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ASPECTS OF THE SEARCH FOR NEURAL MECHANISMS OF MEMORY

Mark R. Rosenzweig

Department of Psychology, University of California, Berkeley, California 94720-1650

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ABSTRACT

The search for neural mechanisms of memory has been under way for more than a century. The pace quickened in the 1960s when investigators found that training or differential experience leads to significant changes in brain neurochemistry, anatomy, and electrophysiology. Many steps have now been identified in the neurochemical cascade that starts with neural stimulation and ends with encoding information in long-term memory. Applications of research in this field are being made to child development, successful aging, recovery from brain damage, and animal welfare. Extensions of current research and exciting new techniques promise novel insights into mechanisms of memory in the decades ahead.

CONTENTS

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INTRODUCTION

Plasticity of the nervous system in relation to learning and memory, now a major field of research, has long been an important theme in psychology and related disciplines. William James (1890) was not the first to attribute habit to the plasticity of the nervous system (p. 105) or to write of molecules storing habits in the nerve cells (p. 127). In fact, concepts of brain plasticity in relation to behavior have appeared in various guises over the past two centuries. But only in the 1960s did clear and replicable evidence show that training and experience produce measurable neurochemical and neuroanatomical changes; further evidence soon followed that these neural changes are required for long-term memory. Since then, related research has flourished and branched out in several directions, encouraging a variety of applications. The search has led to some surprising discoveries, to a number of controversies, to the rejection of some hypotheses, and to the opening of new vistas.

This chapter reviews selectively some of this research and some applications that have stemmed from it. These are topics with which I have been concerned for about 50 years. My initial interest was heightened in a graduate seminar Donald O. Hebb gave at Harvard in the summer of 1947, using as the

text a mimeographed version of his then unpublished book, *The Organization of Behavior* (Hebb 1949), and I benefitted from further exchanges with him over the years.

PRE-20TH CENTURY SPECULATIONS AND RESEARCH

The Advent of the Science of Memory

From classical antiquity through the Renaissance, practices to improve memory were codified in what became known as the art of memory (Yates 1966). But the *science* of memory began only in 1885, when Hermann Ebbinghaus announced the study-test method and experimental results obtained with it. Clinical observations helped to advance knowledge of memory and its neural bases even before Ebbinghaus's discovery (e.g. Wilks 1864, Ribot 1881), but reciprocal interactions between clinical observations and experimental research stimulated further advances. For example, the recent distinction between declarative and nondeclarative kinds of memory arose from research to find what kind(s) of memory is(are) lost and what is spared after certain kinds of brain damage. This distinction was necessary in order to find the different brain regions used in these two kinds of memory and to understand different kinds of amnesia (Squire et al 1993). The distinction between declarative and nondeclarative kinds of memory is still too recent to be incorporated in standardized tests for assessment of memory, because innovations in such tests usually lag about ten years behind the research literature (Butters et al 1995). I hope that discussion of concepts and findings about mechanisms of memory may foster both further research and applications.

Long before the modern period, speculations about learning and memory and their possible bodily mechanisms led to advice about practices to aid memory or avoid its impairment. Some of this advice now seems ludicrous. Will current formulations seem better grounded to scientists of the future? For example, medieval teachings about memory held that because the brain, which stores memory, is cool and moist (as found in dissections), it needs to be protected against overheating of all sorts; therefore hot foods and strong wine are bad for the memory (Carruthers 1990, p. 50). Although we agree that strong wine impairs retrieval of memory, our explanations are not based on temperature.

Early Speculations about Sites of Learning in the Nervous System

The possibility of testing experimentally whether mental exercise can induce growth of the brain was discussed as early as 1783 in correspondence between the prominent Swiss naturalist Charles Bonnet and a Piedmontese anatomist,

Michele Vincenzo Malacarne (Bonnet 1779–1783). Malacarne agreed to undertake a test of the hypothesis, using an experimental design that anticipated one used 180 years later. He chose as subjects two littermate dogs and also pairs of birds, each pair coming from the same clutch of eggs. In each pair, he gave one animal intensive training while the other received none. After a few years of this treatment, Malacarne sacrificed the animals and compared the brains in each pair. A brief review of the results of this experiment [1793, *Journal de Physique* (Paris) 43:73] claimed positive findings—the trained animals were reported to show more folds in the cerebellum than the untrained.

The prominent German physician Samuel Thomas von Soemmering may have known of Malacarne's work when he wrote the following passage in his major book on human anatomy:

> Does use change the structure of the brain?
> Does use and exertion of mental power gradually change the material structure of the brain, just as we see, for example, that much used muscles become stronger and that hard labor thickens the epidermis considerably? It is not improbable, although the scalpel cannot easily demonstrate this. (1791, Vol. 5, p. 91). [In the edition of 1800, the last phrase was changed to "although anatomy has not yet demonstrated this" (p. 394).]

The idea that exercise or training can enlarge particular brain regions was promoted in the 19th century by two doctrines—phrenology and evolution through inheritance of acquired characteristics. I do not include among the phrenologists the neuroanatomist Franz Joseph Gall, although he is often called the founder or inventor of phrenology (e.g. Wells 1847, Ackerknecht & Vallois 1956). For one thing, Gall called his system "organology" and rejected the term "phrenology," which was invented by his younger colleague Johann Gaspard Spurzheim (Zola-Morgan 1995). More importantly, Gall emphasized the innateness of development of the different "organs" of the cerebral cortex, each of which he hypothesized to correspond to a different mental faculty. Gall rejected the ideas that humankind is indefinitely perfectible and that exercise or education could influence the development of the faculties or the organs of the brain (1819, pp. 252–56). Jean-Baptiste Lamarck, the originator of the doctrine of evolution through inheritance of acquired characteristics, held that the brain and each of its special regions develops through appropriate use of the related faculties, and he criticized Gall's belief that brain development is determined innately [1809 (1914)].

When Spurzheim separated from Gall in 1812 and went to England and later the United States, he created the phrenological movement. This included the idea that development of the faculties and their cerebral organs could be stimulated by exercise (Spurzheim 1815, 1847). Davies (1995) showed how the vogue of phrenology fit with aspects of the American spirit, underscoring

the role of heredity and individual differences, but balancing this with the optimistic doctrine of growth and perfectibility through education and exercise. In keeping with their emphasis on differences of individual endowments, the phrenologists urged that programs of education be designed for individuals according to their aptitudes. They also cautioned against overemphasizing intellectual development of children, lest directing too much blood flow to the brain impair development of the body. This point was echoed by other educational theorists, including Herbert Spencer.

Evidence accumulated during the latter part of the 19th century that the brain shows less individual variation in size than other organs and is less affected by changes in body weight. The consensus developed that the gross anatomy of the brain is not affected by experience or training and that the adult brain is essentially fixed anatomically.

Neural Junctions as Sites of Change in Learning

In the 1890s, several scientists speculated that changes at neural junctions might account for memory. This was anticipated, as Finger (1994) points out, by Alexander Bain (1872), an associationist philosopher, who suggested that memory formation involves growth of what we now call synaptic junctions:

> "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" (p. 91).

Such speculations were put on a firmer basis with the enunciation of the neuron doctrine by neuroanatomist Wilhelm von Waldeyer in 1891, largely based on the research of Santiago Ramon y Cajal. Neurologist Eugenio Tanzi (1893) advanced the hypothesis that the plastic changes involved in learning probably take place at the junctions between neurons. He expressed confidence that investigators would soon be able to test by direct inspection the junctional changes he hypothesized to occur with development and training. About 80 years were to elapse, however, before the first results of this sort were announced (e.g. Cragg 1967, Diamond et al 1975, Globus et al 1973, West & Greenough 1972).

Ramon y Cajal, apparently independently of Tanzi, went somewhat further in his Croonian lecture to the Royal Society of London (Cajal 1894). He stated that the higher one looked in the vertebrate scale, the more the neural terminals and collaterals ramified. During development of the individual, neural branching increased, probably up to adulthood. He held it likely that mental exercise also leads to greater growth of neural branches, as he stated with a colorful set of analogies:

> The theory of free arborization of cellular branches capable of growing seems not only to be very probable but also most encouraging. A continuous pre-established network—a sort of system of telegraphic wires with no possibility for new stations or new lines—is something rigid and unmodifiable that clashes with our impression that the organ of thought is, within certain limits, malleable and perfectible by well-directed mental exercise, especially during the developmental period. 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 (pp. 467–68).

But he then considered an obvious objection:

> 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).

We will return below to this assumption of constancy of brain volume and Ramon y Cajal's hypotheses to permit constancy in the face of increased neuronal ramification.

The neural junctions didn't have a specific name when Tanzi and Ramon y Cajal wrote early in the 1890s, but a few years later neurophysiologist Charles Sherrington (1897) gave them the name "synapse." Sherrington also stated that the synapse was likely to be strategic for learning, putting it in this picturesque way:

> Shut off from all opportunities of reproducing itself and adding to its number by mitosis or otherwise, the nerve cell directs its pent-up energy towards amplifying its connections with its fellows, in response to the events which stir it up. Hence, it is capable of an education unknown to other tissues. (p. 1117).

During the first half of the 20th century, psychologists and other scientists proposed memory hypotheses involving either the growth of neural fibrils toward one another to narrow the synaptic gap or more subtle chemical changes at synapses (see review in Finger 1994). But when Karl S. Lashley (1950) reviewed this literature, he concluded that there was no solid evidence to support any of these "growth" theories. Specifically he offered these criticisms: (*a*) Neural cell growth appears to be too slow to account for the rapidity with which some learning can take place; we will return to this point below. (*b*) Because he was unable to localize the memory trace, Lashley held there was no warrant to look for localized changes. Lashley's younger colleague Donald O. Hebb (1949) 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. 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).

TRAINING OR EXPERIENCE PRODUCES CHANGES IN THE NEUROCHEMISTRY AND ANATOMY OF CEREBRAL CORTEX

Ten years after Hebb's book was published, his postulate of use-dependent neural plasticity had still not been demonstrated experimentally. It seemed to many that it would not be possible, with available techniques, to find changes in the brain induced by training or experience. At a symposium in 1957 my colleagues and I proposed that an approach to this problem would be to make neurochemical analyses over specific regions of brain. Such an approach might be able to integrate and permit measurement of small changes taking place over many thousands of neural units. If such changes were found, then subsequent analyses might be able to focus down more closely (Rosenzweig et al 1958, p. 338). In the early 1960s two experimental programs announced findings demonstrating that the brain can be altered measureably by training or differential experience. First was the demonstration by our group at Berkeley that both formal training and informal experience in varied environments led to measurable changes in neurochemistry and neuroanatomy of the rodent brain. Soon after came the report of Hubel & Wiesel that occluding one eye of a kitten led to reduction in the number of cortical cells responding to that eye.

The original clues for our discovery came from data on rats given formal training in a variety of problems. We were seeking to examine possible relations between individual differences in brain chemistry and problem-solving ability. We did obtain significant correlations between levels of activity of the enzyme acetylcholinesterase (AChE) in the cerebral cortex and ability to solve spatial problems (e.g. Krech et al 1956, Rosenzweig et al 1958). When we tested the generality of this finding over six different behavioral tests, we found a surprise: As reported at a 1959 symposium, total AChE activity was higher in the cerebral cortex of groups that had been trained and tested on more difficult problems than in those given easier problems, and all the tested groups measured higher in total cortical AChE activity than groups given no training and testing (Rosenzweig et al 1961, p. 102 & Figure 4). It appeared that training could alter the AChE activity of the cortex! To test this hypothesis further, we conducted an experiment in which littermates were either trained on a difficult problem or left untrained. The trained rats developed signifi-

cantly higher cortical AChE activity than their untrained littermates (Rosenzweig et al 1961, p. 103). (As we found later, this experimental design was similar to Malacarne's in the 18th century.) Control experiments showed that the results could not be attributed to the fact that the trained rats were underfed to increase their motivation or were handled.

Instead of continuing to train rats in problem-solving tests, a time-consuming and expensive procedure, we decided to house the animals in different environments that provided differential opportunities for informal learning. Measures made at the end of the experiment showed that informal enriched experience led to increased cortical AChE activity (Krech et al 1960). The discovery that formal training or differential experience caused changes in cortical chemistry was soon followed by the even more surprising finding that enriched experience increased the *weights* of regions of the neocortex (Rosenzweig et al 1962). A recent review notes, "The initial reports by Rosenzweig, Bennett, Diamond, and their colleagues provided the first evidence that enrichment of the environment could lead to structural changes in the brain" (Bailey & Kandel 1993, p. 399).

Work by students of Hebb (e.g. Forgays & Forgays 1952) provided the models for the environments we used in these experiments. Typically, we assigned littermates of the same sex by a random procedure among various laboratory environments, the three most common being these: (*a*) a large cage containing a group of 10 to 12 animals and a variety of stimulus objects, which were changed daily [this was called the enriched condition (EC) because it provided greater opportunities for informal learning than did the other conditions; all three conditions provided food and water *ad libitum*]; (*b*) the standard colony or social condition (SC), with three animals in a standard laboratory cage; (*c*) SC-size cages housing single animals [this was called the impoverished condition or isolated condition (IC)].

Our first reports of changes in the brain induced by experience were greeted with skepticism and incredulity. Hebb cautioned me that the more important the claims, the more careful should be the tests. Over the next several years, replications and extensions by us (e.g. Bennett et al 1964a) and then by others (e.g. Altman & Das 1964, Geller et al 1965, Greenough & Volkmar 1973) gained acceptance for the idea that training or differential experience could produce measurable changes in the brain. Control experiments demonstrated that the cerebral differences could not be attributed to differential handling, locomotor activity, or diet. The brain weight differences caused by differential experience were extremely reliable, although small in percentage terms. Moreover, these differences were not uniformly distributed throughout the cerebral cortex: They were almost invariably largest in occipital cortex and smallest in the adjacent somesthetic cortex; the rest of the brain outside the cerebral cortex tended to show very little effect (Bennett et al 1964a,b). Thus the learning or

enriched experience caused changes in specific cortical regions and not undifferentiated growth of brain. Later work also showed effects of differential experience in other parts of the brain that have been implicated in learning and formation of memory—the cerebellar cortex (Pysh & Weiss 1979) and the hippocampal dentate gyrus (Juraska et al 1985, 1989).

Further early studies revealed experience-induced changes in other measures, especially in occipital cortex. Increases were reported in cortical thickness (Diamond et al 1964), in sizes of neuronal cell bodies and nuclei (Diamond 1967), in size of synaptic contact areas (West & Greenough 1972), in numbers of dendritic spines per unit of length of basal dendrites (an increase of 10%) (Globus et al 1973), in extent and branching of dendrites (Holloway 1966) [an increase of 25% or more (Greenough & Volkmar 1973)], and in numbers of synapses per neuron (Turner & Greenough 1985); mainly because of the increase in dendritic branching, the neuronal cell bodies are spaced farther apart in cortex of EC rats than in that of IC rats. These effects indicate substantial increases in cortical volume and intracortical connections; they suggest greater processing capacity of the cortical region concerned. They contradict the speculation of Ramon y Cajal (1894) that, with training, neural cell bodies would shrink in order to allow neural arborizations to grow, thus allowing brain volume to remain constant. Instead, larger cell bodies are required to maintain the increased arborization, and the volume of the cortex increases as cell bodies and dendrites grow.

These reports indicated that the number and/or size of synaptic connections increased as a result of training or enriched experience. Some workers declared for one or the other of these possibilities, as when neurophysiologist John C. Eccles (1965) stated his belief that learning and memory storage involve "growth just of bigger and better synapses that are already there, not growth of new connections." But Rosenzweig et al (1972) reviewed findings and theoretical discussions suggesting that negative as well as positive synaptic changes may store memory. Depending upon where in the brain one measures and upon the kind of training or differential experience the organism has undergone, one may find increase in number of synapses, increase in their size, decrease in number, or decrease in size.

Soon after the early publications on neurochemical and anatomical plasticity came another kind of evidence of cortical plasticity—the announcement by Hubel & Wiesel that depriving one eye of light in a young animal, starting at the age at which the eyes first open, reduced the number of cortical cells responding to subsequent stimulation of that eye (Wiesel & Hubel 1963, Hubel & Wiesel 1965, Wiesel & Hubel 1965).

Differential Experience Produces Cerebral Changes Throughout the Life Span, and Rather Rapidly

Further experiments revealed that relatively short periods of enriched or impoverished experience induced significant cerebral effects at any part of the life span. In contrast, Hubel & Wiesel reported that depriving an eye of light altered cortical responses only if the eye was occluded during a critical period early in life. Later, however, other investigators found that modifying sensory experience in adult animals—especially in the modalities of touch and hearing—could alter both receptive fields of cells and cortical maps, as reviewed by Kaas (1991) and Weinberger (1995).

Initially we supposed that cerebral plasticity might be restricted to the early part of the life span, so we assigned animals to differential environments at weaning (about 25 days of age) and kept them there for 80 days. Later, members of our group obtained similar effects in rats assigned to the differential environments for 30 days as juveniles at 50 days of age (Zolman & Morimoto 1962) and as young adults at 105 days of age (Rosenzweig et al 1963, Bennett et al 1964a). Riege (1971) in our laboratory found that similar effects occurred in rats assigned to the differential environments at 285 days of age and kept there for periods of 30, 60, or 90 days. Two hours a day in the differential environments for a period of 30 or 54 days produced cerebral effects similar to those after 24-hr-a-day exposure for the same periods (Rosenzweig et al 1968). Four days of differential housing produced clear effects on cortical weights (Bennett et al 1970) and on dendritic branching (Kilman et al 1988); Ferchmin & Eterovic (1986) reported that four 10-min daily sessions in EC significantly altered cortical RNA concentrations.

The fact that differential experience can cause cerebral changes throughout the life span, and relatively rapidly, was consistent with our interpretation of these effects as due to learning. Recall also that our original observation of differences in cortical neurochemistry came from experiments on formal training. Later Chang & Greenough (1982) reported that formal visual training confined to one eye of rats caused increased dendritic branching in the visual cortex contralateral to the open eye. Recently single-trial peck-avoidance training in chicks has been found to result in changes in density of dendritic spines (Lowndes & Stewart 1994).

Although the capacity for these plastic changes of the nervous system, and for learning, remain in older subjects, the cerebral effects of differential environmental experience develop somewhat more rapidly in younger than in older animals, and the magnitude of the effects is often greater in the younger animals. Also, continuing plasticity does not hold for all brain systems and types of experience. As noted above, changes in responses of cortical cells to

an occluded eye are normally restricted to early development (Wiesel & Hubel 1963), but this restriction may itself be modifiable: Baer & Singer (1986) reported that plasticity of the adult visual cortex could be restored by infusing acetylcholine and noradrenaline. Further work showed that the plastic response of the young kitten brain to occlusion of one eye also depends upon glutamate transmission, because treating the striate cortex with an inhibitor of the glutamate NMDA receptor prevented the changes (Kleinschmidt et al 1987). Thus, whether the brain shows plastic changes in response to a particular kind of experience depends on the brain region, the kind of experience, and also on special circumstances or treatments that enhance or impair plasticity.

ENRICHED EXPERIENCE IMPROVES ABILITY TO LEARN AND TO SOLVE PROBLEMS

Hebb (1949, p. 298–99) reported briefly that when he allowed laboratory rats to explore his home for some weeks as pets of his children and then returned the rats to the laboratory, they showed better problem-solving ability than rats that had remained in the laboratory. Furthermore, they maintained their superiority or even increased it during a series of tests. Hebb 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" (pp. 298–99, italics in the original). The results seemed to show a *permanent* effect of early experience on problem-solving at maturity.

We and others have found that experience in an enriched laboratory environment improves a subject animal's learning and problem-solving ability on a wide variety of tests, although such differences have not been found invariably. One general finding is that 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 (for a review and discussion of various explanations offered for this effect see Renner & Rosenzweig 1987, pp. 46–48).

We were unable, however, to replicate an important aspect of Hebb's report—that over a series of tests, EC rats maintain or 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; this occurred with each of three different tests, including the Hebb-Williams mazes (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. Also, decreases in cortical weights induced by 300 days in the IC (versus the EC) environment could be overcome by a few weeks of training and testing in the Hebb-Williams mazes (Cummins et al 1973). Below, we note a similar effect in birds.

SIMILAR EFFECTS OF TRAINING AND EXPERIENCE ON BRAIN AND BEHAVIOR OCCUR IN ALL SPECIES TESTED TO DATE

Experiments with several strains of rats showed similar effects of EC vs. IC experience on both brain values and problem-solving behavior, as reviewed by Renner & Rosenzweig (1987, pp. 53–54). Similar effects on brain measures have been found in several species of mammals—mice, gerbils, ground squirrels, cats, and monkeys (reviewed by Renner & Rosenzweig 1987, pp. 54–59), and effects of training on brain values of birds have also been found. Thus the cerebral effects of experience that were surprising when first found in rats have now been generalized to several mammalian and avian species. Anatomical effects of training or differential experience have been measured in specific brain regions of *Drosophila* (Davis 1993, Heisenberg et al 1995). Synaptic changes with training have also been found in the nervous systems of the molluscs *Aplysia* and *Hermissenda*, as reviewed by Krasne & Glanzman (1995). In *Aplysia*, long-term habituation led to decreased numbers of synaptic sites, whereas long-term sensitization led to an increase (Bailey & Chen 1983); this is a case where either a decrease or an increase in synaptic numbers stores memory. Thus, as noted by Greenough et al (1990, p. 164), "experience-dependent synaptic plasticity is more widely reported, in terms of species, than any other putative memory mechanisms."

Experience May Be Necessary for Full Growth of Brain and of Behavioral Potential

Sufficiently rich experience may be necessary for full growth of species-specific brain characteristics and behavioral potential. This is seen in recent research on differential experience conducted with different species of the crow family. Species that cache food in a variety of locations for future use are found to have significantly larger hippocampal formations than related species that do not cache food (Krebs et al 1989, Sherry et al 1989). But the difference in hippocampal size is not found in young birds still in the nest; it appears only after food storing has started, a few weeks after the birds have left the nest (Healy & Krebs 1993). Even more interesting is the finding that this species-typical difference in hippocampal size depends on experience; it does not appear in birds that have not had the opportunity to cache food (Clayton & Krebs 1994). Different groups of hand-raised birds were given experience in storing food at three different ages: either 35–59 days posthatch, 60–83 days, or 115–138 days. Experience at each of these periods led to increased hippocampal size, much as we had found for measures of occipital cortex in the rat.

Thus, both birds and rats appear to retain considerable potential for experience-induced brain growth if it does not occur at the usual early age.

ENRICHED EXPERIENCE AND FORMAL TRAINING EVOKE SIMILAR CASCADES OF NEUROCHEMICAL EVENTS THAT CAUSE PLASTIC CHANGES IN BRAIN

By what processes do enriched experience or formal training lead to plastic changes in cerebral neurochemistry and neuroanatomy? We found early that enriched experience causes increased rates of protein synthesis and increased amounts of protein in the cortex (Bennett et al 1964a). Later, training (imprinting) was reported to increase the rates of incorporation of precursors into RNA and protein in the forebrain of the chick (Haywood et al 1970), and enriched experience in rats was found to lead to increased amounts of RNA (Ferchmin et al 1970, Bennett 1976) and increased expression of RNA in rat brain (Grouse et al 1978). Maze training led to increased ratios of RNA to DNA in rat cortex (Bennett et al 1979). We viewed these findings in the light of the hypothesis, perhaps first enunciated by Katz & 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), and much research followed their design: 1. giving animal subjects brief training that, without further treatment, would yield evidence of retention at a test a few days later; 2. administering to experimental subjects an inhibitor of protein synthesis at various times close to training, while control subjects received an inactive substance; and 3. comparing test performance of experimental and control subjects. By the early 1970s considerable evidence indicated that protein synthesis during or soon after training is necessary for formation of long-term memory (LTM), but the interpretation of the findings was clouded by serious problems: The inhibitors of protein synthesis then available for research (such as puromycin and cycloheximide) were rather toxic, which impeded experiments and complicated interpretation; and it appeared that inhibition of protein synthesis could prevent memory formation after weak training but not after strong training (e.g. Barondes 1970).

A new 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 can prevent long-term effects. The discovery by Bennett et al (1972) that ANI is an effective amnestic agent in rodents opened the way to resolving the main challenges to the protein-synthesis hypothesis of LTM formation. ANI is

much less toxic than other protein-synthesis inhibitors, and giving doses repeatedly at 2-hr intervals can prolong the duration of cerebral inhibition at amnestic levels. By varying the duration of amnestic levels of inhibition in this way, we found that the stronger the training, the longer protein synthesis had to be inhibited 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; neither short-term memory (STM) nor intermediate-term memory (ITM) required protein synthesis (e.g. Bennett et al 1972, Mizumori et al 1985, Mizumori et al 1987). Further studies were then designed to find the neurochemical processes that underlie formation of STM and ITM. Lashley's concern, mentioned above, 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 has been 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. Further advantages have been stated 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). Such agents can be used to reveal the roles of different brain structures in different stages of memory formation (e.g. Patterson et al 1986, Serrano et al 1995b).

Using the chick system, several investigators have traced parts of a cascade of neurochemical events from initial stimulation to synthesis of protein and structural changes (e.g. Gibbs & Ng 1977; Ng & Gibbs 1991; Rose 1992a,b; Rosenzweig et al 1992). At some if not all stages, parallel processes occur. Briefly, here are some of the stages: The cascade is initiated when sensory

stimulation activates receptor organs, which stimulate afferent neurons by using various synaptic transmitter agents such as acetylcholine (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 (1995a) were able to predict for a newly available inhibitor of PKC 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 & Rose 1991) and to increase in the density of dendritic spines (Lowndes & 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 is similar to the cascade involved in long-term potentiation in the mammalian brain (e.g. Colley & Routtenberg 1993) and in the nervous systems of invertebrates (e.g. Krasne & Glanzman 1995).

Many of the steps in formation of memory in the chick can also be modulated by opioids and other substances. Opioid agonists tend to impair, and opioid antagonists to enhance, memory formation. 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).

Can Parts of the Neurochemical Cascade 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 discussed more fully elsewhere (Rosenzweig et al 1993). Consider, for example, some very different attempts to state the

duration of STM. Early investigators of human STM (Brown 1958, Peterson & Peterson 1959) reported that it lasts only about 30 sec 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) suggests 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 hr after training.

Squire (1987) was not concerned about an apparent discrepancy: Behavioral measures indicated that STM lasts less than a minute whereas neurobiological experiments in both vertebrates and invertebrates have been interpreted as suggesting STM durations of hours or more. In a discussion entitled "Neuropsychology and neurobiology reconciled" (pp. 148–50), Squire suggested that the findings are not incompatible because they refer to different levels of analysis: "[E]xperimental psychology and neuropsychology employ the terms 'short-term' and 'long-term' memory as system-level concepts.… The neurobiological approach analyzes memory at the level of cells and synapses." It is confusing, he suggested, "to assume that stages of synaptic change must reveal themselves literally at the behavioral level." It seems to me that this accepts the discrepancy rather than reconciling the two sets of findings. Moreover, if the behavioral events are based on the neural processes, then it is hard to see how STM events that last less than a minute can depend upon cellular events that require hours to unfold!

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 & 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 &

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 & 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 inhibit PKA, but do not inhibit CaM kinase, disrupt 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. But many findings in this area support the hypothesis that at least three sequentially dependent stages of memory formation exist, each dependent on different neurochemical processes. A recent review (DeZazzo & Tully 1995) discusses STM, ITM, and LTM and compares the characteristics of the three stages in fruitflies, chicks, and rats.

The Possibility of Treatments to Improve Cognitive Functioning

The results bearing on stages of memory formation are important not only for investigators of the neurochemistry of memory but also for neuropsychologists and others who work with patients suffering from memory disorders. A review by Kopelman (1992, pp. 136–38) finds mixed results in attempts to distinguish losses of ITM and LTM in Korsakoff's and Alzheimer's patients. If it becomes possible to distinguish patients with disorders of ITM from those with impairment of STM or LTM, then perhaps their deficits can be traced to different disorders of the nervous system. Identification of the neurochemical processes underlying each stage of memory formation could lead to rational pharmacological treatments. If investigators could then understand the genetics involved, they might eventually find genetic treatments for some memory defects.

It should not be overlooked that the advent of effective treatments to ameliorate memory might not be an unmixed blessing; it could lead to social and ethical problems, especially if such treatments could enhance normal cognitive functioning, as René Cassin, one of the authors of the International Declaration of Human Rights, and recipient of the Nobel Peace Prize, warned educators, scientists, and jurists in 1968. Psychologists and neuroscientists whose work may improve the cognitive abilities of individuals share the responsibility to prepare for the social and ethical consequences of their work.

EVIDENCE THAT CERTAIN LEARNING-INDUCED NEUROCHEMICAL PROCESSES AND NEURAL PLASTICITY ARE NECESSARY FOR LONG-TERM MEMORY

What Neurochemical Processes Are Necessary and Sufficient to Store Memories of Various Durations?

As evidence accumulated that learning and experience induce chemical changes in the brain and that inhibiting some chemical processes around the time of learning blocks formation of memory, some investigators tried to devise guidelines and criteria to judge whether such changes and processes are necessary and sufficient for formation of memory. Of course, reports of many studies stated one or more criteria against which to test their findings, but Entingh et al (1975) and Rose (1981) tried to list several guidelines or criteria that would be applicable to a variety of studies.

Research on learning and memory, chiefly with chicks, showed that some neural processes appear to fulfill all the following criteria; those set in italics are paraphrased from Rose (1992a) and given in somewhat different order. Evidence for several of these criteria was shown above: (*a*) *There must be changes in the quantity of the system or substance, or its rate of production or turnover, in some localized region of the brain during memory formation.* (*b*) The amount of change should be related to the strength or amount of training, up to a limit. (*c*) *Stress, motor activity, or other processes that accompany learning must not, in the absence of memory formation, result in the structural or biochemical changes.* (*d*) *If the cellular or biochemical changes are inhibited during the period over which memory formation would normally occur, then memory formation should be prevented and the animal should be amnesic.* However, Flood et al (1973) found cases in which the protein synthesis required for LTM formation was only postponed by inhibition of protein synthesis and occurred later than usual, after the inhibition wore off. (*e*) *Removal of the anatomical site at which the biochemical, cellular, and physiological changes occur should interfere with the process of memory formation, depending upon when, in relation to the training, the region is removed.* But some cases have been found in which, after removal of a primary area for memory formation, memory can be formed in a secondary region. (*f*) *Neurophysiological recording from the sites of cellular change should detect altered electrical responses from the neurons during and/or as a consequence of memory formation.* (*g*) *The time course of the change must be compatible with the time course of memory formation.* (*h*) As Entingh et al (1975, p. 232) pointed out, the brain sites involved in learning and memory storage should be identified by converging evidence from neurochemical changes, localized in-

hibition of neurochemistry, and electrophysiological recording; lesion studies should be added to this list.

Martinez & Derrick (1996) in this volume discuss whether long-term potentiation (LTP)—which involves neurochemical, electrophysiological, and neuroanatomical changes—is a memory mechanism. While conceding that convincing proof does not exist that LTP is involved in memory, they believe that after 20 years of research on it, "LTP remains the best single candidate for a cellular process of synaptic change that may underlie learning and memory in the vertebrate brain" (p. 198). They review findings of a cascade of neurochemical events underlying LTP that is similar to those found in research on memory formation.

Is Learning-Induced Neuroanatomical Plasticity Necessary for Storage of Long-Term Memory?

Whether learning-induced anatomical changes in the nervous system are necessary for storage of long-term memory has been discussed by several authors, including Morris (1989), Greenough et al (1990), and Martinez & Derrick (1996). Greenough et al (1990, pp. 162–65) note several observations that relate number of synapses and degree of dendritic branching to the amount and sites of learning or experience; evidence for most of these points is given above, and in some cases I here augment the statements of Greenough et al: (*a*) The amount of dendrite per neuron in occipital cortex of the rat reflects the amount of stimulation or complexity in the environment—e.g. the measures are greatest in rats from the enriched condition, least in those from IC, and intermediate in those from SC. (*b*) Similar effects of training or experience occur in young, adult, and old rats. (*c*) Changes in brain measures are induced rapidly by training. (*d*) The changes in dendritic branching are paralleled by changes in numbers of synapses per neuron. (*e*) The synaptic and dendritic changes occur not only in rodents but also in cats and monkeys. (*f*) The synaptic and dendritic changes caused by enriched experience are similar to those induced by traditional learning tasks. Later (pp. 174–76) Greenough et al note (*g*) that learning-based morphological changes are greater than and different from changes induced by mere activity. Also, (*h*) the changes occur in brain regions involved in the learned tasks; if learning is confined to one side of the brain, the synaptic and dendritic changes are also confined to that side. Note that some of the points on this list correspond to some given just above for neurochemical processes.

The fact that training and experience usually lead to increased spacing of cortical neurons should be taken into account in interpreting certain other findings, such as a report by Witelson et al (1994) that received considerable coverage in the news media. They reported, based on a small number of cases,

that women have a larger number of neurons in a region of the cortex related to language than do men and speculated that this might be related to women's greater proficiency in language. Actually the measure was not the total number of neurons in the region but *neurons per unit of volume of cortex*. This means closer spacing of neurons, which could as well suggest simpler and less extensive connections of neurons in this region of women's brains, perhaps reflecting less verbal training and experience. At the least, it does not seem compelling to interpret closer packing of neurons as evidence for greater cognitive proficiency.

CHANGES INDUCED BY LEARNING OCCUR IN A VARIETY OF NEURAL NETWORKS

Hebb's main interest was considering how complex neural networks ("phase sequences" and "cell assemblies") could account for phenomena such as perception and memory. He put forth his postulate of synaptic changes only to show that such changes could support the formation of neural networks. But, as Gallistel (1990) notes, most neuroscientists have been more concerned with how synaptic changes can store information than with how neural networks can compute memories. Investigators have proposed a variety of neural circuits and networks in which information could be stored and memorial responses computed; we can classify much current research according to the kinds of networks proposed (Rosenzweig et al 1996), as a few examples will show. The neural circuits range from simple neural chains to parallel distributed circuits.

The simplest neural chain is a monosynaptic reflex arc, and this has been used to describe the mechanism of simple learning (habituation) in the gill withdrawal reflex of *Aplysia* (e.g. Kandel et al 1987, Kupfermann & Kandel 1969). Because the change occurs within the reflex arc, it is sometimes referred to as an intrinsic change (Krasne & Glanzman 1995).

Many simple neural circuits receive input from (or are by-passed by) superordinate circuits, and learning-induced plasticity may occur at the superordinate level. Thus, in eyelid conditioning in mammals, it appears that the site of plasticity necessary for the conditioning is in a higher-order circuit in the cerebellum (Lavond et al 1993), whereas the basic reflex circuit in the brainstem shows no change during training. Considered in relation to the reflex arc, this is sometimes called an extrinsic change.

Even where synaptic changes have been found in a monosynaptic reflex arc, changes sufficient for learning and memory may also take place in other parts of the nervous system. Thus, the gill-withdrawal response of *Aplysia* persists and can be altered by training after surgical removal of the abdominal

ganglion (Mpitsos & Lukowiak 1985). The central nervous system of *Aplysia* enters a suppressed state after the animal has eaten or engaged in sexual activity, but even when the CNS is inactivated, the animal still shows the gill-withdrawal response, mediated by the peripheral nervous system. Thus the neural circuitry of the gill-withdrawal response includes cells of the peripheral nervous system, and "the neural circuitry of this behavior is more complex than was hoped, and much of it consists of small diffuse cells that are inaccessible to the neurophysiologist" (Leonard et al 1989, p. 585).

Much current theorizing suggests that the same ensemble of neurons can encode many different memories, each neuron participating to a greater or lesser extent in a particular memory (e.g. McNaughton & Morris 1987). Recent research suggests that modification of the gill-withdrawal response in *Aplysia* may depend on parallel distributed processing (involving synaptic plasticity) in a large ensemble of neurons rather than on a few neurons in a monosynaptic reflex arc. Thus, it appears that approximately 200 of the 1000 neurons in the abdominal ganglion of *Aplysia* respond to a touch to the siphon (Zecevic et al 1989) and that these neurons are involved in respiration as well as gill withdrawal (Wu et al 1994). The different kinds of responses mediated by these neurons appear to be generated by altered activities of a single, large distributed network rather than by separate small networks, each dedicated to a particular response.

Investigation of learning and memory in birds and mammals indicates that they involve neural sites widely distributed in the brain, as Hebb believed likely for cell assemblies. Thompson and his associates (Lavond et al 1993) emphasize that their research on the neural circuit necessary for eyelid conditioning is restricted to "the simplest substrates of aversive conditioning" (p. 318), and they are certain that other structures, including "the hippocampus and cerebral cortex certainly play important roles in more complex learning, as well as being influenced in aversive classical conditioning" (p. 318). Noninvasive imaging techniques now indicate that several brain regions are specifically activated during eyelid conditioning in human subjects. Thus Logan & Grafton (1995) report that brain regions that exhibit significant differences between the unpaired-stimulus control condition and the well-trained state include not only several cerebellar sites but also the pontine tegmentum, ipsilateral inferior thalamus/red nucleus, ipsilateral hippocampal formation, ipsilateral lateral temporal cortex, and bilateral ventral striatum. Similarly, a review of several human neuroimaging studies using various delayed-response tasks to investigate working memory shows that there is typically activation of the dorsal prefrontal cortex, but other regions are also selectively activated depending upon the specific stimuli and task (McCarthy 1995). Tracing the circuits involved is a challenging task that should provide major advances in our understanding of learning and memory.

RESEARCH ON USE-INDUCED BRAIN PLASTICITY IS YIELDING AND SUPPORTING A VARIETY OF APPLICATIONS

Animal research on the effects of experience on brain plasticity and learning is being applied to several areas of human behavior and in other cases has been used as converging or supporting evidence. Thus it is being used to promote child development, successful aging, and recovery from brain damage; it is also being applied to benefit animals in laboratories, zoos, and farms. Let us consider a few of these kinds of application or influence briefly below.

Applications to Child Development

The findings on the effects of differential experience in animals have influenced research on child development or at least have been offered as supporting evidence in favor of giving children adequate experience. An indication of the importance of this approach comes from a major report, "Starting points: Meeting the needs of our youngest children" (1994), issued by the Carnegie Task Force on Meeting the Needs of Young Children. The tenor of the findings is indicated by this quotation:

> Beginning in the 1960s, scientists began to demonstrate that the quality and variety of the environment have direct impact on brain development. Today, researchers around the world are amassing evidence that the role of the environment is even more important than earlier studies had suggested. For example, histological and brain scan studies of animals show changes in brain structure and function as a result of variations in early experience.
>
> These findings are consistent with research in child development that has shown the first eighteen months of life to be an important period of development. Studies of children raised in poor environments—both in this country and elsewhere—show that they have cognitive deficits of substantial magnitude by eighteen months of age and that full reversal of these deficits may not be possible. These studies are based on observational and cognitive assessments; researchers say that neurobiologists using brain scan technologies are on the verge of confirming these findings.
>
> In the meantime, more conventional studies of child development—using cognitive and observational measures—continue to show short- and long-term benefits of an enriched early environment (p. 8).

This is one of the latest contributions to a back-and-forth debate between those who hold that child development proceeds mainly from innate factors with only a small influence of the environment and those who hold that environment can make a major contribution. Gall and Spurzheim differed on this question early in the 19th century.

It is disheartening to note that despite demonstrations over 30 years that lack of adequate intellectual stimulation can cause mental retardation and that

appropriate stimulation can foster normal development, few sustained attempts have been made to apply these findings. Hunt (1979), for example, in a chapter in the *Annual Review of Psychology*, presented evidence for the importance of early experience to children's intellectual development. He reviewed several studies showing substantial effects of specific kinds of environmental interventions on particular aspects of child development. One was his own study (Hunt et al 1976) demonstrating the importance of specific caretaking to assure language development of infants in a Teheran orphanage. Hunt also reviewed animal research on effects of differential experience on problem-solving, neuroanatomy, and neurochemistry—research whose inspiration he attributed to Hebb's 1949 book, and which included some of the experiments of the 1960s–1970s described above.

Several factors have complicated attempts to apply research on environmental enrichment to improve the cognitive status of children raised in poor environments. One is that some proponents have overestimated the potential effects of relatively short periods of enrichment and then have been disappointed that the effects were not larger. This has been one of the problems confronting the Head Start program which began in 1963 in the United States (Zigler & Muenchow 1992). Although this and related programs have proved beneficial and cost effective, they were unable to bring participating children up to the scholastic levels of children living in better environments. Another problem is that the human programs involve a variety of interventions, so it is difficult to determine whether the positive effects are attributable to enriched experience and training or to other causes such as improved nutrition and health care. In the words of a recent review of the effects of nutrition on child development, however, "Adequacy of the social and educational environment is as significant as nutrition for mental development (or possibly more significant)" (Sigman 1995, p. 54).

The authors of a new series of studies (Drews et al 1995, Murphy et al 1995, Yeargin-Allsopp et al 1995) conclude that the principal causes of mild retardation (IQ scores between 50 and 70) in an American city appear to be poverty and lack of education of mothers (fewer than 12 years of education). These researchers claim that many cases of mild retardation are preventable and/or treatable by appropriate early training and experience. David Satcher, the Director for the Centers for Disease Control and Prevention, which supported these studies, announced that the Centers will start a demonstration program in 1996 "aimed at promoting the cognitive, communicative, and behavioral development, as well as the health, of children born to women with fewer than 12 years of education" (Satcher 1995, p. 305). Satcher cited the report of the Carnegie Corporation, mentioned above: "[It] goes beyond questions of intellectual function and underscores the importance of early (birth to 3 years) experiential and social factors in brain development. The report em-

phasizes long-lasting effects of early environmental experience on both brain structure and cognitive function" (Satcher 1995, p. 305).

The problems of finding exactly which factors are most important in enhancing cognitive development should not overshadow the benefits of programs that provide environmental enrichment to children in need of it. I believe that current programs should be expanded to include more children and to retain them for longer periods. Unfortunately, in the United States such programs appear to be in jeopardy in the present political climate.

Enriched Experience Aids "Successful Aging"

Enriched experience, beginning early in life, also helps to ensure maintenance of ability into old age. Thus, infantile handling or later enriched experience helps prevent hippocampal damage caused by stress in rats. Meaney et al (1988, 1991) handled some neonatal rat pups during each of their first 21 days and left other pups unhandled. They examined cognitive function of the rats at different ages from 3 months to 24 months and also measured basal and stress levels of glucocorticoids, numbers of hippocampal neurons, and numbers of glucocorticoid receptors. Chronic excess of glucocorticoids is toxic to neurons, particularly those of the hippocampus, and aged rats are particularly vulnerable (Sapolsky 1992). Handled rats showed improved spatial memory, higher numbers of hippocampal corticoid receptors, and a more rapid return of corticosterone to basal levels after response to a stressful situation. In old age, the handled animals had lower basal levels of corticosterone and lost fewer hippocampal neurons than the unhandled ones.

Young adult rats given 30 days of EC experience beginning at 50 days of age, like rats given infantile handling, showed higher expression of the gene encoding glucocorticoid receptors in the hippocampus, and they also showed induction of genes for nerve growth factors in the hippocampus (Mohammed et al 1993, Olsson et al 1994). The investigators suggest that enriched experience in adulthood, like infantile handling, may protect the aging hippocampus from glucocorticoid neurotoxicity.

Some kinds of learning and performance decline with age after middle adulthood, but other kinds of learning and memory do not. People who continue to learn actively can maintain high levels of performance. For example, professors in their 60s perform as well as professors in their 30s on many tests of learning and memory (Shimamura et al 1995).

Beyond the age of retirement, stimulation and activity continue to contribute to health and mental status. This claim is borne out in a longitudinal study that has assessed the mental abilities of more than 5000 adults, having followed some for as long as 35 years (Schaie 1994). Among the eight variables found to reduce the risk of cognitive decline in old age, three are particularly relevant here: 1. Living in favorable environmental circumstances, as would be

the case for persons of high socioeconomic status. Such circumstances include above-average education, histories of occupational pursuits that involve high complexity and low routine, above-average income, and the maintenance of intact families. 2. Substantial involvement in activities typically available in complex and intellectually stimulating environments. Such activities include extensive reading habits, travel, attendance at cultural events, pursuit of continuing education activities, and participation in clubs and professional associations. 3. Being married to a spouse with high cognitive status. Our studies of cognitive similarity in married couples suggest that the spouse who scores less well on tests of cognitive ability at the beginning of marriage tends to maintain or increase his or her scores vis-à-vis the spouse who originally scored higher (Schaie 1994, p. 312).

Terry et al (1995) report that loss of synapses correlates strongly with the severity of symptoms in Alzheimer's disease. Enriched experience produces richer neural networks in the brains of all species so far studied. If similar effects occur in humans, as seems likely, the resulting reserves of connections may protect intellectual function from the effects of Alzheimer's disease.

In adulthood and old age, is use of the nervous system better characterized by the phrase "wear and tear" or by the phrase "use it or lose it" (Swaab 1991)? The research reviewed here, along with many comments on Swaab's paper, mainly support the characterization "use it or lose it." But enriched experience and use of the cognitive faculites are especially effective early in life and set the basis for later use and maintenance of the brain and of mental ability.

Applications to Recovery from or Compensation for Brain Damage

In all parts of the life span, training and enriched experience help in recovery from or compensation for effects of brain damage. We showed this in experiments with rats in the 1970s (Will et al 1977), and research along this line continues. To what degree does experience actually aid in recovery, and to what degree does it only help to compensate for the effects of brain injury? At a minimum, psychological interventions can improve the quality of life of people with injuries of the brain or of the spinal cord. Beyond this, various combinations of physiological and behavioral interventions may combine to bring improvement.

In attempts to promote recovery from brain damage, some neuroscientists are transplanting fetal brain cells into the region of a brain lesion. Psychologists are taking part in this research. Sometimes such neural transplants or implants help to restore function, but often, for reasons that are not yet fully understood, they do not.

A few years ago, investigators started to study the separate and the combined effects of enriched environment and neural transplants (Kelche et al

1988). Under some conditions, neither the enriched experience nor the transplant alone had a beneficial effect but the combination of the two treatments yielded 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). The results of such animal research may someday benefit human patients. At present the attempts to help patients with Parkinson's disease by implanting fetal brain cells are garnering mixed results. Perhaps the differences among clinics in success of cell grafts reflect the kinds and amounts of training and stimulation given their patients; such behavioral factors may well interact with the skill of the neurosurgeon. The combination of brain tissue implantation with cognitive training and stimulation may help researchers to elucidate further the neural bases of learning and memory.

Research on Enriched Environments Is Benefiting Animals in Laboratories, Zoos, and Farms

Animals not only contribute to research on mechanisms of memory and effects of environmental enrichment, but they also benefit from such research, as I have described in somewhat more detail elsewhere (Rosenzweig 1984). Newer standards for housing animals in laboratories reflect findings that animals benefit in development of brain and behavior from adequate space and facilities for species-specific activities like running, investigating, and so forth. Zoos are also providing more natural settings and apparatus that permit animals to engage in species-specific activities. Two of my former students who worked with rats in enriched laboratory environments have since worked to improve settings for zoo animals. Some farms have found that animals thrive better in more natural settings.

CONCLUDING COMMENT

The last half century has been a fascinating period in which to observe and take part in the search for mechanisms of memory. The invention of new concepts and the emergence of new experimental techniques have allowed important progress and rejection of inadequate hypotheses. Exciting new techniques promise novel insights. Behavioral research continues to distinguish the various types of learning and memory. Clinical research in interaction with biological research continues to explain problems of learning and memory and to yield methods of alleviating cognitive deficits. The next half century will see many more surprises and advances in this complex and engrossing field.

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