great Biologist and His Quest for the Origins of Behavior. New York: Knopf.

Winder, D.G., Mansuy, I.M., Osman, M., Moallem, T.M., and Kandel, E.R. (1998) Genetic and pharmacological evidence for a novel, intermediate phase of long-term potentiation (I-LTP) suppressed by calcineurin. Cell 92:25–37.

Zuckmayer, C. (1966) Als wär's ein Stück von. Fischer Taschenbuch: Frankfurt.