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ABSTRACT

The National Institute of Education takes a fundamental approach to the problems it is addressing. This implies the creation of an intellectual framework for the problem areas, which can be used to systematize existing knowledge and research approaches and suggest promising new directions for research and development. Neural mechanisms of learning and memory constitute the ultimate foundations upon which learning of basic skills rests. This conference grew out of such concerns. Twenty review papers were prepared and circulated in advance by leading investigators, each describing a major research approach, well-established findings, current gaps in knowledge, current research efforts and near-future prospects, and relations to other approaches. At the conference, presentation of highlights of each review by its author was followed by a prepared discussion of the paper by another leading investigator, and then by general discussion. The review and discussion papers, revised on the basis of discussions at the conference, will be published as the report of the Conference in late 1975 by the MIT Press. The report, in addition to being very useful to investigators in the field and to students, will be used by NIE in formulating its policy on future support of research in this area. (Author/CKJ)

Current Reseach Approaches to

Neural Mechanisms of Learning and Memory

Preliminary Report on a Conference held at Asilomar Conference Grounds Pacific Grove, California

U. S. Department of Health, Education & Welfare
National Institute of Education
Washington, D.C. 20208
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The full report of this conference

Neural Mechanisms of Learning and Memory

will be published by the

MIT Press in late 1975.

Points of view or opinions stated in the full report or in material in the body of this preliminary report are not necessarily those of the National Institute of Education or the U.S. Department of Health, Education, and Welfare.

PREFACE

The National Institute of Education (NIE) was created by the Congress in 1972 with the mission of:

- helping to solve or to alleviate the problems of, and achieve the objectives of, American education;
- advancing the practice of education, as an art, science and profession;
- strengthening the scientific and technological foundations of education; and
- building an effective educational research and development system.

The National Council on Educational Research, NIE's policymaking body, in pursuit of these objectives has established several priority areas for the Institute's work. One of these areas is that of Basic Skills - improving student performance in such essential skills as reading and mathematics. Prime responsibility for NIE's basic research on human learning is assigned to the Basic Skills Group.

NIE seeks, to the extent possible, to take a fundamental approach to the problems it is addressing. This implies the creation of an intellectual framework for the problem areas, which can be used to systematize existing knowledge and research approaches and suggest promising new directions for research and development. Neural mechanisms of learning and memory obviously constitute the ultimate foundations upon which learning of basic skills rests. NIE was fortunate in being able to enlist the help of Drs. Mark R. Rosenzweig and Edward L. Bennett of the University of California, Berkeley. They in turn, with the help of a nationally constituted planning committee, organized the Conference on Neural Mechanisms in Learning and Memory described herein. Twenty review papers were prepared and circulated in advance by leading investigators, each describing a major research approach, well established findings, current gaps in knowledge, current research efforts and near-future prospects, and relations to other approaches. At the Conference, presentation of highlights of each review by its author was followed by a prepared discussion of the paper by another leading investigator and then by general discussion. The review and discussion papers, revised on the basis of discussions at the conference will be published as the report of the Conference in late 1975 by the MIT Press. The report, in addition to being very useful to investigators in the field and to students, will be used by NIE in formulating its policy on future support of research in this area. Such support will be designed to complement that of other Federal agencies such as the National Institutes of Health, the National Institute of Mental Health, and the National Science Foundation and various private foundations and will, of course, be aimed at that research most likely to lead to the improvement of education. Representatives of several of these agencies and foundations were present at the Conference, and NIE will be in continuing contact with them as it proceeds with its program.

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SCIENCE WRITER'S REPORT OF THE CONFERENCE

Irving S. Bengeldorf

"Solid state physics has become a more mature science, and therefore the problems are harder both to identify and to solve.

"If you look at biology, things are very different. There are enormous numbers of problems waiting to be solved in biology. Take memory, for example. There's a mechanism there, but nobody knows what it is. Some people say that memory is superconductive, somebody says it deals with protein molecules, some say you have electrical impulses going back and forth all the time, but the fact is that the explanation is completely unknown. Something makes you remember and it must be something that has to do with chemistry or physics, somehow, but nobody knows what it is. So if you want to make an impact, solve the problem of memory. I don't say that it's an easy problem to solve, but it's an easy problem to identify ... you can work towards that goal."

---Dr. Ivar Giaever, physicist at the General Electric Research and Development Center (Schenectady, N.Y.) and co-winner of the 1973 Nobel prize in physics, explaining why his research interest shifted from solid state physics to biology. Quoted in General Electric R&D Review, pg. 7, 1974.

I. OVERVIEW

A. Introduction

From ancient times, mankind has wondered about the mysteries of learning and memory, and in the last hundred years has progressed to empirical investigation of learning and memory. A conference on these two perplexing aspects of animal and human behavior was held the last week of June 1974 at the Asilomar Conference Grounds, Pacific Grove, California. Entitled CURRENT RESEARCH APPROACHES TO THE NEURAL MECHANISMS OF LEARNING AND MEMORY, the conference consisted of the presentation of 40 scheduled papers, with each paper followed by discussion from the conference participants.

Such biological and behavioral research on memory is likely to lead to applications such as the following:

improved methods of teaching to foster more rapid learning and more effective memory.

more efficient retrieval of information from memory.

better treatment of learning disabilities and impaired memory, both congenital (e.g. retardation) and resulting from injuries or diseases.

prevention of learning disabilities and memory impairment through better understanding of their causes.

decrease in the effects of aging on memory.

Obviously, this short report can only present the highlights of such a massive presentation of data. So this report is written in three parts. Part II consists of very short summaries of the material discussed at the conference. It is designed to give the reader a very quick synopsis of the meeting. For those who have more time, Part III consists of more detailed summaries. Finally, for those with a professional need for more complete details (e.g. journalists), they may get a copy of a particular scientist's paper by writing either to Dr. Mark R. Rosenzweig, Department of Psychology, University of California, Berkeley, CA 94720, or to Dr. Edward L. Bennett, Laboratory of Chemical Biodynamics, Lawrence Berkeley Laboratories, University of California, Berkeley, CA 94720. It is anticipated that a book completely reporting these proceedings will be available in fall 1975.

Or, for more information, you may contact the particular scientist directly. A list of the conference participants and their addresses will be found at the end of this brochure. To help the reader, each summary of information presented at the conference is followed by the name of the scientist (in parentheses) who presented that specific information.

This conference on learning and memory generated an air of optimism as participants exchanged and discussed new evidence about the previously unsuspected degree of plasticity of the nervous system. And oversimplified ideas--such as learning and memory being encoded into large molecules--were largely disregarded. The conference also gave an opportunity to scientists in many diverse disciplines to hear and interact with each other, and this should enrich further research.

B. Basic Information about Brain Anatomy and Brain Function

Although the human brain, undoubtedly, is the most complex biological structure "invented" during almost three billion years of biological evolution, significant advances are being made in the understanding of its structure and function.

Computer engineers, who strive to miniaturize man-made electronic components, are green with envy as they consider the human brain. For in a volume of about 1.4 liters (1.5 quarts), and weighing about 1.4 kilograms (3 pounds), the human brain is crammed with approximately 10 billion individual nerve cells or neurons. In addition, the human brain also contains many more glial cells--brain cells that help the neurons by bringing food supplies, removing waste, and forming insulating sheaths.

But what is even more amazing than the incredible number of neurons in a human brain, is the exceedingly complex pattern of neuronal connections--certain kinds of individual neurons can be connected directly to about 10,000 other neurons! Clearly the complexity of the human brain's functions poses difficult problems for the many kinds of investigators.

How do the neurons with their complex connections make possible our behavior--seeing and hearing, thinking, making skilled movements, as well as learning and remembering? Fundamentally, they act by transmitting and receiving signals. When stimuli such as light or sound reach the sense organs, they trigger off tiny bursts or volleys of bioelectrical energy that travel along the sensory nerves to the brain. When muscular responses are required, volleys of nerve impulses are transmitted by motor nerves to the muscles, causing the muscle cells to contract. Complex networks of cells sort out and process the neural information in the brain. The spot where a branch of one neuron makes a functional contact with another is called a "synapse." At some synapses the information is exchanged in bioelectrical form, but at most synapses the incoming impulse causes release of a tiny amount of a chemical substance and it is this chemical mediator that either excites or inhibits the postsynaptic neuron. Some neurons also release hormones into the circulation; by means of these chemical messengers they can communicate with cells located at a distance. By monitoring the electrical impulses and the chemical messengers, investigators can study the flow of information within the body. How memories are stored in terms of neural structures and activities was the theme of this Conference.

C. Research on Learning and Memory

The Conference avoided the pitfall of becoming bogged down in attempts to define learning and memory. There are many ways and situations in which behavior changes as a result of experience; some investigators concentrate on rather narrow and specific examples, while others believe it best to define learning broadly. Some participants considered learning and memory as universal processes with some single fundamental mechanism underlying these functions in most organisms. Other participants, however, considered learning and memory to occur by diverse processes in diverse organisms. To these latter scientists, learning and memory is unlike the most universal processes of molecular biology, wherein amoebas and elephants are the same. Clearly, a great deal of information concerning learning and memory is being obtained from research with such a diverse range of creatures--from invertebrates to humans.

Empirically we know that as a human infant grows and matures into an adult, he develops an ability to learn--to tie shoelaces, to read and write, to solve problems in Euclidean geometry--and he also develops an ability to remember--faces, names, numbers, events, scenes, etc. What changes take place within a brain that permits an animal or a human to learn and to remember?

We know it is simply not due to a change in the number of neurons. At birth, a human infant has almost the same number of neurons as does a human adult. What does change, as a human matures from infant to adult, is the detailed pattern of the interconnections among the individual neurons. Obviously, learning and memory somehow must be tied up with this complex network of connections that develops among neurons. But this raises two interesting questions:

1) To what extent is the pattern of neuronal interconnections in the adult brain determined by genetics--by inheritance?

2) To what extent is the pattern of neuronal interconnections in the adult brain determined by the individual's experiences--by his early environment and throughout his life?

It is clear from the study of animal brain that both inheritance and early environment are involved. Furthermore, in specific cases we are finding how hereditary and experiential factors interact to produce the adult status.

In the ultimate analysis, we know that everything on earth is made up of atoms or combinations of atoms called molecules. And the brain is no exception. It is this fundamental universal fact that underlies the belief of most scientists that when changes take place in the brain during learning, or the establishment of a memory, these changes must be of a chemical and physical nature--changes that involve the very molecules that make up the neurons. But our understanding of the biochemistry and biophysics of learning is only fragmentary as yet.

The perception of the world around us is often biased by the very objects that make up our world. Thus, because we have filing cabinets, libraries, and electronic computers, we tend to feel that human memory also should be stored somewhere in a specific location of the brain. But, as yet, the specific locations within the brain where memory is stored--if there are such locations--remain unknown.

In conclusion, it is no surprise that in the 25 centuries since Hippocrates posed the problems of learning and memory, diverse investigations have only scratched the surface of these exceedingly complex phenomena. But most of the progress has occurred in the last generation, and the pace is accelerating. In spite of considerable progress in recent years, the Conference demonstrated the neural mechanisms of learning and memory remain wide-open fields for further research.

It is important to continue such physiological and behavioral research for it should lead to a better understanding of normal memory and how to improve it, and also to the possible treatment of individuals with damaged brains, of the mentally retarded, and of elderly humans with declining memories.

The problems are complex, and the rewards promise to be great.

II. SUMMARY HIGHLIGHTS OF THE CONFERENCE

(Readers who want more than just highlights may turn directly to Part III, p. 12, where the same topics are taken up in greater detail.)

A. Information from the Study of Brain Injury, Lesions, Etc.

1) Meaningful breakdown of memory function is often seen in humans suffering brain damage. Such damage may occur through accidental injuries, strokes, diseases such as brain tumors or encephalitis, alcoholism, and surgical removal of brain tissue. The memory pathology is often strikingly clean cut. For example, in the amnesic syndromes (resulting from damage to the hippocampus, mammillary bodies, and related structures), intelligence and "memory" for the immediate present may be quite normal, while retrieval of events that occurred just minutes before may be absent. This dissociation between immediate memory and memory of the recent past suggests two stages of memory with different neurological bases and fits with the distinction between short- and long-term memory made by psychologists. The memory loss in the amnesic syndrome may be the consequence of faulty storage of new information or defective retrieval of information already stored. Damage to other brain structures produces deficits in other aspects of memory function that roughly correspond to components of memory hypothesized by cognitive psychologists (Rozin). Damage to the mammillary bodies appears to impair the order of retrieval of established memories (Lhermitte and Signoret).

2) The study of animals or humans with "split brains"--surgical separation of the brain's right and left hemispheres--demonstrates that the two hemispheres can function independently in specific aspects of learning and memory (Gazzaniga).

3) One must use great caution in interpreting the results of experiments in learning and memory that involve producing surgical lesions in specific areas of the animal's brain because structurally and functionally the brain of an animal after surgery is different from what it was before surgery (Isaacson; Lynch).

B. Behavioral Studies

1) Based upon observations of human memory--not on what goes on at the molecular level in synapses--information-processing models have been proposed to describe the various processes of human memory (Simon). A review of models attempting to describe what goes on in the brain, and the problems involved in the construction of such models, was presented (Arbib, et al.).

2) As mentioned previously, there are considered to be at least two kinds of memory: short-term memory (STM) and long-term memory (LTM). The change from STM to LTM can be prevented by various treatments including the administration of an electroconvulsive shock (ECS).

ECS experiments with animals show the memory-consolidation time (time it takes for STM to be transformed into LTM) is highly variable; it does not have a hoped-for constant value (McGaugh; Chorover). And recent research even challenges the view that STM and LTM can sharply be distinguished from each other in behavioral terms (Riley).

3) Ethology (the study of how animals under evolution have adapted their behavior) cautions the experimenter who studies animals that he always must keep in mind the way the animals live in their natural environment (Manning). Ethologists always have been impressed by the great variety of adaptive behavior exhibited by animals.

4) Criticism was expressed that many psychological experiments with animals for the study of learning and memory are contrived laboratory situations that may bear no relationship to how such animals behave in their natural, wild state (Eisenstein).

5) A lack of valid theories of how animals learn leads to attempts to describe "learning" by definition. These definitions are arbitrary and often impose restrictions that may hinder the construction of a theory (Rescorla).

6) There is no evidence--in spite of such techniques as described in BRAVE NEW WORLD--that humans can learn while they sleep. There is evidence that a stage of sleep, called paradoxical sleep or rapid-eye-movement (REM) sleep, may enhance the permanence of learning and memory (Bloch).

7) A practical way to let lambs and coyotes coexist without sheepherders demanding the extinction of coyotes may come from research on "bait-shyness" (Garcia). When lamb meat, tainted with lithium chloride, is fed to coyotes, the coyotes become violently ill. When they recover, the coyotes no longer will attack a lamb.

C. Developmental Studies

1) Infantile amnesia--the inability to recall events that took place in the first few years of our lives--also is observed in rats in their first few weeks after birth (Campbell). Thus it appears that immaturity of the nervous system, rather than various proposed psychological causes, may be the main reason for infantile amnesia.

2) Studies in kittens and cats show that as a nervous system matures--from birth to an adult animal--the fine structures (spines, protuberances) of both the presynaptic and postsynaptic membranes increase and their forms often undergo reshaping (Scheibel & Scheibel). These changes may underlie the ability to form memories.

3) Young rat pups show pivoting motions that eventually point them in the direction of their nest. But rat pups who have their cerebellum and hippocampus prevented from forming by treatment with low-level x-rays

are more random in their pivoting movements. Apparently, the maturation of these specific brain regions is necessary for the development of such learning ability (Altman).

D. Brain Plasticity, Learning and Memory

1) Discussions at the conference revealed that the brain is a much more moldable and pliant organ than was previously thought. Individual neurons are dynamic structures that can undergo anatomical, biochemical, and biophysical changes in response to environmental changes.

2) Electrical recordings from single neurons in the cat's brain reveal that what a mature cat sees is determined by what it saw as a kitten during a critical period from 3 weeks to 3 months of age. It is a critical period during which the neurons in a kitten's brain are plastic, moldable, and pliant--changeable by the environment (Pettigrew; Spinelli). If humans have a similar type of critical period (perhaps, birth to 4 years?), this could have profound implications for education.

3) In adult rats, when a nerve cell outside of the brain (in an arm or a leg, for example) is cut, the nerve regenerates itself. When, however, a neuron inside the brain is cut, it does not regenerate, but a nearby neuron takes over and fills the place that the cut neuron vacated (Raisman). This process, called "reclamation" instead of regeneration, indicates that connections between neurons in the adult brain are less rigidly predetermined than are interneural connections in the peripheral nervous system. If such processes also occur in adult human brains, they may lead to useful clinical techniques in the treatment of patients with damaged brains.

4) Working at the level of the optical microscope, it is claimed that when a cat learns, or when its brain is stimulated electrically, its brain forms new connections between neurons by growths branching out from their dendrites and axons (Rutledge). Similar neuronal growth is observed in hamsters and rats (Moore; Greenough). These results are interpreted to mean that neurons show changes in their form and function as they take part in increased "interneural traffic"--increased use of their synapses (connections among nerves).

5) Biophysical analysis indicates the correctness of a postulate first proposed in the late 19th century and brought to prominence in this century by Hebb--that synapses get stronger as they are used repeatedly (Cowan).

6) Compared to animals that are reared in "impoverished" environments--few stimuli--those animals (mainly rodents, thus far) that are reared in "enriched" environments--numerous and diverse stimuli--can better learn to perform tasks, show an increased weight and thickness of their brain cortex, and show increased amounts of enzymes involved in brain activity (Bennett; Greenough). If these changes apply to humans, then this would give physiological support to the psychological observations that "enriching environments" enhance higher level mental

activities. Such results are stimulating new research on the role of environment in human education and human development.

7) There still is no definite evidence for the physical nature of the engram--the Holy Grail of psychology. Workers in the field agree that physico-chemical changes must occur in the brain as a result of learning and that these changes store memories; the names "memory trace" or "engram" have been given to such changes. What specific biochemical or anatomical changes occur in the brain when one learns the multiplication tables, for example, is still an open question.

E. Biochemistry and Memory

1) Active cells synthesize protein and messenger-RNA. A great deal of research indicates that when an animal learns, its brain cells show an enhanced synthesis of protein and messenger-RNA (Rose, et al.). A dogma of memory research is that there are at least two memories: Information first is taken in as an unstable short-term memory (STM) that with the passage of time changes into a stable long-term memory (LTM). The conversion of STM to LTM is supposed to involve the synthesis of protein; the administration of an antibiotic that inhibits the synthesis of protein or of messenger-RNA knocks out the change of STM to LTM (Flood & Jarvik; Quartermain). Although such changes are correlated with learning, there is not as yet conclusive evidence that they are required for storage of memory (Flood & Jarvik; Dunn).

2) Recent research on short-term memory suggests that drugs that change the electrical nature of the membranes or outer covers of brain cells have a greater effect on the blocking of the formation of STM than do drugs that inhibit the synthesis of proteins. Thus, protein synthesis may be important for the formation of LTM rather than STM (Flood & Jarvik).

3) At present, the exact role of RNA and its relationship to the electrophysiological events of learning and to memory-related protein synthesis remains somewhat obscure. Research now underway with camptothecin, a drug that is relatively non-toxic and whose inhibition of RNA synthesis is reversible, amy yield new clues in this important area of study (Flood & Jarvik).

4) The processes involved in memory may be greatly influenced by hormones released during emotional (affective) states such as anxiety, fear, anger, hunger, pleasure, etc. Although there is no definite evidence at present, it is possible that these released hormones could affect a crucial and specific number of synapses of neurons in the cortex, the cerebellum, and the hippocampus. This hormonal release either could enhance or impair the consolidation of the memory of the particular behavior that preceded and accompanied the emotional state. Hormones,

perhaps, could exert these effects on neurons through their enhancement or impairment of the neuron's protein synthesis (Kety). One piece of suggestive evidence is that injection of adrenocorticotrophic hormone (ACTH) into a rat results in enhanced synthesis of protein and RNA in both brain and liver cells (Dunn). ACTH is a hormone that is released in response to stress.

5) Although there is considerable evidence that various drugs can improve memory storage in animals, there is as yet no clear evidence of such effects in humans (Flood & Jarvik). Little research of this sort has yet been done with human subjects, so the possibility of positive findings is by no means excluded.

6) The conference had no formal discussion of the phenomenon of "memory transfer"--the injection of brain material from a trained animal into an untrained animal that then may result in the recipient showing evidence of the training given to the donor. The planning committee of the conference felt that there is no clear evidence, at present, that such a phenomenon even exists.

F. Learning and Memory Studies with "Simpler" Systems

1) Many different species of invertebrates (animals without backbones) often are used in studies of learning and memory (Krasne; Sokolov; Rowell). The neuronal circuitry of Pleurobranchaea (a carnivorous sea mollusk) has been worked out in great and elegant detail (Davis). The interactive role of neurons and hormones in the determination of a creature's behavior can be seen from research with Aplysia, a marine creature commonly known as the sea hare. Aplysia's eyes put out a hormone that plays a key role in synchronizing the creature's cycle of daily behavior (circadian rhythm) (Strumwasser).

2) Single neurons or bits of brain tissue (explants) can be grown in glass dishes--in culture. Such cultures of neurons or nervous tissue develop normal characteristics of nervous systems--they show usual electrical behavior, and the usual response to drugs. The study of such readily accessible neuronal preparations not only could lead to a better understanding of the basic neuronal mechanisms underlying learning and memory, but it also could lead to new drugs and treatments for human clinical use (Nelson; Mandel; Seil & Leiman).

III. A MORE DETAILED REPORT OF THE CONFERENCE PAPERS

A. Information from the Study of Brain Injury, Lesions, Etc.

1) Damaged human brains. The brain, just as with any other part of the body, can be damaged by a wide variety of causes: Accidents such as cerebral stroke or a blow to the head; diseases such as a brain tumor or infection by herpes simplex virus; habits such as excessive alcoholism; and surgery such as removal of tumorous tissue. All can lead to general or specific damage to parts of the brain. Sometimes, these brain lesions may impair the individual's ability to learn and to remember. Amnesia--the inability to remember--often is observed in such brain-damaged individuals. Actually, there are several kinds of amnesia, each yielding a specific behavior of non-remembering (Rozin).

One of the more common forms of human amnesias seen in hospitals is called Korsakoff's syndrome; it occurs in severe alcoholics and is associated with damage to the mammillary bodies that are connected to the hippocampus (Signoret & Lhermitte).

The two main goals of investigating the effects of brain damage on memory are:

a) To study the way in which pathology breaks apart memory function, in order to understand how memory processing occurs in the brain, and to provide evidence relevant to psychological models of memory function.

b) To assign particular memory functions to different parts of the brain or different systems within the brain.

Determining such relationships could be clinically useful in the rehabilitation of brain-damaged individuals at any age, and particularly in the treatment of both brain-damaged children and of oldsters with declining memories.

These goals are most fully realized in studies of the amnesic syndromes. These disorders are characterized by preservation of immediate memories (roughly the last 30 seconds of experience--short-term memory) with inability to remember prior recent events (long-term memory). The syndromes suggest a dissociation between short- and long-term memories, a distinction already made on the basis of other evidence by psychologists. The symptoms may result from faulty storage of new information and/or a deficit in retrieval of information. Amnesic syndromes probably result from bilateral damage to any of the structures in the "Papez Circuit," especially the hippocampus or mammillary bodies.

Other lesions in humans can produce other dissociations of normal memory processes, including preservation of long-term memories with short-term memory severely compromised; severe damage to perceptual systems with corresponding memory systems intact, or interference (frontal lesions) with planning and monitoring aspects of memory.

2) Split-Brain research. The human brain consists of two hemispheres--right and left--connected by bundles of neurons called commissures. The largest of these commissures is called the corpus callosum. It may be thought of as a bridge that carries electrical signals between the two hemispheres. Thus, valuable studies can be performed on people who have separated hemispheres--either naturally from birth because of a developmental defect, or through severance of the corpus callosum by surgery.

A few humans who suffer from severe epilepsy have had surgery to cut the corpus callosum to ease their epileptic attacks. It now has been found that it is not necessary to cut the corpus callosum completely to help in epilepsy. Experiments with humans with a severed corpus callosum reveal that the left hemisphere and the right hemisphere are quite different in the way they process information--the left hemisphere deals with numerical information and language, while the right hemisphere deals with spatial information. Thus, in testing, the right hemisphere responds faster to images, while the left hemisphere responds faster to words.

Hemispheric experiments also can be conducted with humans who do not have a severed corpus callosum. If administered into a carotid artery on one side, the sedative sodium amytal has the ability to knock out one of the brain hemispheres for a short period of time, and to leave the other hemisphere intact and functioning. So, while under the influence of sodium amytal in which the left hemisphere has been knocked out temporarily, the patient is given a spoon to feel. Obviously, this information gets into the functioning right hemisphere, but not into the left hemisphere. When the patient comes out of this temporary anesthesia he is asked, "What object did I give you?" The left hemisphere, which answers with words, is unaware of the spoon, and the patient answers, "You gave me nothing."

But, if you show the patient a picture of a number of objects, among which is the spoon, his left hand (controlled by the right hemisphere) immediately points to the spoon. Obviously, the information that he had held the spoon was in his right hemisphere, and in a different form than it would have been had it been in the left hemisphere.

Such experiments suggest that the brain does have discrete localized areas that function specifically with respect to certain aspects of learning and memory. If these specific areas are destroyed or temporarily knocked out then there is interference with the learning and memory functions (Gazzaniga).

This conclusion appears to conflict with that drawn from a study of surgically produced brain lesions in animals (see Isaacson). This discrepancy cannot be attributed to differences between human and animal brains, because hemispherical experiments with split-brain animals also show that a memory can be located within one of the two brain hemispheres.

3) Surgical lesions of the brain. A long-standing dispute involves the argument whether memory is stored in a specific place in the brain, or whether it is distributed throughout the brain. Those who favor the idea that memory lies in a specific brain location point to the fact that there are specific areas in the brain devoted to sight, to speech, to touch, to taste, to smell, etc. Why not a specific region devoted to memory?

Those who argue against a specific seat for memory in the brain point out that surgically one can remove a great deal of the brain and yet memory remains. This and similar surgical studies have convinced some that a very complex phenomenon, such as learning or memory, is distributed throughout the brain; memory is not a "thing" that is "stored" (Isaacson).

The usual experimental techniques in this field involve training an animal to perform a task, and then surgically introducing a lesion into a specific region of the animal's brain. After the animal recovers from surgery, it is retested to see how well it can perform the task as compared to how well it did before surgery. Such experiments must be viewed with great caution, because they may not at all be pertinent to a study of memory. The brain lesions simply may lead post-surgically to different responses of the animal to its environment and should not be mistaken for measures in changes of memory (Isaacson).

Surgically produced brain lesions, no matter how discrete, can cause changes elsewhere in the brain's biochemistry and anatomy. The brain of the animal after surgery is not equivalent to its brain before surgery (Lynch).

No matter where the surgical lesion is produced in the brain, there seems to be no interference with the ability to pick up information (Isaacson). The problem is in the retrieval of information, particularly that information that already was in the brain before surgery. This points to a direction for clinical research that is directed towards helping the retrieval of information. Such research may be useful to human patients who have suffered damage to some part of their brain. Yet, certain losses in memory are associated with the cutting of the corpus callosum (see Gazzaniga).

B. Behavioral Studies

1) Models of memory and learning. To make a model of a phenomenon, one must at least understand some of the broad principles upon which that phenomenon rests. Thus, although some scientists challenge this interpretation, there is evidence that suggests that the phenomenon of human memory is made up of two parts:

a) Short-term memory (STM): Over a short period of time, a few small pieces of information--chunks--can be picked up. But the brain cannot retain them if the individual then is subjected to diversions and interruptions.

b) Long-term memory (LTM): Over a long period of time, an unlimited amount of information--numerous chunks--can be picked up and retained for an unlimited length of time even in the face of diversions and interruptions.

But, if STM and LTM are valid observations concerning human memory, then what kind of model can be proposed to explain them? Postulated models range all the way from those that attempt to describe highly specific chemical and electrical events that occur at the synapses of neurons, to broadly general, hypothetical flow diagrams composed of "black boxes" and connecting arrows. A good review of neural modelling is presented (Arbib).

As in other fields of science, models and flow diagrams are a dime-a-dozen. Their value lies in whether they can be tested by experiment, and if they can, can they then predict some result that at present is not observed. And these tests and predictions often are difficult to attain in neurophysiology. Needless to say, any model that explains remembering also must be able to explain forgetting--the possibility of losing information out of LTM.

It may be premature to expect any success from such modelling, since some scientists believe that the bases for the modelling--that there are multiple memory stores such as STM and LTM--are invalid. The other problem with models is that they are broad, generalized, universal statements, whereas each human operates his memory strategies on a specific, individual basis (Riley).

Just as chemists the world over really do not have to understand the minute details of quantum mechanics to react hydrogen and nitrogen to produce enormous quantities of ammonia for fertilizer, information processing psychologists do not have to understand the molecular events at a synapse to come up with a model for human memory. A complex phenomenon, such as human memory, often needs multiple explanations at different levels of detail (Simon).

A proposed model for human memory postulates two varieties of memory:

a) Recognition memory--the recognition of familiar stimuli;

b) Semantic memory--the storage of information.

If semantic memory is thought of as the memory "textbook," then recognition memory represents the "index." This model is based upon observations of memory in humans and may not relate directly to neurophysiological mechanisms (Simon).

To illustrate just one of the difficulties in trying to make a neural model of human memory, consider the problem of the time-scale. Although it may take a human years to perfect learning of a skill, this has to be explained on the basis of electrical impulses in neurons that last only on the order of milliseconds (Arbib).

2) Electroconvulsive shock. As mentioned above, a great deal of evidence suggests--but does not prove--that there are at least two kinds of memory: short-term memory (STM) and long-term memory (LTM). This belief indicates that when we first acquire a piece of new information, the storage of that information is unstable for a short time (STM). Only after a passage of time does that information become a stable "part" of our memory (LTM). Because STM is unstable it can be knocked out and be prevented from turning into LTM. Anesthesia and electroconvulsive shock (ECS) are two agents that can disrupt and bar the transition from STM to LTM. Thus, treatment of a human with ECS will produce a loss of memory of those events that immediately preceded the ECS treatment.

Experiments consist of training an animal to do a task, and then at a short time after training, to give the animal an ECS treatment. The animal then is tested again--usually a few days later--to see how much of its training it remembers as compared to similar animals that did not receive the ECS treatment. If the idea is valid that there is an original STM that over the passage of time becomes transformed into a LTM, then the longer the time-interval between training and the giving of the ECS, the better the animal should remember its training. This, indeed, is observed (McGaugh).

At one time it was thought that the time that elapsed between an animal learning a task and having the memory of that task consolidated into its LTM was a constant time-interval that could be determined by experiment. But this search has turned out to be futile. There is no evidence for this time-interval being a constant; it varies with many factors such as the particular learning task, and the species and strain of the experimental animal. It was suggested that experiments that try to determine such a constant from ECS research should be abandoned (McGaugh; Chorover).

Incidentally, there is no good understanding of what goes on in the brain--at the level of the individual neurons--when an electroconvulsive shock is passed through a brain.

3) Criticisms of experimental approaches to learning and memory. Ethology (the study of how animals under the selection pressures of evolution have adapted their behavior) cautions the experimentalist with animals that he always must keep in mind the way those animals live in their natural environments. Both laboratory and field observations must be considered. Different kinds of animals learn different things better than other animals, depending upon the way they lead their lives as a result of their evolutionary development. Cats do not respond to color, but to brightness; honeybees, unlike humans, do respond to ultraviolet light. One is not so sure that there is such a thing as "universal behavior" if one watches such diverse creatures as honeybees, rats, racoons, and robins (Manning).

Criticism also was voiced that many psychological experiments with animals to study learning and memory are contrived laboratory situations that may bear no relationship as to how such animals behave in their natural, wild state (Eisenstein). And it was deplored that the lack of valid theories of how animals learn leads to attempts to specify "learning" by definition. "... one must be careful to avoid the impression that a phenomenon has been explained simply because the level of discourse has been changed" (Rescorla).

These definitions of learning are arbitrary and often impose restrictions that then hinder the construction of a theory.

Anecdotes and field studies are interesting, but do they add anything to an understanding of learning? (Rescorla).

How experiments in learning and memory are carried out and evaluated also is of importance. There is a controversy in the scientific literature as to whether associative learning is an all-or-none phenomenon, or does it grow gradually and cumulatively? Evidence indicates that how the scientist measures an animal's response, and how the data are evaluated and tested, will determine which of the two points of view is supported. It is concluded, "In view of the impact such methodological variables may have on the results obtained, it may be necessary to temper the finality of any conclusions drawn from many learning experiments with the knowledge that the results may be due to many variables, only some of which are related to the central nervous system processes underlying learning" (Eisenstein).

4) Sleep and learning and memory. In spite of Aldous Huxley and the techniques he described in BRAVE NEW WORLD, there is no evidence of hypnopedy--that humans can learn while they are asleep.

The evidence does suggest that a distinct stage of sleep called paradoxical sleep or rapid-eye-movement (REM) sleep, seems to enhance learning and memory. Thus, if a rat was trained to perform a task and then slept with some of its sleep time spent as REM sleep, then the rat retained its ability to perform its task better than if it slept after training with no REM sleep (Bloch).

It may be that consolidation of memory (conversion of STM to LTM) is favored during REM sleep. It is of interest that a great deal of REM sleep occurs during human infancy--precisely the time of great development of learning and memory (Bloch; Campbell). On the other hand, infantile amnesia--the inability to recall specific isolated events that took place before the age of 3-4 years--ends at just about the time that adult levels of REM sleep begin to develop. So, the attainment of adult levels of REM sleep somehow is associated with the establishment of memory in the young human.

5) Learning and memory studies in a field setting. A problem in the western United States is the complaint of sheepherders that coyotes

make off with their lambs. Such complaints frequently are coupled with demands to destroy the coyotes.

There is a chance, however, that scientists may be able to work out a sheepherder-coyote detente in which coyotes, lambs, and sheepherders all could coexist.

If a coyote is fed lamb meat tainted with lithium chloride, the chemical makes the coyote violently ill after feeding. After such experience, the coyote will not attack a lamb. It will run up to a lamb, sniff it, and then walk away. Similarly, LiCl treatment of rabbit meat will make a coyote ill and it then will not attack rabbits--at least, for a while (Garcia).

Presumably, if sheepherders put out baits with LiCl-tainted lamb meat, the coyotes that ate the bait would retch and henceforth avoid lambs. And such lamb-avoidance behavior also would be taught to the coyote pups.

The preliminary evidence suggests that once a coyote has been trained to avoid lamb he does not return to his old lamb-devouring days. But he may re-establish his taste for rabbit meat. Some species of animals could not be trained in this manner. Thus, even when rats were fed LiCl-tainted mouse meat, and became violently ill, they still would attack and kill mice. And it was difficult to condition red-tailed hawks to avoid any prey (Garcia).

This experimental research in a field setting offers the practical hope to save the lives of some endangered animal species.

C. Developmental Studies

1) Studies of infantile amnesia. One of the perplexing aspects of human development is that few of us can remember any of the events that took place in our life before the age of 3-4 years. All of us suffer from this infantile amnesia--the inability to recall specific, isolated events that occurred a few years after birth. Yet, this is precisely the time of a human's life when he is undergoing a period of tremendous learning. Research indicates that rats, in their few weeks after birth, also show infantile amnesia (Campbell).

One interesting result of such experimentation with rats is that the younger a rat is at the time it learns something, the more likely it is for the rat to forget. Thus, two groups of rats--one aged 18 days, and the other aged 35 days--are trained to perform a task. After the passage of time, the two groups of rats are tested to see how well they remember the task. The rats who were 35 days at the time of training remember far better than do the rats that were 18 days old at training. Hamsters, which are born at a more mature stage of development, do not show such a difference in memory. So it is probably immaturity of the brain that causes infantile amnesia--in both human babies and rat pups.

2) Maturation of the nervous system. Studies in kittens and cats show that as the feline nervous system matures--from birth to an adult animal--the fine structures (spines, protuberances) of both the presynaptic and postsynaptic membranes increase, and their forms often undergo changes in shape (Scheibel & Scheibel).

3) Studies with newborn rats. Newborn rats cannot locomote. But about the third day after birth, while lying prone, they can begin to pivot their bodies while foraging for the mother rat's nipples. Their pivoting motions are not random, but orient them so that they point toward the nest.

It turns out that a rat acquires most of the cerebellum and hippocampus of its brain after birth. If the head of a newborn rat pup is irradiated with low-level x-rays, then the formation of its cerebellum and hippocampus is prevented. Such x-irradiated rat pups pivot much more randomly than do normal rat pups; their ability to point in the direction of the nest is impaired. Apparently, the maturation of the cerebellum and the hippocampus are necessary for the development of the rat's learning the ability to orient toward its nest (Altman).

D. Brain Plasticity, Learning and Memory

1) Microelectrodes inserted into single neurons. An important series of experiments involving the insertion of microelectrodes into single brain cells has been carried out with mammals such as cats and monkeys. These experiments may have profound implications not only for better understanding of the development of the human brain, but also for the education of humans.

When a single neuron becomes active, it fires--it generates an electrical signal. This can be detected by the insertion of a microelectrode. Microelectrodes inserted into single neurons in the visual cortex--the part of the brain that has to do with vision--reveal that a specific neuron will fire when the animal sees a specific visual pattern. A neuron may fire if the specific visual stimulus is one of a specific movement, or color, or contrast, or shape, or position. Thus, there are certain visual neurons in a kitten's brain that fire only when the kitten's eyes see a horizontal line; others fire when a vertical line is seen, and there are other neurons that fire only when they see a line at a specific angle, inclined in a particular direction between the horizontal and the vertical. Thus, the appearance of objects that the kitten sees is determined by the firing of specific neurons in its visual cortex. These neurons fire when they see the lines that make up the overall appearance of that object (Pettigrew; Spinelli).

In addition, it has been found in cats that the normal development of brain cells in the visual system of the cortex of the mature cat depends upon what the cat saw as a kitten between the age of three weeks to three months. This is a critical period during which the kitten's brain still is plastic in its development. Beyond this critical period, there is little change of the kitten's brain in response to the environment.

We do not know why this critical moldable period of a kitten's brain ends at age three months.

Is there a similar critical period for the human brain? If there is, when does it occur--between birth and four years? Are there particularly sensitive periods when the human youngster easily could learn a language? Or music? We do not know, but obviously our understanding of such critical periods could be of great importance in the education of humans.

The importance of the critical period in a kitten's life is seen from an experiment in which kittens are reared in total darkness. As little as one hour exposure to light at the age of four weeks will insure that the mature cat's visual neurons are normally developed for responding to certain stimuli.

A kitten reared during its critical period in an environment where it sees only horizontal stripes will grow to a mature cat with neurons in the the visual cortex of its brain that can only detect horizontal lines. Such a cat can jump easily onto the horizontal seat of a chair, but keeps on bumping into the chair's vertical legs.

Conversely, a kitten reared during its critical period in an environment solely of vertical lines will mature into a cat with neurons in the visual cortex of its brain that can only detect vertical lines. Such a cat easily can maneuver around a chair's vertical legs, but makes no attempt whatever to jump onto the horizontal seat of a chair.

A similar critical and plastic period for development of the neurons in the visual cortex also seems to exist for humans. This could be of clinical importance in the correction of such early life vision problems as strabismus (cross-eyes) and astigmatism (blurred focus in a specific direction).

Rabbits, however, seem to have visual neurons that are not as plastic as those of cats. This may be due to the fact that rabbit is a prey animal--it cannot afford to have too much of its neuronal organization dependent upon its postnatal experiences because the rabbit must be able to respond to its environment soon after birth. A cat, however, as a predator animal can afford the luxury of needing the time for outside experiences to help mold the organization of its neurons.

It is thought that the kitten is born with both genetically wired neurons and with naive visual neurons that are broadly tuned to respond to all visual stimuli. But as a common visual pattern occurs again and again in its early environment, some of the originally naive visual neurons become sharply tuned to that particular pattern to the exclusion of other patterns. Under the influence of the environment, specific neurons make specific connections to other neurons. This leads to an astonishing correlationship between what the cat sees with its eyes and what neurons fire in its brain (Pettigrew; Spinelli).

There are some data that suggest that the development of the kitten's visual neurons during the critical period is associated with an increase in the number of synapses--the connections between neurons.

2) Correlation of development of behavioral abilities with changes in brain anatomy. Before one can detect whether changes in brain anatomy take place as a result of learning, it would be of interest to see how known changes that are deliberately caused in a nervous system appear at the level of the electron microscope. Such changes can be brought about by surgically cutting either a peripheral neuron (a neuron that is outside of the brain, as in a bundle of nerves called a ganglion) or a central neuron (a neuron in the brain). The course of events after surgery can be followed using the electron microscope (Raisman).

A neuron is an oddly shaped cell in that it has numerous hair-like projections sticking out from it. The longest of these neuronal projections is called an axon. It is the end tip of the axon of a neuron that forms one side of a synapse (the presynaptic side) and it is the next neuron, on the other side of the synapse, that forms the postsynaptic side.

It is found (in adult rats) that if the axon of a peripheral neuron is cut, it will regenerate itself in a few months, the time increasing with the length involved. Three things are observed during this regenerative process:

a) The postsynaptic side of the synapse--on the neuron to which the cut axon originally was connected--survives and does not deteriorate;

b) The original axon regenerates and grows back to once again form the presynaptic side of the synapse;

c) The regeneration reestablishes the status quo; no new synapses are formed, and the old synapse is re-formed.

But central neurons behave differently. If an axon of a central neuron is cut it does not regenerate. Four things are observed:

a) As with the cutting of the axon of a peripheral neuron, the postsynaptic side of the synapse survives and does not deteriorate;

b) Instead of the cut axon regenerating and regrowing toward the synapse, an axon from another adjacent neuron develops a sprout and unites with the surviving postsynaptic side to form a new synapse. So, the new synapse is functionally different because a different axon has grown back. Rather than regeneration, this process is called reclamation.

c) The reclamation process is very efficient; no vacated postsynaptic sides of a synapse are left free;

d) Again, no de novo synapses are formed; the old synapse is reconstituted with a different axon.

If these experiments apply to humans, they suggest that even in an adult, the synapses of the neurons of the brain are not completely fixed, but enough pliancy remains to reclaim vacated synapses. Such knowledge may be useful in the future in the treatment of patients with trauma of the brain.

The question remains as to whether a process similar to reclamation of neurons in the brain--the shifting of axons from one postsynaptic site to another--takes place when we learn. We do not know.

What goes on in the brain, anatomically, when an animal or human learns? There are experiments that support the use-disuse hypothesis, which states that learning comes about through the establishment of new connections between neurons or through the strengthening of existing connections. Both the axons of neurons and other hair-like projections called dendrites are involved in the establishment of interneuronal connections or synapses. Repeated use of these synapses leads to a good memory. If the synapses are not used, then the memory wanes. Thus, as an animal learns a task, its neurons should form new connections by growths branching off their dendrites and their axons. This, indeed, is claimed to be observed in the brains of cats as seen at the level of the optical microscope (Rutledge).

The idea that a synapse changes as it is used repeatedly in a network of interconnected neurons first was proposed at the end of the 19th century, and was brought back into prominence in the late 1940s by Hebb. There are biophysical and mathematical studies that indicate that synapses do operate as Hebb postulated (Cowan).

Work with both hamsters and rats suggests that growth of neurons and the formation of new synapses may be involved in learning and memory (Moore; Greenough). This raises the intriguing question: If the growth of fibers of a neuron is involved in learning and memory, is the regression of fibers of a neuron involved in forgetting?

Although the answer to this question is not known, it is obvious that neurons are much more complex than originally thought. The picture of a neuron that emerges from the above research is not that of the static, two-dimensional object depicted in textbooks, but that a neuron is a very dynamically changing, three-dimensional object with proteins being produced and streaming down its axon, sprouts and spines forming and degenerating, etc.

At the level of research with the whole animal, striking differences in brain structure and function are found if groups of animals (mainly rodents, thus far) are exposed to three different environments:

a) enriched environment, where the animals can experience numerous and diverse stimuli;

b) standard environments, where the animals have the usual laboratory stimuli;

c) impoverished environments, where the animals receive few stimuli.

Remarkable differences develop in brain anatomy, neural biochemistry, brain electrical activity, and behavior among the three groups (Greenough; Bennett).

Animals reared in enriched environments, as compared to animals reared in impoverished environments, show a number of differential behavior and brain effects:

a) Different behavior--they can better learn to perform certain tasks;

b) Increased weights of their brain cortex due to actual increased growth of cortical tissue because of growth of individual cells--with increases seen in the amount of total protein, RNA, and dry weight of brain. The RNA/DNA ratio goes up because as the size of an individual neuron increases, its amount of RNA increases, while its amount of DNA remains the same.

c) Increased thickness of the brain cortex, with more dendritic branches, and more glial cells.

d) Increased amounts of specific enzymes indicative of greater neuronal activity.

e) There is good evidence that the synapses--areas where neurons connect one to another--grow larger in the brains of animals reared in an enriched environment.

Unlike critical early periods of development, these differential effects can develop at any age and are not restricted only to young animals.

In attempts to understand and isolate some of the factors operating in enriched environments some experiments now are being performed in "super-enriched" environments, and in a more "natural" outdoor environment--a 30 x 30-foot dirt-filled area that even gives the animals the opportunity to burrow underground.

It is not known whether the observed changes seen in animals raised in enriched environments have anything to do with learning and memory. But, if they do, and if such rodent experiments also apply to humans, then these results could be significant for society's approach to human education and development.

E. Biochemistry and Memory

1) Memory and the synthesis of proteins and m-RNA. The tremendous success of research in molecular biology in the last few decades was based upon discovery of the fact that the information of heredity was

both stored and expressed as giant molecules--stored as nucleic acids and expressed as proteins.

This knowledge led many scientists to speculate and experiment as to whether the information involved in learning and memory was also stored and expressed as giant molecules.

Although this does not seem to be the case, a great deal of biochemical research has been carried out to see if one could detect what was going on inside neurons when an animal learned and laid down a memory. Were there specific chemical changes that occur in the brain after an animal has had a learning experience?

Many scientists feel that we will not understand the basis of human memory until we understand the biochemical changes that take place in the formation of memory. Since proteins are giant molecules made up of amino acid subunits, one popular method used in such research is to give an animal an injection of a radioactive amino acid, and to follow the injection with a learning experience. Presumably, if learning is associated with an increase in protein synthesis in neurons, then the radioactive amino acid will be incorporated into any new protein the neuron produces as a result of learning.

For example, rats raised in the dark for 50 days were given an injection of radioactive lysine and then were exposed to light for the first time. About 1-3 hours after exposure to the light, the neurons of those areas of the nervous system and brain that are involved in vision--the retina, the lateral geniculate, and the visual cortex--show an increase in the radioactivity of the proteins they contain. The experiments, however, are qualified with the caution that "... to have shown that the enhanced synthesis of certain proteins is a necessary correlate of learning does not ... prove that it is sufficient ..." (Rose).

To understand some of the research carried out in the investigation of the biochemistry of learning and memory, one must understand some of the basic principles of molecular biology.

A neuron in the brain, like all other cell types, contains a nucleus inside of which is deoxyribonucleic acid (DNA), the nucleic acid that carries the information of heredity. Just as a protein is a giant molecule made up of amino acid subunits, DNA is a giant molecule made up of subunits called nucleotides. A string of several hundred nucleotides constitutes a unit of heredity called a gene. And, essentially, DNA is a string of genes (each made of several hundred nucleotides) that carries information that the cell uses to produce proteins. Proteins are not produced directly from the information contained in the DNA-genes, but are produced from "second-hand" information in the form of messenger-ribonucleic acid (m-RNA). The m-RNA is produced from the DNA. This DNA to m-RNA to protein conversion involves many steps, but essentially the operating sequence in a cell is as follows: the information contained in the DNA-genes is copied to form an m-RNA that then is used to produce a protein.

A dogma of memory research is that there are at least two memories: Information first is taken in as an unstable short-term memory (STM) that with the passage of time changes into a long-term memory (LTM). It has been thought by some that in order for a short-term memory (STM) to be converted into a long-term memory (LTM), the cell must produce protein. Thus, if an animal is taught a task and then is injected with certain antibiotics that inhibit the synthesis of protein, or the synthesis of messenger-RNA, then the change from STM to LTM should be prevented. After injection with these antibiotics, the animal should develop an amnesia and not remember what it recently learned.

This, indeed, was observed and reported. But research, particularly with the antibiotic actinomycin-D, suggests that the observed amnesia may not be due to specific inhibition of m-RNA synthesis but is probably due to some general damage to the neurons brought about by the antibiotic. This indicates that all ideas to improve human memory based upon drugs that stimulate protein or RNA synthesis are premature, since there is no definite proof that either protein or RNA synthesis is directly involved in the formation of memory. In spite of a great deal of work concerned with the relationship of RNA synthesis and protein synthesis to memory, it is concluded, "At present, the exact role of RNA and its relationship to electrophysiological events of learning and to memory-related protein synthesis remains obscure" (Flood & Jarvik).

Some newly developed drugs such as anisomycin and camptothecin may provide new research opportunities in this important area of research. Camptothecin, in particular, is a relatively non-toxic, reversible inhibitor of RNA synthesis (Flood & Jarvik). And anisomycin seems to be less toxic as a protein synthesis inhibitor than is cycloheximide. There is some evidence that cycloheximide affects memory not because it is a protein synthesis inhibitor, but because it somehow blocks the retrieval of information already stored in the memory (Quartermain).

It is well known from molecular biology that one way that protein synthesis can increase in a cell is that the cell produces an increase in the synthesis of messenger-RNA. It is the information contained in the messenger-RNA that permits the cell's ribosomes to turn out proteins.

Thus, it is no surprise that a great deal of research has reported that learning in an animal is accompanied by an increased synthesis of RNA in its neurons. But the RNA connection to memory is far from clear and will require further research to clarify. Recent studies indicate that most of the RNA (70 percent) in the brain is of a type known as ribosomal-RNA and is not useful in providing information for the synthesis of proteins as does messenger-RNA. In addition, even if there is a short-term increase in RNA in brain neurons, most of the RNA produced is of a type called heterogeneous nuclear RNA--and its precise biological function is unknown.

And very recent research indicates that although the injected radioactivity (radioactive amino acids) is indeed incorporated into brain cell protein, an equivalent or larger increase, as a result of training, is seen in the liver (Dunn). Since the stimulation of the training experience is sufficient to produce these effects, it appears that increased protein synthesis in the brain following injection of radioactive amino acids could be due to a general response to the stress of the injection. And, indeed, if an animal that has not had a learning experience is injected with adrenocorticotrophic hormone (ACTH)--a hormone released in response to stress--the animal shows an increased incorporation of radioactivity in both brain and liver.

So, it may be that what were considered to be specific changes in proteins taking place in the brain as a result of learning, perhaps may only be general chemical changes as a response to stress.

Can drugs improve memory? A great many experiments have been carried out to see how drugs can influence the acquisition, or the retention, or the retrieval of information (Quartermain). It has been demonstrated that drugs such as strychnine and picrotoxin, under special circumstances, can improve the memories of animals. As yet there has been little research of this sort with human subjects, and no clear evidence has been obtained, but the possibility of positive findings is by no means excluded (Flood & Jarvik).

There also is the problem of forgetting. Suppose a drug is given to an animal and it appears to wipe out the animal's memory. But, frequently, the animal's memory comes back later. Then, one may ask, what really did take place in the brain during the initial episode when the memory appeared to be lost? We do not know as yet.

2) Hormones and the brain. Hormones are chemical messengers. They are molecules--proteins, steroids, or phenols--produced by certain glands in one part of the body. These hormone molecules then travel through the blood stream to affect another part or other parts of the body.

A review of how the development of the brain and the nervous system is affected by hormones was presented (Greenough). The development of the brain is profoundly influenced by the presence of certain hormones at specific times. Thus, the absence of thyroxin during pregnancy can give rise to mentally retarded individuals who suffe rom a syndrome called cretinism. Short exposure of the basal forebrai undle region to testosterone in the prenatal or postnatal period will determine the adult sexual behavior of that individual. And an anima that is subjected to stress in early life is better able to cope with stress in adult life, because the early exposure to stress conditions releases a series of hormones involved in overcoming the effects of stress. In the case of Aplysia, a marine mollusk, it is the release of a hormone that determines when the creature lays its eggs (Strumwasser).

Memory may be greatly influenced by a wide variety of hormones that are released during emotional (affective) states such as anxiety, fear, anger, hunger, pleasure, etc. Although there is no definite evidence at present, it is possible that these released hormones could affect crucial and specific numbers of neurons in the cortex, or the cerebellum, or the hippocampus. The consolidation of a memory of a particular behavior that preceded and accompanied the emotional state could be enhanced or impaired by the hormonal release.

Hormones, perhaps, could exert these effects on neurons through their enhancement or impairment of the neuron's protein synthesis systems (Kety). It is known, for example, that injection of adrenocorticotrophic hormone (ACTH) into a rat results in enhanced synthesis of protein but not of RNA in both brain and liver cells (Dunn). ACTH is a hormone released in response to stress.

F. Learning and Memory Studies with "Simpler" Systems

1) Studies with invertebrates. Since 95 percent of animal species are invertebrates, it is not surprising that some of these animals have been selected as experimental creatures to study learning and memory. There are conveniences and advantages to the use of invertebrates in such studies. The central nervous systems of certain invertebrates are relatively simple--thousands of neurons compared to the billions of neurons in the central nervous system of a mammal. The brain of an octopus, however, is as complicated as that of some mammals. And some invertebrates have large neurons--up to half a millimeter in diameter--that make the neurons convenient for experimentation (such as the insertion of electrodes). There has been criticism of the use of some invertebrates to study learning and memory just because they are convenient to work with. The criticism is along the lines of the story of the drunk who loses his car keys on a darkened street, but searches for them under a lamp post a block away because that is where the light is.

The actual selection of which creatures to use in the study of learning and memory oftentimes may have little to do with their learning ability. Thus, "simple" animals that learn are not necessarily useful physiological preparations. A whole host of factors enters into the selection of a creature to study its learning and memory processes: availability, cost of getting it and maintaining it, its generation time, and what is known about it biologically. Sometimes animals are chosen because it is easier to attract research funds, as is the case with insects that are crop pests or disease vectors. The size and visibility of its nervous tissues also may determine whether the animal is a useful experimental subject (Rowell).

In spite of such criticisms and limitations, there are many invertebrates that are capable of learning. Hermit crabs and honeybees can learn to distinguish colors. And studies have been made on the specifically learned behavior of earthworms, planaria (flatworms), snails and crayfish (Krasne; Sokolov).

The neural behavior of Pleurobranchaea, a carnivorous sea mollusk, has been studied elegantly and in great detail (Davis). The complete neural network of the mollusk has been isolated and individual neurons have been identified that specifically fire when the creature shows specific behavior. It has been established that some aspects of the behavior of pleurobranchaea follow a pattern of priorities that must be determined by genetics--by predetermined, non-pliant, "hard-wired" neuronal circuits. In addition, this snail has a well-developed capacity for learning, as shown by extensive experiments on classical conditioning, avoidance conditioning, and taste aversion learning. All of these forms of learning involve the feeding system, which can be made accessible to neurophysiological study (Davis).

Work with Aplysia, a marine mollusk known commonly as the sea hare, shows that there are neurons in the abdomen (called bag cells) that put out a protein hormone that controls the creature's egg-laying. Aplysia, like all eukaryotic animals (organisms that have nuclei in their cells), shows a daily (circadian) rhythm. It has a built-in oscillator or clock that controls the animal's functions on a 24-hour basis. But it is unknown how the output of the circadian oscillator in Aplysia--or any other organism--is coupled to the animal's behavior. There is evidence that the eyes of Aplysia play a key role in synchronizing the circadian rhythm. There apparently is a hormone released from neurons in the creature's eyes that then travels to a cluster of neurons (ganglion) in the abdomen and stimulates them (Strumwasser).

2) Cultures of single neurons and neuronal tissue. Because an animal's brain is an exceedingly complex structure, scientists have turned to studies of simpler preparations of nervous systems--studies of individual neurons grown in culture, or pieces of brain tissue grown in tissue culture. The study of such simpler preparations could give us clues about the development and function of the more complex integrated nervous system of the human brain.

Single neurons can be isolated, and after a few weeks growth in culture they develop into moderately complex networks of neurons. These neurons show many of the properties of mature differentiated neurons in a brain--they respond similarly to chemicals, they produce similar electrical signals, and if glial cells also are placed in the culture, the axons of the neurons also become covered with an outer sheath of the fatty material called myelin. The cells form an extensive network by developing interconnections or synapses among themselves. If muscle cells are grown in culture, and individual neurons are added, the two types of cells will organize themselves as they do in the body--a neuron will form a synapse--a neuromuscular junction to a muscle cell (Nelson).

Similar cultures can be prepared from explants--fragments of brain tissue (Mandel; Seil & Leiman). One can study these tissues themselves--how much oxygen they consume, what enzymes they produce--or one can look at the responses of these cell cultures to specifically controlled changes in the environment: how they react to the addition of drugs such as morphine or monoamineoxidase (MAO) inhibitors (Mandel).

One of the more interesting results of this tissue culture work is that as an explant grows it retains the form and nature of the original brain tissue from which it came. Thus, if a piece of tissue from the cerebellum of a newborn mouse is grown in culture, then weeks later the increased growth of tissue is organized into networks that closely resemble the neural network of an intact cerebellum. And the same is true for the growth of an explant of the cerebral cortex; its organization resembles that of an intact cerebral cortex (Seil & Leiman).

This work suggests that the cerebellum and the cerebrum are structurally different in their organization of neurons, and that these differences are maintained in the growth of explants. Other evidence indicates there may be plasticity in the functioning of the brain, and in details of the neural circuits, although the basic structural neuronal pattern of the brain is predetermined, under genetic control.

Not only does a growing cerebral neocortical explant look like neocortex, but it also behaves like isolated cortex with a low level of spontaneous electrical activity. Similarly, a growing cerebellar explant behaves like a cerebellum with a high level of self-produced electrical activity (Seil & Leiman).

Thus, neural tissue culture involving both single cells and explants appears to be a promising research technique in the study of learning and memory. Such readily accessible neuronal preparations not only could lead to a better understanding of basic neuronal mechanisms underlying learning and memory, but they also could lead to new drugs and treatments for human clinical use.

CONFERENCE SUMMARY

Mark R. Rosenzweig

Introduction

Can we use some of the varied advice we have received during the Conference in order to help us remember the material of the Conference itself? If we consider the findings on paradoxical sleep presented by the last participant, Vincent Bloch, perhaps a good sleep would be advisable at this time. On the other hand, some of the psychologists of learning tell us that repetition is the best way to guarantee memory. Perhaps then what you should do now is to read rather rapidly the summaries of each of the papers in this volume. But considering that procedure reminds me of what happened with one of the students on our campus toward the end of this last quarter. Working hard right down to the end of the quarter, a student was asked in class by the professor, "What's the difference between ignorance and apathy?" And the student drawled back, "I don't know and I don't care."

Other investigators assure us that memory is favored when material is processed, when it is grouped into easily recognized chunks. Let us therefore identify some of the main themes--some explicit and some implicit--that occurred in several of the papers. Some themes were stated in similar or complementary form by several participants; other themes are topics of divergence or even dissension among investigators. Let us highlight several of these main themes of the Conference, noting some of the progress, some of the problems, and some of the prospects in this area.

Persistence and Change in Problems and Approaches

Early Research: The Golden Decade

Paul Rozin started the Conference by pointing out some enduring themes that arose during what he called the Golden Decade of memory research, beginning in 1882. The first contribution he mentioned was Ribot's book on the Diseases of Memory; then came Hughling Jackson's concept of levels of function of the nervous system and behavioral hierarchies in 1884; Ebbinghaus's important work, the first experimental measurements of memory, in 1885; Korsakoff's paper in 1889; and that decade ended with William James' great book, the Principles of Psychology, 1890, ith its important chapters on memory.

That was a Golden Decade, but it seems to me that the next decade was almost equally fruitful. In the 1890s and the first years of the present century, investigators started to bear down upon problems of learning and memory, to find how to work on some of the principles that had been stated and how to attack them experimentally. Right at the beginning of that next decade, in 1891, there was the enunciation of the neuron

*From Chapter 40, Neural mechanisms of learning and memory (MIT Press, in press).

doctrine, which had been proved by Cajal's work. Just two years later, Tanzi, an Italian neurologist, pointed out that very likely in learning plastic changes would be found to be taking place at the junctions between neurons. These junctions didn't even have a name yet, but a little later in that same decade, Sherrington in his chapter in Foster's Neurophysiology (1887) gave the junctions the name "synapse." Sherrington also stated that the synapse was likely to be strategic for learning. He put it in this picturesque way:

> Shut off from all opportunity 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).

Concerning the experimental attack on learning, 1898 was the date of Thorndike's important work on animal learning, to be followed shortly, but quite independently, by Pavlov's work on conditioning. In 1900 Müller and Pilzecker published an important book on studies on verbal memory, following up Ebbinghaus's work. In the course of that book, they put foward what they called the perseveration-consolidation hypothesis which has engendered so much work since then. That is, they suggested that once activity was started up in the nervous system the activity boiled around for awhile, perseverated, and this led to consolidation of a stable memory trace. In reviewing that book the next year, William McDougall pointed out that this hypothesis might very well account for retrograde amnesia following a blow to the head; the blow would prevent the information from circulating and so prevent consolidation from taking place. McDougall commented on how important this book was from the point of view of human verbal learning and also for possible insights about what happens in the nervous system during learning. In fact, McDougall wrote that it was unfortunate that Müller and Pilzecker didn't spend more of their time on the neural events; their ideas were so good that they should have pushed ahead further and wrapped up the questions of neural events during learning. With hindsight we can see that McDougall, like Tanzi, was expecting things to happen too rapidly.

At the end of the Silver Decade of memory research, in 1902 Shepard I. Franz put out his first article in which he brought together two techniques, the new technique he learned from Thorndike of training animals and the technique of making experimental brain lesions. He brought these together to see the effects on learning and memory of interfering with brain processes. That, of course, set the stage for all of the interesting studies presented at this Conference on effects of manipulation of the central nervous system on learning and memory--not only the varied effects of brain lesions that Robert Isaacson reviewed and that Gary Lynch discussed, but also the striking effects of drugs presented by James Flood and Murray Jarvik and by David Quartermain, and the noteworthy effects of electrical stimulation of the brain on memory that James McGaugh and Paul Gold reviewed and that were discussed by Stephan Chorover and Vincent Bloch.

When Paul Rozin reviewed his Golden Decade, he asked what has been accomplished since then, and we can now ask the same question about the twenty-year period that ended in 1902. Rozin found a great increase in detailed knowledge over the succeeding years but without a corresponding increase in theoretical approaches. But this Conference indicates that things have been improving recently. Let us review a few areas in which there has been a great deal of activity, quite a bit of progress, and some new problems. It seems to me that both psychology and neurology, which were the disciplines that were originally concerned with learning and memory, have really made extensive progress as reflected in the chapters of our volume. Detailed and powerful methods of experimental psychology and information processing have provided not only descriptions but also penetrating analyses of the processes of learning and memory. Methods have been devised for the study of animal behavior that have also turned out to be helpful in studying human behavior. Consider, for example, the progress made by applying such methods to split-brain patients and to preverbal children. Having learned to communicate with animals that couldn't talk, we can now communicate with very young children and find out about their cognitive processes. And, of course, some methods that were elaborated to study human behavior have proved to be extremely effective with animals, as Al Riley pointed out in his chapter. Also, as Robert Rescorla and Peter Holland have shown, the concepts of learning have been generalized and freed from restricted definitions that used to hem them in. Nevertheless, it is clear that there are plenty of basic problems that remain on the level of behavioral analysis of memory.

One of the controversies that was taken up here concerns whether there really are multiple memory stores, as Herbert Simon holds, or whether, as Riley maintains, the duration of memory depends on the level of processing, there being really only one kind of store. Rozin presented and discussed findings bearing on this issue, pointing out that patients such as H. M. may not be restricted to short-term memory, provided certain cuing techniques are employed. Clearly this is a critical area for further research.

The Entry of New Disciplines

New disciplines have joined those that originally shared this area, and that has been a big part of the history of research on learning and memory in the last thirty years or so. Electrophysiology is a prominent example. In the 1940s it looked as though electrophysiological research might provide the key to unlock the secrets of memory. That didn't prove to be correct then, but now we are finding refined techniques of intra-cellular recording becoming a major tool, as the reports of Davis, of Krasne, of Eisenstein, and of Sokolov have testified. But, of course, as some of the speakers pointed out, on the electrophysiological level, too, there are still basic problems. What is the nature of accomodation? What is really meant by rebound? What is the link between the axon potential and the release of the synaptic transmitter? Anatomists have also contributed immensely valuable techniques and talents. For one thing, neuroanatomy has become quantitative. Recall the 1959 book of Bok, the Dutch neuroanatomist. In the foreword to that book Bok pointed out that just as civilization progressed historically from astrology to astronomy, so he hoped that we would get from histology to histonomy, and he entitled his book "Histonomy." Bok didn't receive much attention at that time, but anatomy has been growing more quantitative ever since. I might note, too, that we have had the Psychonomic Society since 1959.

Through the techniques of quantitative neuroanatomy as well as of neurochemistry, it has become clear that training and enriched experience bring about many significant changes in the brain. This was demonstrated in the reviews of Bill Greenough and Les Rutledge and in Ed Bennett's discussion. Bennett and Greenough showed that simply placing rats for a few days or weeks in differential environments (enriched or impoverished) leads to significant changes in their brains. Among these changes are differences in activities of brain enzymes, amounts of nucleic acids, weights of parts of the brain, and aspects of neural circuitry including branching of dendrites, numbers of dendritic spines, and sizes of synaptic contacts. Other work, too, is showing that the brain is much more plastic anatomically than would have been supposed a dozen years ago. Striking evidence for this plasticity is found in the chapters by Moore, Raisman, and Lynch. They report the sprouting of new neuronal contacts when tracts of brain fibers are cut or when tissue is implanted in the brain. Reports of measurable changes in the brain as consequences of experience--reports that seemed startling and controversial when we first announced them in early 1960s--have now been generally accepted. Subsequent reports of neural sprouting and formation of new contacts in the brains of even adult animals, while not obtained in learning situations, nevertheless demonstrate capacities for plasticity that may well underlie learning. Moreover, work cited here and research in progress indicate that functional changes in neural connections may occur rapidly enough to encode long-term memories.

Electron microscopy is now finally permitting work on the synapse of the sort that Tanzi had called for in 1893. But in this and other attempts to do quantitative neuroanatomy, the detailed work remains prohibitive and breakthroughs are needed. There have been important recent advances in staining techniques and intracellular dyes, but still much staining remains a "cookbook" affair. (A rather special contribution of electron microscopy has been evidence for the homunculus!--see Rozin's postscript.)

Biochemists have also entered the fray, becoming interested in recent years in learning and memory. They can analyze now for specific materials in very small samples of tissue, in some cases even single cells. But the chapters of Rose, Hambley, and Haywood, and of Dunn have revealed unsolved problems of identifying and interpreting the biochemical changes that occur with experience. Some of these problems are caused by the multiplicity of cellular components, and some occur because the grain of the analyses still remains too coarse to identify specific proteins involved. Edward Bennett suggested in conversation at the Conference an attractive analogy that consolidation of long-term memory is something like the development of the new Polaroid color film; a process gets under way, goes through a number of steps, and you see the picture becoming clearer and clearer, changing colors, until eventually it reaches the final state and it is fixed for all time. There are a number of aspects about this analogy that make it attractive. It is clear that there must be a succession of chemical steps involved. Also one can trigger off these processes immediately after the picture is taken, which is usually the case, or it is possible to prevent this from occurring and to have the development take place later on. Flood and Jarvik gave evidence here indicating that there can be a delay in some of the consolidation processes. For example, if certain inhibitors of protein synthesis are given, the consolidation process, or at least certain biochemical processes necessary for long-term memory, can be delayed up to hours and then take place later on. What initiates these processes may well be a chemical trigger, as Adrian Dunn and David Quartermain discussed. Similar concepts, although phrased in terms of arousal of affective state, were offered by Jim McGaugh and Paul Gold and by Seymour Kety. But then again, as Rose pointed out, it may be oversimple to think of any linear sequence of biochemical stages that would be possible to account for all of the aspects of memory consolidation.

In the reports of Manning, Garcia and Levine, and Rowell we learned about work of ethologists and zoologists who are determining the place of learning in the life of diverse species of animals. If, as it is sometimes said, there is one best species to study any research problem, then there are millions of species whose behavior needs careful scrutiny. Are there some ethological principles that could help us here? What kinds of ethological niches favor the development of ability for rapid and powerful learning? On the other hand, are there sorts of ethological niches that make learning a dispensable luxury and plasticity unnecessary?

While new disciplines and techniques are brought to bear, older techniques have come under question. Thus Bob Isaacson in his review raised doubts about the value of experimental brain lesions for the study of memory, and Gary Lynch added further criticism of this technique in his discussion. Isaacson concluded "that no type of brain damage yet studied has produced deficits in information storage mechanisms." This is not to deny that brain lesions cause impairment on tests of memory but rather to point out that the deficits are likely to reflect other processes than storage of information. Thus some lesions alter perception and thereby interfere with retrieval, while others affect the ability of animals to stop reponding to stimuli as they could do preoperatively. Lynch showed that even localized lesions cause widespread biochemical and morphological reactions in the brain, so that changes in behavior may involve quite different regions from those lesioned. In spite of these cautions, such participants as Rozin, Signoret and Lhermitte, and Gazzaniga drew far-reaching conclusions about mechanisms of memory storage from the study of brains damaged by disease or by surgical intervention. Have the results and implications of detailed experimental studies based on animal subjects failed to reach the clinical investigators? Are those who deal with brain-injured human beings less critical than the experimenters with animal subjects? This seems doubtful, especially since researchers such as Gazzaniga and Rozin conduct experimental studies with animals as well as with human subjects. Furthermore, Rozin and Gazzaniga drew upon results of animal experiments as well as upon studies of patients, and Isaacson cited some results of research on human subjects. Was the conclusion of Isaacson unduly pessimistic? Unfortunately the reports on effects of brain damage in human subjects were scheduled for the initial session of the Conference, while those on studies of brain lesions in animals came four days later, and a direct confrontation of views was not demanded. Thus, although we have cogent reviews and discussions of research in this area, we do not have a full critical evaluation of the two approaches in terms of each other.

With the entry of many disciplines into this field of research, the types of preparations that are being studied have also grown in diversity. Consider the variety of subjects or preparations discussed in the papers of this Conference. These range from normal adult human beings (Simon) to cultures of nerve cells (Mandel; Nelson and Christian). Other subjects include human beings with various forms of brain damage or disease (Rozin; Signoret and Lhermitte) and persons in whom the corpus callosum has been severed, creating a split brain (Gazzaniga). Normal mammals are studied under field conditions (Manning; Garcia) and under laboratory conditions (Rescorla; McGaugh and Gold; Flood and Jarvik; Riley; Greenough; Bennett). Mammals with a variety of brain lesions are investigated (Isaacson) and are compared with certain types of brain-lesioned human beings. Invertebrates of many species are being studied for the relative simplicity of their nervous systems (Krasne), and in many cases, still further simplification is obtained by working with only portions of the nervous system (Davis; Eisenstein; Sokolov; Strumwasser). Portions of the nervous system are grown in culture and studied in terms of their anatomical development and electrical activity (Seil and Leiman). Extending this scale, or perhaps off in another dimension, are the artificial brains of the neural modellers (Arbib, Kilmer, and Spinelli; Cowan). This is a challenging new approach, even if its application to learning is premature, as Arbib and his colleagues suggested, but on the other hand the reports of Arbib *et al.* and Cowan indicated that was probably an overmodest evaluation.

Unity or Diversity?

This impressive variety of subjects and neural preparations may reflect in part the determination to sample widely the phenomena of learning and memory throughout the animal kingdom. But beyond the desire for representative sampling, the variety of subjects studied reflects two opposed theoretical approaches: On the one hand, there is the assumption of basic unity of processes underlying learning and memory. From this point of view, whatever is learned from study of one kind of preparation will apply to all others, and therefore the clearest, most readily analyzed example should be studied. On the other hand, there is the belief that different basic processes will be found to be responsible for learning and memory in different kinds of animal and that a plurality of processes probably occurs in more complex animals. Several participants in this Conference came down strongly on the side of unity and parsimony; these included Davis, Eisenstein, Gazzaniga, and Krasne. Thus Krasne stated, "Indeed, it is entirely possible that the nervous system is highly parsimonious in its use of plastic processes and that but a single kind of persistent and input-inducible functional change in nerve cells is utilized for all types of learning." The moral for Krasne is to study these processes in invertebrates. Certainly some discoveries made with invertebrates have later been shown to be true for vertebrates as well. For example, synapses where transmission is electrical rather than chemical were first demonstrated in invertebrates but are now an active subject of research in vertebrates. On a behavioral level, the concept of central programming of motor functions, first worked out with reference to invertebrates, was later found useful in regard to understanding of mammalian behavior. Perhaps the same route will be followed in the study of learning and memory. But Gazzaniga, although also a proponent of unity, took the opposite point of view: "... it is my guess that the opportunities for real insights in the biology of memory are best obtained at this time by considering clinical and human experimental data." Other participants took issue with the assumption of the unitary nature of learning. For example, recall this statement of Seymour Kety:

> "I have always been more impressed with the prolific diversity of nature, and the unity of memory processes, like the unity of biochemistry, seems to be something of an oversimplification...
>
> "So profound and powerful an adaptation as learning or memory is not apt to rest upon a single modality. Rather, I suspect that advantage has been taken of every opportunity that evolution has provided. 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 neurotransmitter, hormone or metabolic process that plays upon the nervous system and was found to subserve a learning process has been preserved and incorporated.
>
> "Invertebrate learning has much to teach us, especially since it can be studied more rigorously than the processes that occur in the mammalian brain. We must be aware, however, that it may give us only one part of a remarkable concert of memory processes that are possible and which have come into play in nervous systems of greater complexity and with more varied behavioral options."

So important and basic a theme as unity vs. diversity of basic processes involved in learning and memory was not, of course, resolved at this Conference. But you will find cogent statements on both sides in these papers, and you will also find much data with which to evaluate the claims made on both sides.

Age as a Variable

As well as species of subject, age is another variable considered here. Byron Campbell and Xenia Coulter reviewed the intriguing problem of "infantile amnesia"--why children can't recall events from their first few years even though they are clearly learning at the time. Rats are also poor at recall during their early weeks, even though they learn simple material as rapidly as do adults. Guinea pigs, which unlike the rat are born relatively mature, do not show deficits of early memory. Thus, it appears that capacities for learning and for memory show different rates of development, and this may provide useful clues to determining the neural mechanisms involved in learning and memory. The Scheibels point to early anatomical changes in neural circuits that could provide a basis for memory storage. Altman and Bulut considered types of impairment that can be inflicted upon the developing nervous system; they also explored behavioral tests that can be employed to measure the capacities of very young rodents.

Shared Assumptions--and Limitations

Certain widely shared presumptions may limit or restrict research at any given time. Such prevailing views undoubtedly exist even at a Conference like this one where many disciplines and points of view were represented. It is not easy to identify such presumptions, since they often go unstated and form an accepted common ground, but let me try to indicate one. (The reader may perceive others, and more will undoubtedly be seen later by hindsight.) I refer to the implicit assumption in many papers that THE problem of the neural basis of learning and memory is how information can be stored in neural terms. In other words, what is the form of the engram? An equally important problem is how stored information can be retrieved, in terms of neural processes. This may well be a more difficult problem than that of storage, especially since few investigators have addressed the question or seem to have a handle on it. A few of the participants did consider or allude to the problem of retrieval--Rozin and Arbib et al. What happens in neural terms when information cannot be retrieved on one occasion, although it can on a subsequent occasion? If we knew perhaps we could uncover rich stores of hidden memories.

Multidisciplinary Research--Problems and Potentialities

The contribution of many disciplines to this research has meant a powerful and multipronged attack. But it is not without its own problems. Many of us do benefit in our research from techniques developed in sister disciplines, but there is usually a time lag in such borrowings, and sometimes one field will be using techniques that have been superseded in another. The group that gathered for this Conference was obviously a select group of researchers in its willingness to cohabit for a week to try to teach each other, and perhaps even to learn. But even here there have been some traces I think of nervousness and unease, some cases of clear misunderstandings of each other. The friendly interaction and informal exchanges have, I think, been helpful to clear the air. Some of these problems between disciplines can be alleviated by the understanding that many of us are really working at different levels of analysis, as Herbert Simon expressed so clearly in his paper. To quote just one sentence, "In this world there is need for chemistry as well as physics, biology as well as chemistry, and information processing psychology as well as physiological psychology." Solving problems at one level does not necessarily solve them at another, although it should provide help and encouragement.

One of the bywords of the Conference--John Garcia was the person to introduce it--was that most researchers early learn their own song, like the Oregon junco, and are then incapable of learning any other song and maybe even any other dialect. Hopefully, part of the result of conferences such as this one will be to encourage further interdisciplinary collaboration. Several members of our group already do move easily among different levels and disciplines. It seems to me that in reading some of the chapters of the Conference, it is rather hard to tell whether the author is a psychologist, a zoologist, or a physiologist. If many of these types of learning can interact within one skull, this is obviously advantageous. We might think too towards the training of students who will be capable of fruitful interdisciplinary exchange as well as having a firm basis in their own discipline; that is, how can we help to prepare investigators who will join the chorus as well as singing in their own song? This may be a tall order, but it is vital; as Hallowell Davis put it at another meeting, "We're down on what we're not up on."

Levels of Analysis

Several of the disciplines represented here work at different levels of analysis. This suggests that a useful alternative way to summarize or at least to outline the themes of this Conference is in terms of the levels of the phenomena being considered and the scope or precision of the questions being asked. As Herbert Simon pointed out in his paper, "There are numerous examples in modern science of the need for multiple explanations of complex phenomena at different levels of fineness of detail." Arnold Leiman and I have prepared Table 1 (pp. 42-43) which attempts to indicate some of the levels of analysis employed at this Conference, from purely behavioral descriptions of learning and memory to the study of synaptic plasticity in cultures of nerve cells. Along with each level are shown typical questions being asked and the names of some participants who took up questions at the various levels. Like most classificatory schemes, this one relies on individual judgments, and different but equally useful alternatives could undoubtedly be prepared. This is probably not exactly the table that Simon could have drawn up, nor may all those named agree with their location in the table, but the scheme may be helpful to the reader and it can be used to bring out certain features that have not yet been commented upon, as well as to reinforce other points that have already been mentioned.

It appears that the fullest available treatments are at the top level, behavioral descriptions. Most individuals restrict their work to a single

Table 1

Levels of Analysis of Learning and Memory

and the Neural Processes Involved

For each level, the table shows some investigators and also typical questions studied.

A. Behavioral Descriptions of Learning and Memory
(Rescorla & Holland; Manning; Garcia & Levine; Riley)

How do learning and memory occur? That is, what are adequate formal descriptions of stimulus conditions or manipulations under which learning occurs? What are the typologies of behaviors that allow us to infer learning and memory?

What rules relate changes of behavior to stimuli and to the events intervening between presentations of stimuli?

How do adaptive specializations that have occurred during evolution constrain or limit learning and memory? Can an ethological analysis of the behavior of a particular species in its environmental niche lead us to predict features of its learning and memory, including novel or unusual forms of adaptiveness?

B. Formal System Approaches to Learning and Memory (Block Diagrams)
(Simon; Riley; Arbib et al.; Cowan)

What hypothetical processes could account for the observed features of learning and memory? The range of efforts extends from rather general descriptions to formal mathematical or network specifications to hardware devices.

C. Molar or General Neural Processes
(Rose et al.; Flood & Jarvik; Dunn; Quartermain; Kety; McGaugh & Gold; Chorover; Bloch)

Are there generalized chemical processes occurring in all or many cells and underlying learning and memory? Are there systemic or regional chemical modifications that mediate learning and memory?

What are the time-dependencies of such processes? (This question also goes under the name of "consolidation of memory.")

Similar questions are asked about molar anatomical and electrophysiological events that may encode memories.

(Table 1 cont.)

D. Regional Localization of Neural Processes Involved in Learning and Memory (Rozin; Signoret & Lhermitte; Gazzaniga; Isaacson; Lynch; McGaugh & Gold)

Are certain regions of the brain differentially involved in learning and memory? What can be found about regional brain functions in learning and memory from study of brain injury or brain disease in human beings? Are some processes revealed more clearly when the brain is "simplified" or "reduced" by injury? Can tests of learning and memory aid in differential diagnoses of brain injury and in establishing programs of re-education?

Utilizing the advantages of animal experimentation (e.g., precise location of lesions, opportunities for repetitive testing and for control of environment, accurate comparisons with control animals), what can be learned about regional functions of the brain in learning and memory? Can the bases of compensation and recovery after brain lesions be determined?

E. Changes in Synapses and in Neural Circuits as Bases of Learning and Memory (Rutledge; Raisman; Moore; the Scheibels; Greenough; Bennett; Pettigrew)

Can evidence be found for development or changes in complex neural circuits that could underlie memory in adult as well as in young individuals? How can observed neural changes be tested for relations to learning and memory?

F. Use of Simpler Systems for Detailed Study of Neural Processes in Learning and Memory (Krasne; Davis; Rowell; Eisenstein; Sokolov; Strumwasser; Nelson & Christian; Mandel; Seil & Leiman)

Can synaptic changes be identified that account for examples of learning and memory in simpler systems? Can simpler organisms, parts of organisms, or tissue preparations be found in which the synaptic processes underlying learning and memory can be identified exhaustively? Using these simpler systems, can one develop a molecular biology of learning?

G. Study of Learning, Memory, and Neural Changes in Developing Subjects (Campbell & Coulter; Altman & Bulut; Greenough; Bennett; the Scheibels; Seil & Leiman; Pettigrew; Spinelli)

This is not a separate level of analysis but represents a different approach which can be studied at a number of levels including behavioral, regional, network, and cellular.

Can a developmental perspective help to solve questions about neural processes involved in learning and memory, either because of the relative simplicity of younger organisms or because asynchronies of growth help to separate out factors that seem to be inextricably entwined in the adult?

level or to adjacent levels of analysis. Simultaneous work is going on relatively independently at the different levels, often with little mutual knowledge or interaction. The long-run goal is to discover the rules or transformations that permit translation from one level of analysis to another. Accomplishing this is as formidable as it is desirable. A major purpose of our Conference and of its publication is to foster and facilitate work in this direction.

PROSPECTS FOR APPLICATION OF RESEARCH ON NEURAL MECHANISMS OF LEARNING & MEMORY*

Mark R. Rosenzweig and Edward L. Bennett

*From Chapter 1, Neural Mechanisms of Learning and Memory, (MIT Press, in press)

Introduction

The chapters of this volume offer a rich and varied panorama of research largely directed toward understanding the biological processes involved in learning and memory. Such basic research is undertaken with the hope, often implicit but amply justified by history, that it will eventually lead to applications that become socially beneficial. As such basic research is pursued, it may supply concepts and techniques that can be applied to problems such as improving classroom teaching and alleviating the difficulties of the retarded, the aphasic, and the senile, and fostering the fullest development of human intellectual potential. To a large degree, of course, responsibility for application is incumbent on those individuals and groups who are keenly aware of specific social problems upon which scientific knowledge needs to be focussed. Becoming aware of current scientific resources, they may be able to select concepts and techniques that will provide a solution. Or, finding the absence of suitable knowledge, they can call attention to the need. The recognition of a need has been a prime factor in achieving outstanding applied advances, according to a recent study, "Interactions of science and technology in the innovative process: Some case studies" (NSF, 1973). We hope, therefore, that this volume will not only aid and encourage basic researchers but that it will also serve as a survey of the state of the art that can be drawn upon for applications and used to find areas where fresh efforts are needed. We already have evidence that the Conference will aid researchers, since some of the participants have told us that their experiences at the meeting have led them to make changes in their research programs. We hope in the longer run to see evidence that the Conference and this volume have led to applications.

What are some specific applications to practical problems of learning and of teaching that may come, sooner or later, from the lines of basic research described in the chapters of this volume? For an overview of the many and varied directions of research, we can describe 7 levels (see also Table 1, pp. 46-47):

A. Behavioral descriptions of learning and memory.
B. Formal system approaches.
C. Molar or general neural processes.
D. Regional localization of neural processes involved in learning and memory.
E. Changes in synapses and neural circuits as bases of learning and memory.
F. Use of simpler systems for detailed study of neural processes in learning and memory.

G. Study of learning, memory, and neural changes in developing subjects.

Let us note some possible applications that may emerge as research is pursued at each of these levels; in many cases, of course, applications will come from joint results at more than one level. Occasionally an application of a research advance may be rather prompt and direct. But the study of major advances shows that they usually involve combinations of specific discoveries made over a span of many years.

Possible Applications of Research at Various Levels

A. Behavioral descriptions of learning and memory

Behavioral studies have shown that learning takes place over a much wider range of circumstances than earlier observers and theorists had supposed. Knowledge of this range can broaden the perspective of researchers and can suggest a greater variety of measures and experimental strategies that may prove useful. For example, in searching for neural correlates and bases of learning and memory (C - F below), it may be better to use simpler behavioral paradigms than the rather complex instrumental learning which has often been employed for this purpose. Our recognition of the diversity of learning situations may enable a closer understanding of the specific rules governing particular forms of information acquisition and storage.

B. Formal system approaches

Where in the human learner are the main limitations or constraints in the amount of information that can be stored or retrieved? This has become a meaningful question and one on which fruitful research has been done since the 1950s when the learner was first conceptualized as an information processing system--one that has identifiable, sequentially arranged components for the initial detection, temporary storage, permanent storage, retrieval, and use of information. Given the limited channel capacity that has been found, how can information be "packaged" better for efficient learning and retrieval? (Research utilizing the information processing approach has demonstrated that much more information can be acquired when it is grouped in "chunks" rather than being presented in small units.) How can a person's time be allocated most efficiently for learning? Since channel capacity is limited and since repetition and depth of analysis favor long-term storage, a major factor in assuring storage may be to motivate the learner to spend sufficient time and effort on the material. Thus the formal system approach may lead to renewed stress upon motivational factors in learning and memory.

C. Molar or general neural processes

What conditions (e.g., diet, health, diseases) favor or impair the general processes that mediate learning and memory? What kinds of intervention (e.g., diet, drugs, general health measures) can improve learning, retention and retrieval?

Since various antibiotics and other drugs are found to impair formation of long-term memory in animal experiments, clinicians should be alerted to the possibility of such effects in therapeutic use of these drugs.

Senile decline of memory and mental retardation that is not caused by disease or birth trauma represent major problems for which no biological correlate has yet been established. A few reports suggest that retardates may be characterized by abnormal dendritic spines or by decreased concentrations of synaptic vesicles. If such neural abnormalities could be established as causes of memory disorders, this would be a first step toward prevention and treatment of retardation and of senility. In the case of hyperkinetic children, a variety of drugs has been employed on an empirical basis in the attempt to improve learning. Again the establishment of the cellular bases of learning and memory could lead to a more rational selection of therapeutic agents.

D. Regional localization of neural processes involved in learning and memory

Can relations be clearly established between damage to certain parts of the brain and certain disorders of learning and memory? If so, then tests of learning and memory can aid in diagnosis of brain damage.

Can particular brain regions important in learning and memory be shown to be susceptible to certain deleterious agents? This appears to be true in a few cases (e.g., Korsakoff's syndrome resulting from damage to mammillary bodies due to lack of vitamin B in alcoholism; impairment of formation of long-term memory in cases of hippocampal lesions caused by herpes encephalitis). Designation of such specific regional effects can help to focus research on prevention and therapy for such damage.

E. Changes in synapses and neural circuits as bases of learning and memory

Research done at the molar level (C above) could be made sharper and more productive if we could establish the detailed processes underlying learning and memory. Just as research and application in the area of public health was greatly advanced when the germ theory of infection was established, so we can expect major advances in research on learning and memory when we have discovered the detailed cellular bases of these phenomena.

F. Use of simpler systems for detailed study of neural processes in learning and memory

In relation to the statement in the paragraph above (E), it may well be true that the cellular processes underlying learning and memory can be identified and studied more exhaustively in simpler organisms, in parts of organisms, or in tissue preparations rather than in intact complex mammals. Just as work with the bacterium E. coli is the basis for modern understanding of hereditary mechanisms in human beings as well as in all living beings, so some researchers in this area hope to make fundamental contributions to understanding of learning and memory through their studies of simpler systems.

G. Study of learning, memory, and neural changes in developing subjects

Research with developing subjects may help to solve questions about neural processes involved in learning and memory, and the answers found may in turn help to aid the education of children. For example, there have been many hypotheses to attempt to account for the paucity of memories of early childhood--"infantile amnesia"--for a period at which the child is clearly learning a great deal. Now research with animals has demonstrated that the immature brain learns quickly but also forgets quickly; retention requires repetition even more at an early age than later. It remains to determine what aspects of neural immaturity are related to poor retention, and animal studies can furnish this knowledge. At least it is already clear that neural immaturity is responsible for infantile amnesia, rather than other hypothesized factors such as lack of verbal facility or repression of infantile personality trauma. Therefore it should be possible to apply this knowledge to the scheduling of learning tasks in relation to age and also to the planning of training for the early childhood years.

The Relevance of Research with Animal Subjects

Since social concerns with learning and memory have to do with problems of human learners, it may be asked why many researchers work with animal subjects and how this may be relevant to human questions. A glance at the history of research on learning and memory shows not only that almost from the beginning there has been an interpenetration of research with human and animal subjects but also that many of the most influential concepts about human learning and many of the most useful experimental techniques have come from the animal laboratory. Thus the classical conditioning of Pavlov was based on animal research and was applied to study and theorizing about human behavior. This provided some of the main support for the influential school of behaviorism (1913-). Subsequently the work of Skinner and others on operant conditioning of animals (1938-) led to reinterpretation of many aspects of human behavior; it is also one of the pillars of the effective techniques of behavior modification. The persistent efforts of experimental psychologists to study the perceptions of non-verbal animals led to elaboration of powerful techniques that have been employed in the last decade to study the perception of the preverbal child. By use of these techniques, the infant has been discovered to be a more active and keener perceiver than his limited motor capacities had led us to suppose.

The attempts to teach systems of communication to chimpanzees have led to revised concepts about language and to unexpected aid for aphasic patients. Since chimps do not have the vocal structures necessary for speech, experimenters in the last decade have taught them manual sign language (the Gardners) or the use of arbitrary colored shapes as symbols (Premack). The success of the animals and their growing levels of competence and abstraction have met many of the criteria established for language behavior. Those who wish to maintain distinctions between human and animal ability are being forced to look more closely at language and to establish new criteria. As an unexpected by-product of this research, the artificial language devised by Premack for the chimp has been found useful to permit several aphasic patients to re-establish communication (Glass, Gazzaniga, and Premack, 1973).

Techniques developed to study human behavior have also been usefully applied to animal subjects. Thus the principle of the Békésy audiometer has been applied by Blough and others to the study of sensory thresholds of animals. Riley showed at this Conference how experimental designs worked out for human experimentation are being employed to test the occurrence of selective attention in animal subjects.

Undoubtedly the interpenetration of human and animal research will continue, to the enrichment of both. This is one of the implications of the Darwinian revolution that began over a century ago and whose fruits we are still reaping.

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