

*Samuel H. Barondes . Joseph E. Bogen*

*Alan Cowey . David R. Curtis*

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# **The History of Neuroscience in Autobiography**

*Lynn T. Landmesser . Rodolfo R. Llinás*

*Alan Peters . Martin Raff*

*Wilfrid Rall . Mark R. Rosenzweig*

*Arnold B. Scheibel . Gerald Westheimer*

## **Volume 5**

Edited by Larry R. Squire



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# The History of Neuroscience in Autobiography

VOLUME 5

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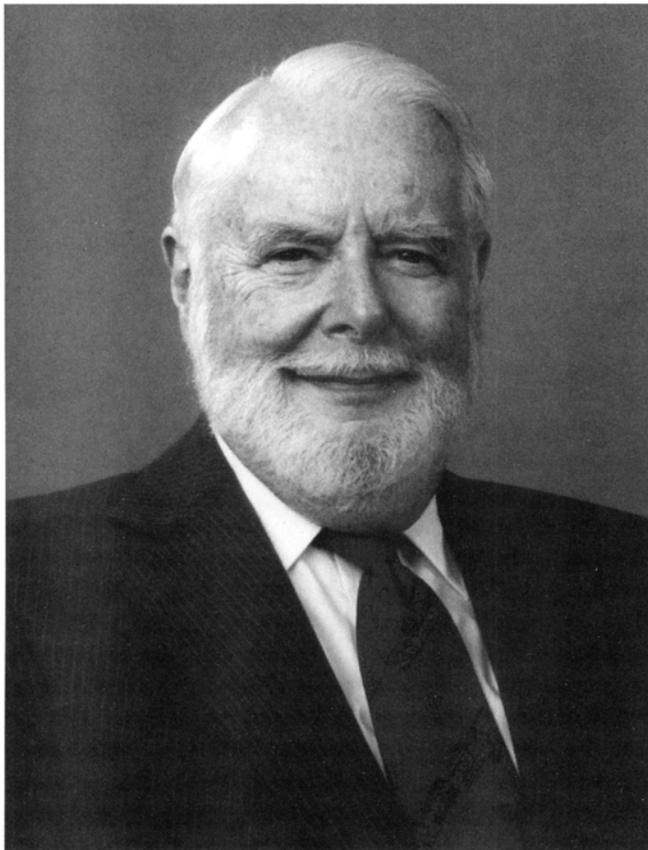
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# Mark R. Rosenzweig

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September 12, 1922

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*In his early studies, Mark Rosenzweig discovered brain mechanisms of auditory localization and of the precedence effect in localization. He is best known for research with collaborators that was the first to demonstrate neurochemical and neuroanatomical plasticity of the brain in response to differential experience. These discoveries changed the thinking of neuroscientists and others about the brain.*

*Rosenzweig and collaborators also investigated the neurochemical processes underlying the successive stages of memory formation.*

# Mark R. Rosenzweig

**P**reparing this account brings back the excitement of discovering unexpected aspects of the nervous system as well as the satisfaction of systematically testing alternative hypotheses. It also shows occasions when I failed to follow up leads or insights that later proved important.

## Family Background and Early Education

I do not know of any scientists among my forebears, but there were relatives noted for logical reasoning and skill in use of language. Perhaps that heritage, combined with fortunate circumstances, was enough to permit me a scientific career.

My grandparents emigrated from Russia to the United States in the 1880s. My father and his two brothers became lawyers; their four sisters were office workers. My father was known for keen legal analysis and for activity in community affairs. My mother grew up in Buffalo, New York, at that time a city with a large German-speaking population. She received high school diplomas in both German and English, and she was always interested in languages. She and my father were actively engaged in my sister's education and my own. They played word games with us to improve our vocabularies. We enjoyed a warm family life.

I was born and grew up in Rochester, New York and went to public schools where I was valedictorian in both grammar school and high school. In high school, I was selected for the Honor Work Program, a program for highly achieving students. In this program we were allowed to complete the curriculum according to our own schedules and to spend the rest of the time on individual or joint projects, such as chemical experiments, library time, writing and presenting skits, or cartooning.

## College

In fall 1940 I entered the University of Rochester. In some ways I found college a letdown after the high intensity of the Honor Work Program. I was not sure what to make my major field. Courses in history interested me strongly, but the introductory course in psychology fascinated me, and I decided to major in psychology. The chair of the Department of

Psychology, Elmer A.K. Culler, and some of his colleagues, including K.U. Smith, specialized in physiological psychology. The attack on Pearl Harbor and the entry of the United States into the war occurred during my sophomore year. Because of poor vision, I could not qualify for officer training, so I decided to continue my studies as long as possible. By taking a heavy program, I earned the B.A. in 1943 and then continued work toward the M.A.

A major area of research in the department was auditory perception and its physiology. We benefitted from the collaboration of Karl Lowy, an otolaryngologist with a strong scientific background, and summer visits by auditory physiologist Harlow Ades. I chose an M.A. research project that fit into the program of the laboratory, but the results yielded the first surprise in my research career. I trained cats to respond to a change in intensity of an auditory stimulus and then planned to map the frequency representation of the auditory cortex by removing areas of cortex and finding frequencies to which the cats could no longer respond. First, as a test, I removed the entire primary auditory area, and I found that the cats were still able to respond to stimuli throughout the frequency range! Auditory cortex was not required for intensity discrimination. Later it was found that auditory cortex is necessary for accurate auditory localization. I completed requirements for the M.A. before being drafted in 1943. A report based on my M.A. thesis, written during naval service, was my first scientific publication (Rosenzweig, 1946).

## Naval Service

Dr. Lowy had arranged for me to join a Navy physiology laboratory in Bethesda when I would be drafted. I had visited the laboratory, and all seemed to be in order. But when I was drafted, the Navy needed technicians for its radar program. Some electronic training in my M.A. program showed in my record, so I spent the next 2 years training and serving as a radio technician (the word *radar* was not public yet). Despite the poor vision that kept me out of officer training, my service involved reading detailed, fine-grained electronic circuit diagrams. While I was stationed at the Anacostia Naval Base in Washington, DC, President Roosevelt died, and I marched in his funeral procession. Later I shipped out across the Pacific and was stationed on a seaplane tender in Tsingtao Harbor, China.

The tender served the seaplanes that brought mail to us and other naval vessels in Tsingtao harbor, a somewhat circuitous function. This was my first experience in another country, and I tried to make the most of it. I arranged on days of liberty to be shown around the city and nearby countryside by members of the staff of a small advertising newspaper intended for American servicemen, in exchange for improving the writing of

the newspaper. The Chinese staff helped me to understand Chinese customs and architecture.

## The Years at Harvard

### *Doctoral Studies at Harvard*

While still at the University of Rochester, I had applied for entrance to the doctoral program in psychology at Harvard and had been accepted. Soon after my discharge from the Navy in the spring of 1946, I entered Harvard in the fall, where I did research in the Psycho-Acoustic Laboratory. Professor Edwin Newman enlisted me to do research on dichotic listening in human subjects for a project that he and Professor Hans Wallach had devised. This research provided the empirical basis for a well-known paper on the precedence effect in auditory localization (Wallach, Newman, and Rosenzweig, 1949).

Some graduate courses or seminars at Harvard were particularly impressive. In the summer of 1947, Donald O. Hebb came as a visiting faculty member and taught a seminar, using as textbook a mimeographed version of *The Organization of Behavior: A Neuropsychological Theory*, which had not yet found a publisher. I wish I had had the foresight to save that historical version. I also enjoyed Edwin G. Boring's seminars in the history of psychology, and later I was to write some articles on history of psychology and neuroscience.

Dr. Robert Galambos joined the laboratory as a research associate in 1947 and I learned electrophysiological recording from him. Professor Georg von Békésy joined the laboratory in 1947; in 1961 he was awarded the Nobel Prize in Physiology or Medicine for his research in the physiology of audition. Von Békésy suggested I learn histological techniques with him to aid him in his research, but I did not want to be diverted from the research I had begun on the neurophysiology of binaural perception in the cat, so I declined his offer. Had I accepted it, my research career might have gone off in a different direction.

Békésy impressed me strongly with his insistence on finding alternative ways to test a hypothesis and not being content with any single test, and I have tried to follow that practice. Later on, during a few returns to Cambridge, I benefitted from conversations with him.

Late in his career, Békésy took a professorship at the University of Hawaii. In Honolulu for a meeting in 1972, I heard that he was gravely ill, and I went to see him in the hospital. Békésy was heavily sedated, and his voice seemed to come from far off. He surprised and shocked me by murmuring, "I wasted my life studying audition. I should have studied pain."

In the research on binaural perception, I investigated how the electrophysiological responses evoked by stimulation of the two ears interacted at the auditory cortex. Because the responses were variable, I measured and averaged many responses for each stimulus condition, in effect acting as a living example of the later-to-be-invented computer of averaged transients. The results demonstrated that each ear is represented at the auditory cortex of each hemisphere but significantly more strongly in the contralateral hemisphere. They also showed that when the two ears were stimulated with dichotic time differences as little as microseconds, the response to the earlier stimulus partially inhibited the response to the later one. The relative size of responses at the two hemispheres indicated which ear was stimulated first and by how much. These findings were used to interpret dichotic-listening effects in human observers. Brain responses to closely successive dichotic stimuli suggested a mechanism for the precedence effect. I presented and defended my doctoral thesis in 1949 and remained another year at Harvard as a postdoctoral fellow to round out some aspects of the research.

During my postdoctoral year I taught the undergraduate course in physiological psychology. Some graduate students in the Department of Social Relations wanted to enroll in the proseminar in physiological psychology, but they were refused because feelings were still raw between Psychology and the recently formed Social Relations. I was told that if I wished, I could give them a noncredit seminar, which I did. One of those students was James Olds, who later went on to do postdoctoral research with Hebb at McGill. He and Peter Milner became famous for discovering "pleasure centers" (reinforcement centers) in the rat brain. In later years, Olds always addressed me as "Professor" in recognition of the seminar he took with me.

My 1949 doctoral thesis also demonstrated that electrodes placed on the skull could pick up electrical activity of all the auditory stations from the cochlea to the cortex. I noted that in his unpublished 1941 doctoral dissertation, J.E. Hawkins had shown that short-latency auditory deflections recorded at the cortex were subcortical in origin because they persisted after ablation of the cortex. In a publication based on my thesis I called attention to the fact that "the activity of subcortical centers can be studied without surgical invasion of the nervous system" (Rosenzweig, 1951, p. 148). At the time, I did not make much of this, and I did not follow it farther. Only later did others realize that these responses could be used to test the integrity of successive stations of the auditory system in infants and in adults with hearing impairment.

Starting in the 1970s, Robert Galambos and members of his group developed this into a practical hearing and neurological test and began using it to identify newborns with hearing loss. Now such tests are mandatory for infants in most of the United States so that problems of hearing can be detected and remedied early.

### Marriage

While at Harvard I met my future wife, Janine Chappat, a young French scholar who was doing postdoctoral research in education and cultural anthropology. Janine had been studying at the University of Oxford, England, when the sudden defeat of France in 1940 made it impossible for her to return there, and the occupation of northern France led to her classification in England as an enemy alien. Although friends in England were very hospitable and supportive, Janine decided to continue her studies in the United States. When I met her, she had recently concluded 2 years of fieldwork in New Mexico, supervised by anthropologist Clyde Kluckhohn, studying how children of Anglo, Hispanic, and Navajo communities learned about the other groups.

Janine and I married in the summer of 1947, and we have shared a life of love and mutual support. We had a brief honeymoon in France where Janine was reunited with her family for the first time after the war. That was the first of our many trips to France, including some half-sabbatical leaves. It paved the way to my doing research later with French colleagues and lecturing in French, and it was one of the factors that led me to become active in international psychology. (My activities in international psychology have been reported elsewhere [Rosenzweig, 1998].)

While in Paris in 1947 I paid my respects to Professor Henri Piéron at the Collège de France. Piéron was well known for his research in sensory physiology, and he was a leader in international psychology. He had been president of the 11th International Congress of Psychology in 1937, and he was soon to become the first president of the International Union of Psychological Science, 1951 to 1954. France in 1947 was still suffering from the aftermath of the war. Rationing was still in force, and the general mood was gloomy. Piéron shared that sentiment. Leading me to a window at the back of the Collège de France, Piéron pointed down to an abandoned excavation with muddy water in the bottom. "That was to have been our new laboratory," he said, "but now it will never be built." Fortunately that pessimism was excessive, because the overall situation soon improved, and French psychology and neuroscience rebounded.

In the summer of 1949, because of Janine's skills in French and anthropology, we took part in an anthropological/sociological survey in southwestern Nova Scotia, conducting interviews in the string of French-speaking villages that line the shore of the Baie Ste. Marie. This was the Acadian country of Longfellow's *Evangeline*. The French spoken there gave us many surprises because some words had meanings that had changed over the centuries in France, and there were many maritime terms (e.g., "Debark from bed." "Moor (tie) one's shoelaces."). We welcomed the birth of our first child, Anne Janine, in 1950 while we were still at Harvard. She celebrated her first birthday in Paris. Then we drove from Massachusetts to California, with Anne walking much of the way in

her playpen in the back of our Plymouth Suburban. Suzanne Jacqueline was born in 1952 and Philip Mark in 1955, and we have six grandchildren. When our children were young, we spoke only French at the dinner table so they would be bilingual. This also resulted in my learning French backwards, so to speak, adding an underpinning of children's sayings and games to my adult French. (A further benefit of mastering French was that it gave me another language in which to make puns.)

Later, as I gave research papers abroad and as I became active in the International Union of Psychological Science (IUPsyS), our children accompanied us on visits to 10 countries. The children developed a taste for travel and, among them, later learned Chinese, German, and Spanish to supplement their English and French. Our daughter Anne, a lawyer, is active in international organizations that foster human rights and labor rights. She and her husband travel abroad frequently. Our daughter Suzanne and her husband enjoy travel, and they have instilled this in their four wonderful children. Our son is a professor at the Institute for Management Development in Lausanne, Switzerland, and he conducts workshops in many countries. He and his wife have two wonderful bilingual children.

### Appointment at the University of California, Berkeley

During 1948 to 1949 the well-known psychologist Edward C. Tolman spent the academic year at Harvard, shut out of his office at the University of California when he and a few other professors refused to sign a loyalty oath required by the regents. Early in 1949 he interviewed me and some others for an opening at Berkeley in physiological psychology. After some correspondence, I was offered a position as assistant professor. Now I felt a dilemma because the American Association of University Professors had censured the regents of the university because of their actions.

I consulted Professor Tolman, and he replied generously, "If you are interested in the position, take it. There are enough senior professors to maintain the fight against the loyalty oath, and we don't want to cripple the future of the university by stopping recruitment of young people." So I accepted the position but arranged to remain at Harvard for one more year. Tolman's stance as a nonsigner of the oath was later justified by the courts. Although the Regents of the University of California claimed that all academic appointments were for one year only and did not have to be renewed, the judges found that in practice the university did have tenure, and they ordered the non-signers reinstated.

During my last spring at Harvard, David Krech of the psychology department at Berkeley spent a few months there, and we became

acquainted. He, like Tolman, was a nonsigner of the California Loyalty Oath and was returning from a year spent in Europe. Krech and I were later to collaborate at Berkeley.

## Research at Berkeley, The Early Years

### *Arrival at Berkeley*

Soon after my arrival at Berkeley, I established a laboratory to continue research on neural mechanisms of binaural perception. To determine the contributions of different neural stations to binaural perception, my students and I recorded electrophysiological responses at different levels of the nervous system as we delivered dichotic stimuli to anesthetized cats, and we published several papers on the results. I summarized some of this research in a *Scientific American* article (Rosenzweig, 1961). I also conducted research on other topics, including perception of words as a function of their frequency of usage, word association, and history of topics in psychology, but soon another intriguing topic began to occupy me increasingly.

### *Edward Tolman*

First, however, I should add a little more about Edward Tolman who was a major influence on me and on the study of learning and memory. At a time when behavioral psychology reigned in the United States, Tolman was a “cognitive behaviorist,” and his work prefigured the cognitive movement. Also, at a time when investigators were searching for THE key to learning and memory, Tolman (1949) held that there are many kinds of learning, and there may be many mechanisms of memory. Tolman’s eminence in research was reflected by his election as president of the American Psychological Association (1937) and as vice president of the American Association for the Advancement of Science (1942). The 14th International Congress of Psychology was to have been held in the United States in 1954 and Tolman was to have been its president, but partly because anticommunist legislation in the United States would have made it difficult for many foreign psychologists to attend, the congress was shifted to Canada, and Tolman was copresident along with Canadian psychologist Edward A. Bott. Although Tolman had many productive students, he did not try to establish a school but instead encouraged students to pursue their own directions.

In 1958 Krech and I headed a committee to arrange to have a portrait painted of Tolman, and the artist had completed the face and hands when Tolman died in 1959. On one of my last visits to Tolman at his home, he recalled visiting a retired colleague at another university and walking with him down a corridor where the colleague’s portrait hung. “Wouldn’t that

be embarrassing,” Tolman reflected, “to walk under one’s own portrait?” Tolman might have been even more embarrassed at the thought that the portrait hangs in the lobby of Tolman Hall, the building that was named for him in 1962.

### *Beginning the Search for Neural Correlates of Problem-Solving Behavior*

Soon after I arrived at Berkeley, my colleague David Krech asked me to consider with him what might be neural mechanisms of the individual differences in tests of problem-solving behavior he had been finding among rats of inbred strains. As a “ratrunner” of long standing, he had been impressed by sizable individual differences of problem-solving ability among rats of the same strain, sex, and age. I suggested that we might investigate whether individual differences in cortical acetylcholine metabolism might correlate with individual differences in problem-solving ability. Krech turned to his friend Melvin Calvin, head of the campus Laboratory of Chemical Biodynamics, and Calvin agreed to encourage any of the younger chemists in his laboratory to collaborate with us, if the project interested them. So one noon in the fall of 1953 I met in the Faculty Club for lunch with three chemists and explained our project. One of them, Edward L. Bennett, decided that it might be interesting to collaborate with psychologists for a few months, and thus began a fruitful collaboration that lasted for over 40 years. We benefitted from the continued interest and support of Professor Calvin.

### *Status of the Field in the 1950s*

Reviewing briefly the state of the field will provide some context for our research. It may also help to explain the skeptical initial reaction to our discoveries. In the 1950s pessimism prevailed about being able to discover the neural bases of learning and memory. For example, Karl S. Lashley, in a highly critical review in 1950, surveyed the literature on possible synaptic changes as a result of training and concluded that there was no solid evidence to support any of the “growth” theories. Specifically, Lashley offered these criticisms: (1) Neural cell growth appears to be too slow to account for the rapidity with which some learning takes place. (We will return to this point later.) (2) Because he was unable to localize the memory trace, Lashley held that there was no warrant to look for localized changes.

I witnessed the vehemence of this opinion at a small, informal lunch in New York in 1950 during a meeting of the Association for Research in Nervous and Mental Diseases. When someone asked Lashley his opinion of Hebb’s recently published book, Lashley stated sharply that the ideas in the book were garbled versions of his own ideas that Hebb had

misunderstood. A few years later, Hans-Lukas Teuber stated in his *Annual Review of Psychology* chapter on physiological psychology that

The absence of any convincing physiological correlate of learning is the greatest gap in physiological psychology. Apparently, the best we can do with learning is to prevent it from occurring, by intercurrent stimulation through implanted electrodes..., by cerebral ablation..., or by depriving otherwise intact organisms, early in life, of normal sensory influx (Teuber, 1955, p. 267).

Edwin G. Boring, the historian of psychology with whom I studied in the latter 1940s, also testified to the lack of progress on this problem in the 1950 edition of his history of experimental psychology:

Where or how does the brain store memories? That is the great mystery....The physiology of memory has been so baffling a problem that most psychologists in facing it have gone positivistic, being content with hypothesizing intervening variables or with empty correlations (Boring, 1950, p. 670).

In general it seems safe to say that progress in this field is held back not by lack of interest, ability, or industry but by the absence of some one of the other essentials for scientific progress. Knowledge of the nature of the nerve impulse waited on the discovery of electric currents and galvanometers of several kinds. Knowledge in psychoacoustics seemed to get nowhere until electronics developed. The truth about how the brain functions may eventually yield to a technique that comes from some new field remote from either physiology or psychology. Genius waits on insight, but insight may wait on the discovery of new concrete factual knowledge (Boring, 1950, p. 688).

In fact, some major advances were already beginning to occur in research on the neural mechanisms of learning and memory. Some of these resulted from applications of recently developed techniques such as single cell electrophysiological recording, electron microscopy, and use of new neurochemical methods. Another major influence encouraging research on neural mechanisms of learning and memory was Donald O. Hebb's monograph, *The Organization of Behavior*, that was finally published in 1949.

Hebb was more positive about possible synaptic changes in learning than his mentor Lashley. Hebb noted some evidence for neural changes and did not let the absence of conclusive evidence deter him from reviving hypotheses about the conditions that could lead to formation of new

synaptic junctions and underlie memory. In essence, Hebb's hypothesis of synaptic changes underlying learning resembled William James' formulation of 1890:

When two elementary brain-processes have been active together or in immediate succession, one of them, on recurring, tends to propagate its excitement into the other (James, 1890, p. 566).

And this in turn resembled the still earlier formulation of associationist philosopher Alexander Bain:

for every act of memory, every exercise of bodily aptitude, every habit, recollection, train of ideas, there is a specific grouping or coordination of sensations and movements, by virtue of specific growths in the cell junctions (Bain, p. 91).

Hebb's "dual trace hypothesis"—that a labile short-term memory trace may be followed by a stable long-term trace—also resembled the "consolidation-perseveration" hypothesis of Müller and Pilzecker (1900). Much current neuroscience research concerns properties of what are now known as *Hebbian synapses*. Hebb was somewhat amused that his name was connected to this resurrected hypothesis rather than to concepts he considered original (Milner, 1993, p. 127).

Still, a decade after Hebb had revived these long-standing hypotheses, the postulate of use-dependent neural plasticity had not yet been demonstrated experimentally. This was to change in the early 1960s when our group announced that both formal training and informal experience in varied environments led to chemical (Krech, Rosenzweig, and Bennett, 1960) and anatomical plasticity of the brain (Rosenzweig, Krech, Bennett, and Diamond, 1962). Soon after came the reports of Hubel and Wiesel that occluding one eye of a kitten led to reduction in the number of cortical cells responding to that eye, but only if the occlusion occurred during an early critical period (Wiesel and Hubel, 1963, 1965; Hubel and Wiesel, 1965).

## A Failed Approach

Attempts to explain learning and perception in terms of fields of neural activity persisted through much of the 20th century. To explain conditioning, Pavlov posited fields of excitation and inhibition irradiating across the cerebral cortex. In 1940 Hilgard and Marquis criticized these concepts as being purely inferential and lacking any accepted neurophysiological foundation.

Wolfgang Köhler called on a similar field theory to explain phenomena of visual perception. I heard prominent scientists criticize this concept. In 1959, when Köhler was inducted as president of the American Psychological Association, the outgoing president, Harry Harlow, praised Köhler's accomplishments. That evening, Harlow told me, "That was the hardest thing I ever had to do," because he thought so little of Köhler's work.

Lashley disproved Köhler's field theory by an experiment in which he implanted metal foil over the visual cortex of rats. Although the foil would have distorted any electrical fields, it did not impair the ability of the rats to make correct visual discriminations. Shortly after Lashley's death, some of his former students published a volume of his main papers. Surprised to find the metal-foil experiment missing from the volume, I queried Donald Hebb, one of the editors. Hebb replied that Köhler's field theory was too silly to merit a refutation. When Köhler lectured once at Berkeley about his field theory, vision scientist Gordon Walls questioned whether Köhler understood that in the human brain the primary visual fields of the two hemisphere lie closely parallel on the inner surface near the occipital pole. Because of this juxtaposition, electrical fields from the visual cortex in one hemisphere would interfere with perception mediated by the other hemisphere, which is not the case.

Hans Wallach, who had collaborated with Köhler in Germany and again in the United States, told me that he regretted that Köhler had wasted his time theorizing about electrical fields of the cortex rather than pursuing research in areas that he knew better.

## Unexpected Discovery of Brain Plasticity

### *Our Approach and Early Findings*

The strategy of our group was stated in a symposium paper I gave in 1955: We proposed that to find "changes in the nervous system that accompany learning" a "biochemical analysis which could integrate changes over thousands of neural units might provide an entering wedge." Further analysis might then focus more narrowly on the exact sites of change (Rosenzweig, Krech, and Bennett, 1958b, p. 367).

We decided to use the activity of the enzyme acetylcholinesterase (AChE) as an index to acetylcholine (ACh) metabolism. We hypothesized, wrongly as it would turn out, that AChE was a stable characteristic of the individual. Measurement of AChE activity was feasible with a recently devised automatic titration apparatus. Our first experiments attempted to account for individual differences in behavior in Krech's "hypothesis" apparatus. This was a four-unit Y-maze that was unsolvable because the correct visual and spatial cues were changed on successive trials. Nevertheless, rats tended to show hypotheses, that is, they would show runs

of choices in which they favored visual hypotheses (light or dark) or spatial hypotheses (right or left). As subjects, we used mainly two strains of rats maintained by the department: the S1 strain (descendants of rats that had been selectively bred in the 1930s for maze-bright behavior by our Berkeley colleague Robert C. Tryon) and the S3 strain (descendants of Tryon's maze-dull strain).

Findings we published during the first few years of our research provided baselines for unexpected discoveries we were soon to make. This provided an illustration of Louis Pasteur's dictum: "Chance favors the prepared mind." Some of the main early findings were these:

1. Within both the S1 and S3 strains, there are significant correlations between behavioral scores and cortical AChE activity (Rosenzweig, Krech, and Bennett, 1958a, 1960), thus justifying the original purpose of this project.
2. There are significant strain differences in cortical AChE activity, with the S1 (maze bright) strain showing significantly higher values than the S3 rats (Bennett, Rosenzweig, Krech, Karlsson et al., 1958).
3. AChE activity differs significantly among regions of the cortex (Bennett, Krech, Rosenzweig, Karlsson et al., 1958), although previous investigators had concluded that there were not significant regional differences. The enzyme lactic dehydrogenase did not show such differences, nor differences between the S1 and S3 strains, so the correlations between AChE activity and behavior could not be ascribed to general differences in cerebral metabolic levels (Bennett, Krech, Rosenzweig, Karlsson et al., 1958).
4. Cortical AChE activity increases with age in the rat until about 100 days and then declines (Bennett et al., 1961).
5. At the start of our work we assumed from work of others that AChE would provide an index to metabolism of the ACh system, and we later obtained direct support for this, finding that brains of S1 rats showed significantly higher concentrations of ACh than did brains of S3 rats, just as the S1s showed significantly greater AChE activity (Bennett, Crossland, Krech, and Rosenzweig, 1960).

### *Early Finding of Plasticity of Brain Chemistry*

To try to explore further the correlations between behavior and brain chemistry, we tested different groups of rats in different spatial mazes, and we obtained a surprising result. As I reported at a symposium at the University of Pittsburgh in 1958, there were systematic differences among the

cortical AChE values of rats that had been tested in different apparatuses (Rosenzweig, Krech, and Bennett, 1961). We had been assuming that the brain AChE value of an animal was an independent variable, but now it appeared that the value depended in part on the experience the animal had undergone! To test further this unexpected finding, we compared animals subjected to behavioral tests with animals not subjected to testing, and we found the tested animals to differ significantly from the untested in cortical AChE activity.

Rather than continue the expensive process of testing animals in various mazes, we then decided to explore the results of informal learning by placing rats for prolonged periods in environments that were either more enriched or more impoverished than the standard colony (SC) housing of three rats to a cage. For the enriched condition (EC), we placed 10 to 12 rats in a large cage provided with varied stimulus objects, as students of Hebb had done (Forgays and Forgays, 1952). We also gave this group a small amount of maze training. For the impoverished condition (IC) we placed rats in individual cages. In initial experiments of this sort, we placed littermates in the three conditions at weaning, at about 25 days of age, and we kept them there for 80 days. Analysis of cortical samples at the end of the period showed significant differences among the groups: Contrary to our expectation, AChE activity per unit of tissue weight in the cerebral cortex was significantly *lower* in EC than in IC animals, with SC being intermediate. In the rest of the brain, however, AChE activity was significantly highest in the ECs and lowest in the ICs.

### *Surprising Discovery of Plasticity of Brain Anatomy*

Another surprise helped us to interpret this unexpected result. After years of dividing AChE activity by tissue weight of each sample to obtain enzymatic activity per unit of tissue weight, we were astonished to find that the tissue weights of the samples differed significantly among experimental groups! Specifically, for a cortical tissue sample of fixed surface area, the weight was greatest for EC rats and least for IC rats (Rosenzweig, Krech, Bennett, and Diamond, 1962). So the anatomy as well as the chemistry of the brain was altered by experience! This effect was larger in the occipital region than in other regions of the cortex. Subsequent work showed that the increased weight of cortex in the EC rats was paralleled by increased protein in the samples (Bennett, Diamond, Krech, and Rosenzweig, 1964). Anatomical measurements of brain sections showed the cortex of EC rats to be significantly thicker than that of IC rats, by about 5% (Diamond, Krech, and Rosenzweig, 1964). This difference was not large, but because the brain shows relatively little anatomical variability, it was highly significant statistically.

We and coworkers also found that enriched experience in rats led to increased amounts of RNA (Ferchmin et al., 1970; Bennett et al., 1976) and increased expression of RNA in rat brain (Grouse et al., 1978). We also found that maze training caused differences not only in brain anatomy but also in cortical RNA/DNA ratios (Bennett et al., 1979).

Having found differences in gross anatomy of the brain caused by differential experience, we then proceeded to investigate more detailed neuroanatomical features. In a review article in the *Scientific American* (Rosenzweig, Bennett, and Diamond, 1972), we described several such neuroanatomical differences induced by enriched experience in the occipital cortex:

1. The cross-sectional area of cortical pyramidal cell bodies increased significantly (by about 13%). For more on this effect, see Diamond, Johnson et al. (1975).
2. The number of neurons per unit of volume of occipital cortex decreased slightly with enriched experience, probably because the number of neurons remained fixed while the thickness of the cortex increased.
3. On the contrary, the number of glial cells per unit of volume of cortex increased significantly (by 14%).
4. Pyramidal neurons of EC rats showed significantly more dendritic spines than those of IC rats, especially on the basal dendrites. For more detail on this effect, see Globus et al. (1973).
5. The size of synaptic junctions increased significantly. See also West and Greenough (1972).

### *Our Finding Countered the Dogma of Fixity of Brain Weight*

Our finding of changes in cortical weights with differential experience ran counter to the established dogma that brain weights are strictly fixed. Consider, for example, the following quotations from the outstanding neuroanatomist Santiago Ramón y Cajal (Cajal, 1894), which turned out to be pertinent to our research in more than one way:

If we are not worried about putting forth analogies, we could say that the cerebral cortex is like a garden planted with innumerable trees—the pyramidal cells—which, thanks to intelligent cultivation, can multiply their branches and sink their roots deeper, producing fruits and flowers of ever greater variety and quality (Cajal, 1894, p. 467).

But Ramón y Cajal then considered an obvious objection to his hypothesis:

You may well ask how the volume of the brain can remain constant if there is a greater branching and even formation of new terminals of the neurons. To meet this objection we may hypothesize either a reciprocal diminution of the cell bodies or a shrinkage of other areas of the brain whose function is not directly related to intelligence (p. 467).

To preserve the supposed fixity of brain volume, Ramón y Cajal hypothesized a diminution of cell bodies to compensate for the greater branching of neurons, but as we found, the cell bodies increase in volume with enriched experience. His other hypothesis, that other regions of the brain shrink as the cortex expands, may be supported by our finding of diminution of the noncortical parts of the brain as a consequence of enriched experience. Nevertheless, we found an overall increase in brain weight (and presumably in brain volume), overthrowing the longstanding dogma of fixity of the brain.

*Cerebral Effects of Experience Occur Rather Rapidly,  
Across the Life Span, and in Many Species*

Originally we placed rats into the differential environments at weaning and kept them there for 80 days, because we wanted to allow a good chance for effects to occur. Having found clear effects of differential experience on brain measures, we then tried varying both the age at onset and the duration of differential experience. We obtained similar cerebral effects in rats assigned for 30 days to the differential environments (EC vs IC) either as 50-day juveniles or as 105-day young adults. Walter H. Riege (1971) in our laboratory found similar effects in rats assigned to the differential environments at 285 days of age and kept there for periods of 30, 60, or 90 days. Although the capacity for these plastic changes in the nervous system, and for learning, remain in older subjects, the cerebral effects of differential experience develop somewhat more slowly in older than in younger animals, and the magnitude of the effects is often smaller in the older animals. The fact that cerebral effects of differential experience occur across the entire life span marks a strong difference from the effects reported by Hubel and Wiesel that can be induced only during an early critical period.

Further work showed that 2 hours a day in the differential environments over a period of either 30 or 54 days produced cerebral effects similar to those of 24-hour-a-day exposure for the same number of days (Rosenzweig, Love, and Bennett, 1968). Just 4 days of differential housing

produced clear effects on cortical weights (Bennett et al., 1970) and on dendritic branching (Kilman et al., 1988). Ferchmin and Eterovic (1986) found that four 10-minute daily sessions in EC significantly altered cortical RNA concentrations.

Experiments with several strains of rats showed similar effects of EC versus IC experience in both brain values and problem-solving behavior, as reviewed by Renner and Rosenzweig (1987, pp. 53–54). Similar effects on brain measures have been found in several species of mammals—mice of several strains, gerbils, two species of ground squirrels, cats, and monkeys (reviewed by Renner and Rosenzweig, 1987, pp. 54–59). Further work has extended these brain effects to birds, fish, fruit flies, and spiders. The ubiquity of effects across species led neurobiologist Abdul Mohammed to exclaim that these effects occur “from flies to philosophers” (Mohammed et al., 2002, p. 127).

*Control Experiments Verified that the Cerebral Effects  
Were Caused by Differential Experience and Not by  
Other Variables*

It was possible that the unexpected cerebral effects were not the result of differential experience but of other aspects of the experimental situation, so we promptly ran a number of experiments to control for other possible causes. The results of the control experiments did not support the importance of any of the other variables, as the following examples show.

**Handling.** Handling rats, particularly young ones, is known to increase the weight of their adrenal glands. Because the EC rats were handled more often than SC or IC rats, perhaps cerebral differences were caused by handling or stress. In control experiments, some rats were handled for several minutes each day for either 30 or 60 days; littermates were never handled. No differences developed between the handled rats and the unhandled ones in brain weight or brain enzyme activity, although there were differences in adrenal weights. In further experiments, rats in both EC and IC were handled once a day, and the usual brain differences were found at the end of the experimental period (Rosenzweig, Krech, Bennett, and Diamond, 1968).

**Stress.** Stress might have been a cause of the cerebral effects we found. IC rats might have suffered from “isolation stress” and EC rats might have suffered from “information overload.” To test the possible effects of stress on brain measures, we conducted five experiments in which some rats were given intermittent unavoidable electric shocks for 12 minutes daily. At the same time, littermate controls were placed in similar enclosures but with no shock and in a different room. Although the stress of shock affected body weight and adrenal weight, it had little effect on brain measures. None of the four cortical regions showed a significant difference. Total cortex did

weigh 2.3% less in the shocked rats ( $p < 0.05$ ), but when allowance was made, through analysis of variance, for the reduction in body weight in the shocked rats, the difference shrank and became nonsignificant. Even if the absolute weights were considered, the pattern of differences over cortical areas did not parallel that of EC-IC differences. AChE activity was analyzed in only one of these experiments. It showed no significant difference between shocked and control rats for any brain region. For more on experiments on possible effects of stress on brain measures, see Rosenzweig, Bennett, and Diamond (1972b) and Rosenzweig and Bennett (1976b).

In a later experiment, Riege and Morimoto in our laboratory subjected some rats to a daily period of stress in which they were briefly tumbled in a revolving drum or given a mild electric shock. They also kept rats in EC and IC. There was a clear double differentiation in effects: The stress was effective in producing a significant increase in the weight of the adrenal glands, but it did not cause changes in the brain measures we studied. Meanwhile, the environmental EC-IC treatment produced the usual brain effects but did not affect adrenal weights (Riege and Morimoto, 1970).

The experiments on stress also included the variable of handling because the stressed rats were removed from their cages daily and taken to another room for the stress treatment, while the control rats remained in their cages. We concluded, therefore, that the combination of stress and handling did not give rise to the EC-IC brain effects.

**Accelerated Maturation.** Some of the changes we found between EC and IC rats go in the same direction as changes that occur in normal maturation—greater cortical weight, greater glial/neural ratio, and fewer neurons per unit of cortical volume. Thus, it seemed possible that enriched experience accelerates maturation or that impoverished experience retards it. But we found that some changes with enriched experience go in the opposite direction from what is found in normal growth. Also, as we have seen previously, typical EC-IC brain effects can be induced in animals placed in the differential environments as adults. Thus, the EC-IC differences cannot be attributed to differences in rate of maturation of animals in the differential environments.

**Differential Locomotion.** Rats in an EC cage are more active than those in IC, so we wanted to determine whether locomotor activity might account for the EC-IC effects. In our initial publication on the EC-IC effects, we reported a control experiment in which some IC rats had free access to a running wheel while others were never allowed such access. The experimental (running wheel) rats averaged more than 100,000 revolutions during the experimental period. At the conclusion of the 80-day period, there was no significant difference in AChE measures between the experimental and control groups; the small differences found were opposite in direction from those seen in EC-IC groups (Krech, Rosenzweig, and Bennett, 1960).

**Hormonal Mediation.** Although stress had been ruled out as the cause of the EC-IC cerebral effects, other hormones might have mediated these effects. We therefore tested the hypothesis that the pituitary gland is essential to occurrence of these effects (Rosenzweig, Bennett, and Diamond, 1972b). The pituitary was chosen not only to eliminate its secretions but also to control for effects of glands controlled by feedback relations with the pituitary—the thyroid, the adrenal cortex, and the gonads.

Three experiments were run, and results were analyzed only for those animals in which we could verify complete hypophysectomy at sacrifice. Although hypophysectomy stunts bodily growth and reduces brain growth somewhat, significant EC-IC differences nevertheless occurred in both the brain weights and brain chemical measures of the operated as well as in the control animals. We therefore did not pursue further experiments in the endocrine direction.

### Skepticism and Incredulity Greeted Our Initial Reports of Brain Plasticity

Our first reports that differential experience induces measurable changes in the brain were greeted with skepticism and incredulity. The responses reminded me of an old story: A villager was accused of returning a borrowed teapot in poor condition. Vehemently he replied, “In the first place, I never borrowed it; in the second place, I returned it in perfect condition; in the third place, the teapot was already dented when I got it!” Thus, on the one hand, some critics told us that such changes could not exist. On the other, we were told that it is well known that one can induce changes in a rat’s brain just by looking at it cross-eyed. We were asked whether changes were found in the thickness of the soles of the paws and in all other tissue of ectodermal origin. At a meeting where I reported on increase in number of synaptic contacts (dendritic spines) with experience, John C. Eccles stated his firm belief that learning and memory storage involve “growth just of bigger and better synapses that are already there, not growth of new connections” (1965, p. 97). Donald Hebb, whom I had gotten to know better when he spent the summer of 1953 as a visiting professor in Berkeley and with whom I maintained contact, cautioned me that the more important the claim, the more carefully one must test it.

Beyond normal scientific caution, questions of turf may have been involved. I have the impression that neurophysiologists were reluctant to believe that psychologists and their collaborators could be the first to present evidence of changes in the brain as a result of experience.

Over the next several years, reports of replications and extension by us (e.g., Bennett et al., 1964) and by others (e.g., Altman and Das, 1964; Geller et al., 1965; Greenough and Volkmar, 1973) gained acceptance for

the idea that training or differential experience could produce measurable changes in the brain. Thus in 1972 neurobiologist B.G. Cragg wrote "Initial incredulity that such differences in social and psychological conditions could give rise to significant differences in brain weight, cortical thickness, and glial cell numbers seems to have been overcome by the continued series of papers from Berkeley reporting consistent results. Some independent confirmation by workers elsewhere has also been obtained" (Cragg, 1972, p. 42).

## Enriched Environments and the Brain

### *Our Work Introduced Enriched Environments to the Neuroscience Community*

We did not invent the concept of the "enriched environment," but I believe that our publications introduced the concept and the term to the neuroscience community. Our first paper with "enriched and impoverished environments" in the title appeared in 1962 (Krech, Rosenzweig, and Bennett, 1962). In the National Library of Medicine website, PubMed, the first citation for enriched environment is a paper from our group (Diamond, Krech, and Rosenzweig, 1964). This was followed later the same year by a paper by Altman and Das (1964), which cited four of our papers (1960 to 1964) showing effects of enriched environments on brain chemistry and brain anatomy. Our first papers reporting effects of environment on brain plasticity had used the term "environmental complexity" (Krech, Rosenzweig, and Bennett, 1960; Rosenzweig, Krech, Bennett, and Diamond, 1962). The next PubMed citation for enriched environment after 1964 was another paper from our group (Diamond et al., 1966). The period 1970 to 1974 showed seven citations for enriched environment, and thereafter the citations to this term increased exponentially, reaching 46 for 1995 to 1999 and 122 for 2000 to 2004.

Although the term "enriched environment" has become widely used, there is no standard definition for it and some investigators avoid it, preferring "complex environment." We tried to make clear from the beginning that our enriched laboratory environment is enriched only in comparison with the standard animal colony cage. A natural environment may be much richer in learning experiences than even an enriched laboratory environment. For inbred laboratory animals, however, it is no longer clear what the natural environment would be. Laboratory rats and mice have been kept for more than 100 generations in protected environments, and inbreeding has made their gene pool different from the natural one.

We tried in two ways to ask how our enriched laboratory environment might compare with the natural environment. First, we tried raising laboratory rats in a seminatural outdoor environment at the Field Station for

Research in Animal Behavior of the University of California at Berkeley. This environment consisted of a 30 × 30 foot concrete enclosure filled with dirt to a depth of 2 feet above the concrete base and with screening over the top. Food and water were provided ad lib, and a few stimulus objects were placed in the enclosure. For a diagram of this environment, see Rosenzweig, Bennett, and Diamond (1972b, p. 24). Groups of a dozen male laboratory rats thrived in the outdoor setting and, when the weather was not too wet, dug burrows, something their ancestors had not been able to do for more than 100 generations. In each of eight experiments, the rats kept for 1 month in the outdoor setting showed greater cortical development than their littermates that had been kept in enriched laboratory cages. This indicates that even the enriched laboratory environment is indeed impoverished in comparison with a natural environment. We had hoped to test the rats from the outdoor environment to find whether their increased cortical development was accompanied by increased problem-solving ability. Unfortunately, however, in the outdoor setting the rats became too savage to handle, so we were unable to conduct behavioral tests with them.

In a second attempt to compare effects of laboratory and natural environments on brain development, we used Belding's ground squirrels (*Spermophilus beldingi*), in collaboration with our colleague Paul Sherman who was studying a population of the squirrels in the Sierra near Tioga Pass, California. Feral ground squirrels, unlike laboratory rats, have not been altered by living for many generations in captivity. We live-trapped pregnant ground squirrels in the Sierra and brought them to the field station in Berkeley. The young were weaned at about 30 days of age and assigned to EC and IC conditions where they were kept for 40 days. Ten male and 10 female squirrels were in each condition. Just before sacrifice, feral (F) juveniles of the same age were live trapped where the pregnant ground squirrels had been obtained, and their brains were analyzed along with those of the EC and IC squirrels. In weights of cerebral cortex, values from F and EC squirrels were equal, and both exceeded the IC squirrels significantly ( $[F = EC] > IC, p < .01$ ). In total RNA of occipital cortex,  $(F = EC) > IC, p < .05$ . In total DNA of occipital cortex,  $F > (EC = IC), p < .05$ . In skeletal development, measured by hindfoot length,  $F > EC > IC; F > IC, p < .01$ . Thus, in two out of three brain measures, EC squirrels equalled F squirrels, although F exceeded EC in skeletal development (Rosenzweig, Bennett, and Sherman, 1979). A further study substantially replicated these findings (Rosenzweig, Bennett, Sherman, and Alberti, 1980). At least in the case of ground squirrels, the laboratory enriched environment seemed to support brain development as well as did the natural environment. Clearly, the difference between results of the studies with rats and ground squirrels shows that this question still lacks a general resolution. Nevertheless, this has not prevented the increasing use of enriched laboratory environments.

The latter study (Rosenzweig et al., 1980) also showed plastic responses of the brain during hibernation. For this study, ground squirrels were live-trapped at about 80 days of age. Some were sacrificed for baseline values and others were placed for 5 months in EC or IC cages or in a cold room at 5°C where they hibernated. The nonhibernating squirrels continued to gain in brain and body weights during the experimental period, whereas the hibernators lost in both, showing significant decreases in weights of certain brain regions (hypothalamus, caudate nucleus, and medulla), and decreases of DNA in these regions, indicating loss of cells.

*Enriched Experience Improves Ability to Learn  
and Solve Problems*

Hebb (1949, p. 298) reported briefly that when he allowed seven laboratory rats to explore his home for some weeks as pets of his children and then returned the rats to the laboratory, they then showed better problem-solving ability than most rats that had remained in the laboratory throughout. Moreover, he stated, although he did not present evidence for this, that they maintained their superiority or even increased it during a series of problems in the Hebb-Williams maze. Hebb (1949, pp. 298–299) concluded that “*the richer experience of the pet group during development made them better able to profit by new experience at maturity—one of the characteristics of the ‘intelligent’ human being*” (italics in the original). Thus, the results seemed to show a *permanent* effect of early experience on problem-solving at maturity, and this conclusion continues to be cited.

We and others have confirmed the first conclusion of Hebb’s exploratory study; that is, experience in an enriched environment improves learning and problem-solving on a wide variety of tasks, although such differences have not been found invariably. The more complex the task, the more likely it is that animals with EC experience will perform better than animals from SC or IC groups (Renner and Rosenzweig, 1987, pp. 46–48).

We were unable, however, to replicate Hebb’s report that over a series of tests, EC rats maintain or even increase their superiority over IC rats. On the contrary, we found that IC rats tend to catch up with EC rats over a series of trials in a test; this occurred in three different tests, including the Hebb-Williams maze (Rosenzweig, 1971, p. 321). Thus, we did not find that early deprivation of experience caused a permanent deficit, at least for rats tested on spatial problems. Rather, the rats showed a persistent capacity to benefit from experience.

Somewhat similarly, decreases in cortical weights induced by 300 days in the IC (vs the EC) environment were overcome by a few weeks of training and testing in the Hebb-Williams maze (Cummins et al., 1973). Similarly, Fuller (1966) found restricted experience beagles to be inferior to pets in reversal learning, but only on the first five reversals; thereafter there was no significant difference.

*Enriched Environments as Therapy, in Animals and People*

Once the brain was seen to respond to environmental influences not only in young but also in mature animals, investigators soon began testing whether environmental enrichment might aid recovery from brain disorders that have identifiable neuropathy. An intriguing report of 1964 stated that an enriched environment aided rats in recovering from effects of neonatal cortical lesions (Schwartz, 1964). We began in 1974 to replicate and extend this effect (Will et al., 1977), and research along this line continues. One of the major questions is the extent to which experience actually aids in recovery or only in compensation for the effects of brain injury. At a minimum, in people behavioral techniques aid the quality of life of patients with injuries of the brain or of the spinal cord. Beyond this, there may be interaction between the physiological and behavioral interventions. By 1976 an edited volume was published entitled *Environments as Therapy for Brain Dysfunction* (Walsh and Greenough, eds.), treating such topics as recovery from brain injury, malnutrition, endocrinopathies, and sensory deprivation. Chapters considered the relevance, generalizability, and limitations of animal models for therapy, and work on these questions continues. Investigators have asked which is most effective in promoting recovery from brain injury in an animal's environmental enrichment, physical exercise, or formal training? A review of research on this topic during the period 1990 to 2002 shows that enriched experience is the most potent of these treatments (Will, Galani, Kelche, and Rosenzweig, 2004).

Soon after we began publishing on effects of differential environments on brain and behavior, people began asking us about possible applications to human behavior, all the way from child development to successful aging. Thus, in 1965 I was invited to address the Division of Child Psychology at the American Psychological Association (APA) convention (Rosenzweig, 1966). Many of the developmental psychologists who attended my talk were surprised to learn that an enriched environment stimulates brain growth not only in infant but also in adult rats. On such occasions I was always careful to point out limitations in what we had found and to be cautious about extrapolations of animal research (e.g., Rosenzweig, Bennett, and Diamond, 1972b, p. 28). Nevertheless, invitations to speak and write about possible applications continued to come, and I accepted many of them (e.g., Rosenzweig, 1976, 1979, 1980, 1981a, 1981b, 1986, 1999a, 1999b, 2002; Rosenzweig and Bennett, 1979). At an international symposium on cognitive decline in old age, I summarized the research as follows (Rosenzweig and Bennett, 1996, p. 63):

It's a fortunate person whose brain  
Is trained early, again and again,  
And who continues to use it

To be sure not to lose it,  
So the brain, in old age, may not wane.

Although I did not do research on effects of environment with human subjects, I was active in an innovative program to promote higher education for disadvantaged and under-represented youth. In 1964 physicist Owen Chamberlain and I became cochairs of the newly established Berkeley faculty Special Opportunity Scholarship Committee. We obtained faculty and university financial support for an on-campus summer precollege program for promising high school students and continued that with a year round contact program. This soon became a federal Upward Bound program. After a few years, for the students who completed the preparatory program we were able to secure admission to the University of California and to other universities and colleges; they became the first in their families to obtain higher education. The faculty committee, renamed in 2005 as the Committee on Student Diversity and Academic Development, continues its work. The favorable results it has obtained suggest that even at high school age, students from family backgrounds and high schools that do not predispose to postsecondary education can be prepared and encouraged to undertake successful college studies. The results also suggest that public schools are falling short of what they should accomplish.

I did in fact attempt to do research on the effectiveness of the Special Opportunity Scholarship program. After the program had been going for a few years, I proposed to the faculty committee that we attempt to measure the effectiveness of the program in the following way: Each year we would draw up a pool of twice as many candidates as the program could accommodate, and then we would select at random those to be accepted. Both those accepted and those rejected would then be followed up over the next 6 to 10 years to determine whether the program was making a difference. I was unable, however, to convince my fellow committee members that such research was appropriate, so the attempt was not made.

### *Should All Laboratory Animals Be Housed in Enriched Environments?*

There is a growing movement to house all laboratory animals in enriched environments, with exceptions only for specific research purposes. Some proponents cite evidence from work such as ours that indicates that enriched experience is necessary for full growth of the nervous system and behavioral capacities, as well as for animal well-being. Others favor this as part of the movement to improve animal welfare.

The history of enriching environments of the laboratory animals goes back at least to psychologist Robert Yerkes' work with primates in the 1910s to 1920s. Hebb, who did research at the Yerkes primate laboratory, helped to extend the concept of enrichment to laboratory rodents in the 1950s. Our publications, beginning in 1960, popularized use of enriched environments by showing that they contributed to full development of the brain as well as to behavioral capacities. Providing enriched environments is not without its problems. For one thing, definitions of enrichment vary, although most attempt to foster species-specific behaviors. It is important for investigators to avoid the temptation to anthropomorphize in choosing enriched conditions. Thus, it is amusing to see photographs of enriched environments for laboratory rodents that show cages filled with brightly colored objects. Although the colors may be attractive to the researchers, they do nothing for rats or mice who do not discriminate hues. There are also concerns because enriched environments are more expensive than standard housing: They take up more space and require more care.

Some investigators have expressed concerns that enriched environments may differ among laboratories and thus decrease the reproducibility of results. In a recent attempt to deal with these concerns, investigators from three laboratories performed an experiment in which they raised female mice of two inbred strains in either standardized cages or following an enrichment protocol. They then tested the mice on four common behavioral tests. The results were highly consistent, indicating that standardization among laboratories was almost as good as within laboratories (Wolfer et al., 2004). The authors note that it remains to be seen whether similar results would also be obtained for male mice who may respond to enrichment with increased dominance behavior and aggression.

The growing concern about enriched environments is shown by *ILAR*, the journal of the Institute for Laboratory Animal Research, which devoted its Spring 2005 number to this topic. The 12 articles in this issue range from enriched housing for laboratory rodents to enriched housing for nonhuman primates, and from theoretical to practical concerns.

In the near future, whether to use enriched environments may no longer be a matter of choice for the individual investigator or research unit. Enriched environments are part of revisions of animal welfare standards that the Council of Europe is preparing as recommended practices for its 45 member nations, and these standards could affect practices in other countries as well. The website of the Council of Europe reports that a working party, at a meeting of September 22 to 24, 2004, completed a revision of its recommendations for protection of vertebrate animals used for experimental and other scientific purposes and submitted it for adoption. The changes proposed include not only increasing the minimum recommended cage sizes but would also require that laboratory animals

be housed in enriched environments that permit the expression of normal behaviors.

Whatever the fate of regulations concerning enriched environments, the clear evidence of the importance of animal environments in determining the results of research shows the necessity of describing animal housing clearly and accurately in all reports of research.

### *Stimulant Drugs Enhance Effects of Environment on Recovery*

Our finding that a daily 2-hour period of exposure to EC was sufficient to produce cerebral effects allowed us to test whether stimulant drugs altered brain measures directly or only in conjunction with EC. In this research, we gave some animals a low dose of methamphetamine just before putting them into EC for a daily 2-hour period, whereas other animals received the drug at a different part of the day when they were in their individual home cages. The drug enhanced cortical weight only when it was active during the daily EC period (Bennett, Rosenzweig, and Wu, 1973). The drug-environment interaction was even clearer with shorter daily periods of EC or in shorter-duration experiments. Effects on AChE measures were somewhat larger, but not significantly so, in the drug-EC groups. A low dose of the depressant pentobarbital sodium reduced the effect of EC experience on cortical weights, but again only if the drug was active during the daily period of EC. Thus, it was the combination of drug and environment that counted in determining cortical weights.

Considering this finding and research on recovery of function, we proposed testing "whether the conjunction of enriched environment and an excitant drug may be even more favorable for recovery from brain damage than is either treatment alone" (Bennett, Rosenzweig, and Wu, 1973, p. 327). We did not follow our own suggestion, but in the last two decades others have conducted fruitful research on this topic with both animal subjects and human patients.

In an early study of this sort, Feeney et al. (1982) removed motor cortex unilaterally in rats and studied their behavior 24 hours later in locomotion on a narrow beam. After a single trial, subgroups received either a single daily injection of saline, a low dose of amphetamine, or the depressant haloperidol. Further tests of locomotion showed that amphetamine improved recovery, while haloperidol impaired it, in relation to the saline controls. Confining the animals in a small cage to prevent locomotion for 8 hours after drug administration blocked the effects of the drugs, so they were effective only in combination with behavioral practice.

Reviews of research with both animal and human subjects have shown the generality of these effects (e.g., Davis et al., 1987; Feeney, 1997, 1998; Goldstein and Hulsbosch, 1999). More recently, Walker-Batson

has reported that amphetamine plus intensive speech therapy aids recovery from aphasia (Walker-Batson et al., 2001), and Walker-Batson and her colleagues have reviewed neuromodulation paired with learning in rehabilitation for various deficits resulting from stroke (Walker-Batson et al., 2004).

An obvious extension of this research would be to combine enriched experience or training with other pharmacological treatments. Hamm et al. (2000) reviewed research in which traumatic head injury in rats was followed by a number of different drug treatments, including agents that affected the monoamine system, the cholinergic system, the glutamnergic system, nerve growth factor, and basic fibroblast growth factor. Each agent led to some improvements, but none was as effective as exposure to an enriched environment. It will be interesting to see results of research that combine some of these pharmacological treatments with enriched experience.

In attempts to promote recovery from brain damage, some neuroscientists are transplanting fetal brain cells into the region of a brain lesion. Some investigators have studied the separate and the combined effects of enriched environment and neural transplants (e.g., Kelche, Dalrymple-Alford, and Will, 1988). Under some conditions, neither the enriched experience nor the transplant alone had a beneficial effect, but the combination of the two treatments yielded a significant improvement in learning. Further work indicates that formal training of rats may be more effective than enriched environment in promoting the effects of brain cell grafts on recovery of learning ability (Kelche et al., 1995). These results of animal research may find application in attempts to aid human patients. Perhaps the differences among clinics in success of brain cell grafts reflect, in part at least, the kinds and amounts of training and stimulation given the patients; this may interact with the skill of the neurosurgeon. The combination of brain implants with training and stimulation may become an increasingly important area of interaction between research and application in the field of plasticity of brain and behavior.

### *Recent Research Involving Enriched Environments Falls into Three Main Categories*

Research for the period 2000 to 2004 that involves enriched environments falls into three main categories, two of which were pioneered by work of our group:

1. By far the most frequent category is enriched environment as therapy. This has been studied recently for many kinds of brain injury, including trauma, brain infarcts, focal ischemia, and transient global ischemia. Spinal cord injuries have also been studied. In addition to injury, other studies

have taken up therapy for cocaine exposure, epilepsy, prenatal stress, immune challenges, and lead poisoning. Although most of this research uses animal subjects, some is being done with human subjects.

2. The next most frequent category is effects of enriched environments on gene expression. This was anticipated by our studies showing greater expression and variety of RNA in EC than in IC animals.
3. The third most frequent category of recent research involving enriched environments concerns effects of environmental treatments on neurogenesis. A group including Marian Diamond was the first to report that EC increased neurogenesis in the dentate gyrus of adult rats (York et al., 1989).

Other groups in addition to ours have recently written reviews of the neurobiological effects of enriched environments and have extended the research into new directions, notably Mohammed et al. (2002) and also Rampon and Tsien (2000) and van Praag, Kempermann, and Gage (2001).

## The Neurochemical Cascades that Underlie Learning and Memory Formation

### *Similar Neurochemical Cascades Underlie Different Kinds of Learning and Occur in Different Species*

Having found that learning or enriched experience led to plastic changes in the nervous system, Edward Bennett and I decided to try to find the mechanisms that lead to such changes. We had found early that enriched experience causes increased rates of protein synthesis and increased amounts of protein in the cortex (Bennett et al., 1964a). Later, others reported that imprinting increased the rates of incorporation of precursors into RNA and protein in the forebrain of the chick (Haywood et al., 1970), and, as mentioned previously, we and coworkers found that enriched experience in rats led to increased amounts of RNA in rat brain. We viewed these and related findings in the light of the hypothesis, perhaps first enunciated by Katz and Halstead (1950), that protein synthesis is required for memory storage.

Tests of the protein synthesis hypothesis of memory formation were initiated by Flexner and associates in the early 1960s (e.g., Flexner et al., 1962, 1965), but the interpretation of the findings was clouded by serious problems. The research involved administering to experimental subjects an inhibitor of protein synthesis at various times close to training, while control subjects received an inactive substance, and comparing test performance of experimental and control subjects at a later time. Unfortunately,

the inhibitors of protein synthesis then available for research (such as puromycin and cycloheximide) were rather toxic, which impeded experiments and complicated interpretation. Also, it appeared that inhibition of protein synthesis could prevent memory formation after weak training but not after strong training (e.g., Barondes, 1970).

A recently discovered protein-synthesis inhibitor, anisomycin (ANI), helped to overcome these problems. Schwartz et al. (1971) reported that ANI did not prevent an electrophysiological correlate of short-term habituation or sensitization in an isolated ganglion of *Aplysia*, but they did not investigate whether ANI could prevent long-term effects.

Then Bennett discovered that ANI, administered shortly before training, prevents formation of long-term memory (LTM) in rats (Bennett, Orme, and Hebert, 1972). This opened the way to resolving the main challenges to the protein-synthesis hypothesis of formation of LTM. ANI is much less toxic than other protein synthesis inhibitors, and giving doses repeatedly at 2-hour intervals can prolong the duration of cerebral inhibition at amnesic levels. By varying the duration of amnesic levels of inhibition in this way, we found that the stronger the training, the longer inhibition of protein synthesis had to be maintained to prevent formation of LTM (Flood et al., 1973, 1975). We also found that protein must be synthesized in the cortex soon after training if LTM is to be formed; short-term memory (STM) or intermediate-term memory (ITM) do not require protein synthesis (e.g., Bennett et al., 1972; Mizumori et al., 1985; Mizumori et al., 1987). From the time that Bennett showed the value of ANI in studying formation of LTM, this agent has been in frequent use for this purpose.

We then designed further studies to find the neurochemical processes that underlie formation of STM and ITM. Lashley's concern, mentioned previously, that some kinds of memory appear to be formed too quickly to allow growth of neural connections, ignored the distinction between STM and LTM, even though William James (1890) had already distinguished between these stores (although under different names). Observing this distinction was necessary if one was to look for different mechanisms of the two kinds of memory traces that Hebb distinguished: transient, labile memory traces, on the one hand, and stable, structural traces, on the other.

Much of our work on the neurochemistry of STM and ITM was done with chicks, which have several advantages for this research, including the following: The chick system is convenient for studying the stages of memory formation because chicks can be trained rapidly in a one-trial peck-avoidance paradigm and can be tested within seconds after training, or hours or days later. Large numbers of chicks can be studied in a single run, so one can compare different agents, doses, and times of administration within the same batch of subjects. Unlike invertebrate preparations, the

chick system can be used to study the roles of different vertebrate brain structures and to investigate questions of cerebral asymmetry in learning and memory. The chick system permits study of learning and memory in the intact animal. The successive neurochemical stages occur more slowly in the chick than in the rat, thus allowing them to be separated more clearly. We have stated further advantages elsewhere (e.g., Rosenzweig, 1990; Rosenzweig et al., 1992).

Although some amnestic agents, such as ANI, diffuse readily throughout the brain, we found that others affect only a restricted volume of tissue at amnestic concentrations (Patterson et al., 1986). We employed such agents to reveal the roles of different brain structures in different stages of memory formation (e.g., Patterson et al., 1986; Serrano et al., 1995).

Using the chick system, several investigators have traced a cascade of neurochemical events from initial stimulation to synthesis of protein and structural changes (e.g., Gibbs and Ng, 1977; Ng and Gibbs, 1991; Rose, 1992a, 1992b; Rosenzweig et al., 1992). At some if not all stages, parallel processes occur. Briefly, here are some of the events: The cascade is initiated when sensory stimulation activates receptor organs that stimulate afferent neurons by using various synaptic transmitter agents such as ACh and glutamate. Inhibitors of ACh synaptic activity, such as scopolamine and pirenzepine, can prevent STM. So can inhibitors of glutamate receptors, including both the NMDA and AMPA receptors. Alteration of regulation of ion channels in the neuronal membrane can inhibit STM formation, as seen in effects of lanthanum chloride on calcium channels and of ouabain on sodium and potassium channels. Inhibition of second messengers is also amnestic, for example inhibition of adenylate cyclase by forskolin or of diacylglycerol by bradykinin. These second messengers can activate protein kinases—enzymes that catalyze addition of phosphate molecules to proteins. We found that two kinds of protein kinases are important in formation, respectively, of ITM or LTM. Agents that inhibit calcium calmodulin protein kinases (CaM kinases) prevent formation of ITM, whereas agents that do not inhibit CaM kinases but do inhibit protein kinase A (PKA) or protein kinase C (PKC) prevent formation of LTM (Rosenzweig et al., 1992; Serrano et al., 1994). From this research, Serrano et al. (1995) in our laboratories were able to predict for a newly available inhibitor of PKC, chelerythrine, its effective amnestic dose and how long after training it would cause memory to decline.

One-trial training leads to increase of immediate early gene messenger RNA in the chick forebrain (Anokhin and Rose, 1991) and to increase in the density of dendritic spines (Lowndes and Stewart, 1994). Many of these effects occur only in the left hemisphere of the chick or are more prominent in the left than in the right hemisphere. Thus, learning in the chick system permits study of many steps that lead from sensory stimulation to formation of neuronal structures involved in memory.

The neurochemical cascade involved in formation of memory in the chick was soon shown to be similar to the cascade involved in long-term potentiation in the mammalian brain (e.g., Colley and Routtenberg, 1993) and in the nervous systems of invertebrates (e.g., Krasne and Glanzman, 1995). DeZazzo and Tully (1995) have compared STM, ITM, and LTM in fruit flies, chicks, and rats. Tully et al. (1996) have shown that the three stages of memory in the fruit fly depend on three different genes.

The fact that similar neurochemical cascades are involved in memory formation in mammals, birds, and invertebrates should not be interpreted to mean that this is the only sequence of events that underlies memory formation. In fact, research has borne out Tolman's prescient 1949 insight that there may be many mechanisms of memory. For example, whereas induction of long-term potentiation (LTP) requires activation of NMDA receptors in some parts of the brain, it can occur in other regions after inhibition of NMDA receptors, and in those regions activation of opioid receptors is required for LTP induction. We also found that opioid agonists tend to impair, and opioid antagonists to enhance, memory formation. We found that different opioids appear to modulate formation of different stages of memory (e.g., Colombo et al., 1992, 1993; Patterson et al., 1989; Rosenzweig et al., 1992). Neuroscientist Seymour Kety foresaw the finding of multiple mechanisms of memory formation in the 1970s, as the following quotation shows:

So profound and powerful an adaptation as learning or memory is not apt to rest upon a single modality. Rather, I suspect that advantage is taken of every opportunity provided by evolution. There were forms of memory before organisms developed nervous systems, and after that remarkable leap forward it is likely that every new pathway and neural complexity, every new neural transmitter, hormone, or metabolic process that played upon the nervous system and subserved a learning process was preserved and incorporated (Kety, 1976, pp. 321-322).

*Parts of the Neurochemical Cascade Can Be Related to Different Stages of Memory Formation*

Some of the difficulty in attempting to relate parts of the neurochemical cascade to different stages of memory formation comes from problems of defining stages of memory, as I have discussed more fully elsewhere (Rosenzweig et al., 1993). Consider, for example, some very different notions about the duration of STM. Early investigators of human STM (Brown, 1958; Peterson and Peterson, 1959) reported that it lasts only about 30 seconds if rehearsal is prevented. Agranoff et al. (1966) reported that in goldfish, if formation of LTM is prevented by an inhibitor of protein

synthesis, STM can last up to 3 days, although normally LTM forms within an hour after training. Kandel et al. (1987) wrote that in *Aplysia*, "A single training trial produces short-term sensitization that lasts from minutes to hours" (p. 17) and that long-term memory is "memory that lasts more than one day" (p. 35). Rose (1995) suggested that, in the chick, memories that persist only a few hours involve a first wave of glycoprotein synthesis; whereas "true long-term memory" requires a second wave of glycoprotein synthesis, occurring about 6 hours after training.

Instead of considering that STM can last several hours or even a day or more, it is useful to posit one or more intermediate-term memory (ITM) stages occurring between STM and LTM, as some theorists have done since the 1960s (e.g., McGaugh 1966, 1968). Thus, Gibbs and Ng (1977) referred to a "labile" stage occurring between STM and LTM and later (e.g., 1984) called this the intermediate stage of memory. My coworkers and I have discussed mechanisms of STM, ITM, and LTM in a series of papers (e.g., Rosenzweig et al., 1984, 1992, 1993; Mizumori et al., 1987; Patterson et al., 1988). In investigating effects of protein kinase inhibitors (PKIs) on memory formation in chicks, we reported that those agents that inhibit CaM kinase activity disrupt formation of what some workers with chicks identify as ITM (lasting from about 15 min to about 60 min posttraining); those agents that inhibit PKC, PKA, or PKG but do not inhibit CaM kinase disrupt the formation of LTM (Rosenzweig et al., 1992; Serrano et al., 1994). Other investigators prefer to refer to different phases or stages of LTM rather than use the expression ITM. Thus, studying the LTP analog to memory in slices of rat hippocampus, Huang and Kandel (1994) reported findings similar to those of Rosenzweig et al. (1992) and Serrano et al. (1994) with regard to the roles of two classes of protein kinases: Inhibitors of CaM kinase activity disrupted what Huang and Kandel called a transient early phase of LTP (E-LTP), evoked by moderately strong stimuli and lasting from 1 hr to less than 3 hr after induction of LTP; agents that inhibited PKA but did not inhibit CaM kinase disrupted the formation of what they called a later, more enduring phase of LTP (L-LTP), evoked by strong stimulation and lasting at least 6–10 hr. Weak stimuli evoke only short-term potentiation (STP), lasting only 20–30 min. As mentioned above, Rose (1995) suggests that in the chick, a kind of LTM that lasts a few hours involves a first wave of glycoprotein synthesis, whereas "true long-term memory" requires a second wave of glycoprotein synthesis, occurring about 6 hr after training. Rather than call the memory associated with Rose's first 6-hr-long wave a form of LTM, I believe it is better to designate it by a special term, such as ITM, and to note that there is an earlier STM lasting only a few minutes, as has been shown in many experiments with the chick. The findings in this area, in my opinion, support the hypothesis of at least three sequentially dependent stages of memory formation, each dependent on different neurochemical processes.

## Writing, Editing, Publishing

I succeeded in writing up most of my research promptly and encouraged my students to do the same, believing that science does not exist until it is published. In addition to research, much of my work has involved writing, editing, and publishing, so I will conclude with a bit about these activities.

In 1968 my Berkeley colleague Paul Mussen was invited to be editor of the *Annual Review of Psychology*, and he invited me to share the editorship. The annual meetings of the editorial committee, in which we reviewed progress in the main fields of psychology and decided whom to invite to write chapters, were stimulating occasions. After five years of collegial joint editorship, Paul retired as coeditor and was succeeded by our former Berkeley colleague, Lyman Porter. Porter and I continued as coeditors through 1995. One of my innovations was to have a chapter on psychology in the host country of the congresses of the International Union of Psychological Science (IUPsyS) and the International Association of Applied Psychology. Thus, every two years, readers were informed about psychology in another country.

In the 1970s, a failed publication gave rise indirectly to an influential conference volume. I took part in 1973 in a symposium of the American Association for the Advancement of Science (AAAS) and was disappointed when the promised publication did not materialize. But in the audience at the symposium was an officer of the National Institute of Education (NIE), and he invited me to organize, with financial support from the NIE, an international conference that would summarize and evaluate the current status of research on learning and memory and their neural bases. I asked my chemist collaborator Edward L. Bennett to cochair the conference. We recruited an outstanding group of contributors and spent June 24–28, 1974 presenting and discussing at the conference center in Asilomar, California. The large proceedings volume appeared in 1976 (Rosenzweig & Bennett, Eds.).

From the start of my appointment at Berkeley I taught the course in what was then called physiological psychology. After he joined the department, Arnold Leiman alternated with me in teaching the course. We were not satisfied with existing textbooks in the subject, so Arnie and I wrote our own text, which first appeared in 1982; a second edition appeared in 1989. Arnie had an unmatched scholarly mastery of the field, and he was a gifted teacher, but he was a slow writer. We then changed publishers and gained a talented third author, our Berkeley colleague S. Marc Breedlove, for our next edition (Rosenzweig, Leiman & Breedlove, 1996). The book was adopted widely, and successive editions followed. After Arnie's death, we invited Neil V. Watson to be our coauthor. Meanwhile, Marc Breedlove had left Berkeley, so it was no longer possible just to go down the hall to

discuss some aspect of the manuscript. Instead we collaborated by e-mail, FedEx, and phone. It has been a pleasure to reach students in many countries of the world through the text. Translations of the text have been made into French, Italian, Portuguese, and Spanish, further increasing our scope.

In 1990–1991, as president of the IUPsyS, I conducted a survey about psychology and psychological research among our national member societies. I then edited a volume that described and evaluated the status of psychology internationally (Rosenzweig, Ed., 1992). Later, Kurt Pawlik, my successor as president of IUPsyS, and I organized and edited the *International Handbook of Psychology* with 51 chapters surveying all of modern psychology, written by authors from 19 countries (Pawlik & Rosenzweig, Eds., 2000).

To mark the first half century of the IUPsyS, its executive committee asked me and a few colleagues to write the *History of the International Union of Psychological Science* (Rosenzweig, Holtzman, Sabourin & Bélanger, 2000). This covered the history, not only since the formal founding of the union in 1951, but going back to the first International Congress of Psychology in 1889 and to the International Congress Committee that organized 12 successive international congresses through 1951. We combed the published records and the extensive archives of the union, but wished we could have consulted some recently deceased colleagues who spanned the transition from the International Congress Committee to the formation of the union. This convinced me of the importance of leaving autobiographical accounts and of contributing personal records to archives.

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