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Review : purported memory and/or learning enhancers in the mentally retarded

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REVIEW: PURPORTED MEMORY AND / OR
LEARNING ENHANCERS IN THE MENTALLY RETARDED

by

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Review: Purported Memory and/or Learning
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The idea of a drug which could increase an individual's ability to learn and to remember has been a favorite of investigators for several years. The concept of a "smart pill" is not only fascinating because of its scientific potential but it is also a noble idea for increasing the capabilities of the mentally retarded. The agents which make up the area of memory and learning enhancers have been subject to much experimentation and criticism. It is my intention, in this review, to discuss some of the more prominent purported memory and learning enhancers with relation to the new biochemical concepts of memory and learning. This review will be limited to the discussion of glutamic acid, the amphetamines, and the newer agents, magnesium pemoline and RNA.

Glutamic acid

Glutamic acid was one of the first agents which was thought to have actual effects on an individual's intellectual ability. The known physiological effects of glutamic acid (i.e., its role in protein and carbohydrate metabolism, its ability to remove NH_3 from the system, and its necessity for cell growth) have given way to newer possible connections to intellectual enhancement.

The initial work giving glutamic acid a role in neural functioning was done by Weil-Malherbe (1936). Zimmerman and Ross (1944) showed the possible effects of glutamic acid on learning behavior in white rats. Later studies with glutamic acid have shown positive effects on animal learning, intelligence, and personality in retarded, psychoneurotic, and normal individuals. Other studies have revealed suppression of abnormal electroencephalograph phenomena and control of epilepsy with glutamic acid.

The greatest problem facing the evaluation of this agent--and other agents--is the lack of well-controlled studies. The review by Astin and Ross (1960) attempted to consolidate all previous work with glutamic acid and to evaluate its effect on retarded intelligence. They concluded that the original studies that they reviewed revealed no statistically positive results because of the failure of these studies to use proper control groups. Vogel, Broverman, Draguns, and Klaiber (1966) disputed the conclusions of Astin and Ross and challenged them on their methodology. They focused mainly on 1) the characteristics of subject samples used in the studies reported as positive versus negative results, 2) the manner of administration of glutamic acid, 3) placebo effects, and 4) the environment of the patients. Vogel, Broverman, Draguns, and Klaiber (1966) found that, considering all studies before 1960 dealing with glutamic acid, there was a correlation between the use of control groups and the resultant positivity or negativity of the studies.

In reviewing the subject samples, Vogel (1966) found there was a tendency to get more positive results with glutamic acid with non-institutionalized patients. This tendency was statistically significant with $p < 0.01$. They postulated that institutionalized patients would be used by workers desiring a more uniform group, whereas non-institutionalized patients would be used where more promising patients were desired. They also found that the studies which yielded positive results tended to emphasize responses to glutamic acid with regard to diagnostic categories of retardation, whereas the negative studies tended to ignore this segmental approach.

Another area of discrepancy lies within the administration of glutamic acid. One of the accepted methods presently employed is the individualization of dosages. This technique is to start at low dosages, increase to noticeable toxicity, then lower slightly to achieve a maximum therapeutic effect. Vogel (1966) found that the studies that did vary their dosages tended to get positive results, whereas the groups who used the same dosages tended to get negative results. This was statistically significant with $p < 0.01$.

The parameter of the use of glutamic acid versus glutamate salts was also investigated. The authors reviewed a study by Pond and Pond (1951) which demonstrated that the salt increased epileptic activity whereas the free acid tended to decrease epileptic activity. The authors found no studies

which reported positive results with the use of glutamate salts. They described a study by Albert, Hoch, and Waelsch (1951) in which ten mental retardates were treated with glutamic acid with positive results. The drug was then discontinued and they were started on glutamate for several months without further positive results. Unfortunately, it is studies such as this which have formed the basis for much of our accepted drug research.

It was noted in the intellectual assessment of the patient that in twenty-five of thirty-one positive studies, evaluation was accomplished by clinical methods, (i.e., increased mental activity, alertness, spontaneity, and motivation). The negative studies tended to employ more "blind" testing procedures. The authors condemn the use of the usual study design for patient evaluation. This involves the use of the study group and a control group, both given the same testing devices. Each are then placed on the drug or placebo for a period of time and then retested with similar testing devices. They feel this is inadequate because they believe learning is a product of experience, reward, and exposure. The patient will not show a higher score if he received or encountered no exposure during the time of the study. The authors believe that the best chance for an increase in intellectual function exists where glutamic acid is employed in on-going classroom or training situations. The authors, from their review of all previous glutamic acid studies, stated that they believe no

good study has yet been done. They concluded with, "The application of both methodological rigor and clinical sophistication is required in any psychological research venture; it is clear that the two have not been combined in any optimum balance in the history of the investigation of the effects of glutamic acid upon mental retardation."

Other studies have indicated that if any positive result from glutamic acid did not come from increasing intelligence, it may be from effects which are related to intellectual performance. These include cerebral stimulation, anti-fatigue factors, and increased perception and awareness. This brings up, perhaps, the most notable of agents thought to work in this manner--the amphetamines.

Amphetamines, caffeine, and Deaner

The use of amphetamines and caffeine as stimulants is well known. Who has not taken a cup of coffee to take advantage of that late hour before a paper was due? Only the relatively naive college student has never utilized amphetamine-containing capsules at exam time. The question as to whether these agents actually enhance memory and learning or whether they merely act as a stimulant is a long-debated one. Recent work goes back as far as Cattell (1930) who noted that 200 or 400 mg. of caffeine citrate had no effect on intelligence levels or other tests of factual knowledge.

Cutter, Rittle, and Strauss (1940) in a study involving mentally retarded children had equally poor results. They gave the children 5 mg. of amphetamine daily for three months and 7.5 mg. daily for the next three months. Their double-blind study could demonstrate no effect of the medication on intelligence test scores. Another study by Flory and Gilbert (1943) on college students showed that dosages up to 300 mg. of caffeine citrate and 15 mg. of amphetamine sulfate daily had no effects on reading rate, reading comprehension, and vocabulary.

Morris, MacGillvray, and Mathieson (1955) gave amphetamine sulfate to "mentally defective" subjects in the following dosage scheme: 5 mg. daily for one week, 10 mg. daily for one week, and 15 mg. daily for two weeks. They concluded, "It is apparent that treatment with amphetamine does not increase intelligence, learning capacity, speed and accuracy of voluntary attention, fluency, or memory in mental defectives." Laufer and Denhoff (1957) working with hyperkinetic children, found that the favorable effects of amphetamine are to counteract the symptoms of the hyperkinetic syndrome...to maintain attention for longer periods. As for the mentally retarded children, they state that amphetamines, "Will not confer any more intelligence than the child now has...but will allow them to form their intelligence more effectively". Along these lines, Pond (1966) notes that some investigators have reported increased attention to

academic work, stimulation of effort in its accomplishment, and a greater spontaneous interest in schoolroom tasks in children with behavior problems taking amphetamine (Dexedrine). Connors, Eisenburg, and Barcai (1967) in a pre-publication draft found that "...a battery of performance tests derived from an earlier factor analytic study showed reliable increases on a factor thought to effect assertiveness and drive, while a factor primarily measuring intellectual ability was unaffected by the drug".

A recent study by Weiss and Laties (1962) attempted to answer the following questions: 1) can caffeine and the amphetamines actually produce superior performance or do they merely restore to a normal level performance degraded by fatigue, boredom, or other influences?; 2) are the performance-enhancing effects of these drugs counter-balanced by untoward effects? They concluded that caffeine and amphetamine prolong the amount of time during which an individual can perform physically exhausting work, and have proven effects on reaction time, motor control, and coordination. With regard to learning, they state, "Amphetamine seems to hasten conditioning, to restore in part the degraded rate at which a new discrimination is learned by sleepy subjects, and to increase the rate at which subjects acquire proficiency in a motor skill". There is no data on whether these effects are permanent or transient.

A minor purported memory and learning enhancer is 2-dimethyl-aminoethanol (Deaner). This agent was studied by

Clausen, Fineman, Henry, Wohl (1960). Deaner is a precursor to acetylcholine which was reported to increase ones power of concentration, increase ones attention span, and create an affable mood. In their study, they used thirty-six organic mental retardates and four mongoloids. They used Deaner in dosages of 75 mg. daily for four weeks. They concluded that there were no changes attributable to the drug.

The agents reviewed thus far have shown potential as far as enhancing memory and learning but, unfortunately, are probably only effective as stimulants. The work up to now only indicates a need for further work with more detailed investigation with better controlled experiments. I now will discuss some of the more recent theories on memory and learning enhancement, and their possible biochemical basis.

Theories of learning

The mechanism for learning has, perhaps, the greatest diversification of opinions in the field of science. To understand them and to extract concrete information from them, one must not segregate them from each other, but must consider them as logical components of the entire process of learning. The basic ingredients behind most learning theories consist of the components: drive, cue, response, and reenforcement. This means that first there occurs the motivation to learn followed by environmental signals which elicit responses;

retention of the learned stimulus is maintained through reward (or punishment) by reinforcement.

One major area of interest is known as the Gestalt Theory. This was adapted when theorists disagreed with the old notion of studying personality and behavior by its component parts and putting them together to get a true picture. The Gestalt theorists emphasize the unique wholeness and the entirety of the person. They believe that a person's personality and behavior are determined by the environment at the present time, i.e., that the brain is a constantly changing electrical field.

One of the best examples of Gestalt theory is the field theory of Lewin. He believes that behavior is determined by an entire set of internal and external factors which are affecting the person at any one time. Within the person, he sees a perceptual-motor area and an inner-personal area. The perceptual-motor area is not too important for Lewin's learning theory. The inner-personal area, on the other hand, is very significant.

The inner-personal area continually differentiates into cells which correspond to personal facts which exist at any specific time. With increasing age, more cells exist-- corresponding to more personal, psychological facts. These are constantly changing. Also with age, the boundaries between adjacent cells become less permeable. There is less communication between regions in adult life. This means that the adult is capable of more specific, independent thinking.

Interestingly, Lewin explains mental retardation with this theory; that is, whatever causes mental retardation, results in less differentiation of the inner-personal region. The final result is an inner-personal region with a fewer number of cells, but with the same decreased permeability that occurs in the normal adult. This accounts for the rigid, stereotype activity found in mental retardation because there is no influence from the other existing regions.

The Gestalt theory is almost completely contrary to the theory of D.O. Hebb. Whereas the Gestalt theory emphasizes the entire individual at a specific time, Hebb sees the individual as an accumulation of perceptual and conceptual experiences. When a set of sensations is experienced again and again for the same nerve path, a functional unit Hebb calls a "cell assembly" is organized in the brain. Control and organization of the cell assembly occur in the course of repeated excitation. Once concepts have been firmly implanted, they become independent of any specific pathway. Several cell assemblies can be activated with one experience. Hebb places several assemblies in a group called a "phase sequence" which are in turn a part of a larger functional unit, the "phase cycle".

In Hebb's theory, there is a definite relationship between early and later learning. Depending on the phylogenetic scale, learning undergoes changes with age. Since learning utilizes and builds on previous learning, perception is never free from the transfer of previous learning. Early learning is

probably the most important. It is here that perceptual elements are grouped into the basic cell assemblies; these are the foundation for the later learning to build on. Early learning occurs mostly through the eyes, and apparently is not dependent on motivation; it is facilitated by the establishment of new internal connections. In a child, this occurs best when he is presented with a situation in which much is familiar but enough is new to keep his interest. This is the beginning of later learning. If too much new material is presented, the phase sequences cannot adapt easily enough and interest is impaired.

In testing different organisms, it is noted that the higher an animal is on the phylogenetic scale, the slower is its learning in infancy. Generally speaking a man requires nearly twenty years to reach his intellectual maturity, whereas a dog may require only one year. Early learning is considered slow increment learning whereas a dog's learning is "insightful, single-trail, or all-or-none learning". One of the primary differences between a normal child and a mentally retarded child is the slowness in inefficiency with which the mentally retarded child acquires knowledge. Hebb states that mentally retarded children are not impaired in their ability to learn per se, but in those aspects which require a capacity for growth in perceptual and conceptual integration. In a mentally retarded child the strength and number of cell assemblies are reduced and connections between them is impaired. From this it can be reasoned that diseases

which affect the early cell assemblies will cause more retardation than those which affect later assemblies. An infant must have the opportunity for developing its basic assemblies to be able to learn properly in later life. Replacement of the early assemblies is impossible according to Hebb (1949). It has been hypothesized that institutionalized children are more greatly retarded because they do not have enough opportunity for adequate assembly buildup through a variance in sensory experience. When sensory input is lacking, electrical impulses fire diffusely and activate phase sequences which are not usually excited. This has been thought to account for the strange perceptions which occur while in solitary confinement.

What exactly is the structure of Hebb's "cell assemblies"? This is not known. Does it imply that the number of cell assemblies can be increased by an exogenous agent? This, also cannot be answered now. This, however, leads to a discussion of the biochemical aspects of memory and learning and perhaps the ability to increase memory and learning by increasing certain biochemical substrates in the body. This discussion must begin with a discussion of RNA and DNA and the genetic code.

RNA, DNA, and the genetic code

RNA is a complex molecule of purine and pyrimidine nucleotides. When broken into its component parts it

contains nitrogenous bases, ribose groups, and phosphate groups for esterified linkages. RNA differs from DNA only by the presence of an OH group in DNA. The RNA molecule itself is in the shape of a double helix with a right-handed coil around a common axis. Fresco (1960) and Doty (1959) found that not all the nucleotides are included in this structure. Some residues form smaller loops or strands from the main structure (Cavalleri, 1964).

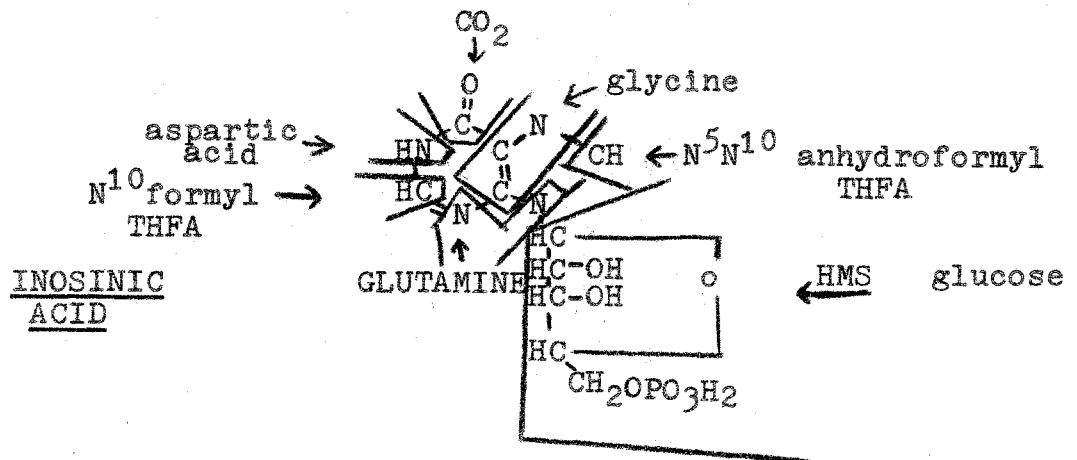
The double helix, itself, is formed by two polynucleotide chains. The chain itself consists of ribose and phosphate groups with purine and pyrimidine bases facing inward. Thus, two chains are connected by hydrogen bonding between the adjacent bases. The helix undergoes one complete turn for every ten bases. The order of the bases on the RNA molecule is thought to be the controlling factor in its synthesis of specific proteins.

Theoretically, DNA is the basic self-replicating molecule. This occurs by breaking of the hydrogen bonds resulting in a single poly-nucleotide chain. Each base on the chain is specific for another base e.g., adenine for uracil and cytosine for guanine. The cell has a pool of bases, sugars, and phosphates from which this single strand draws to form its complement.

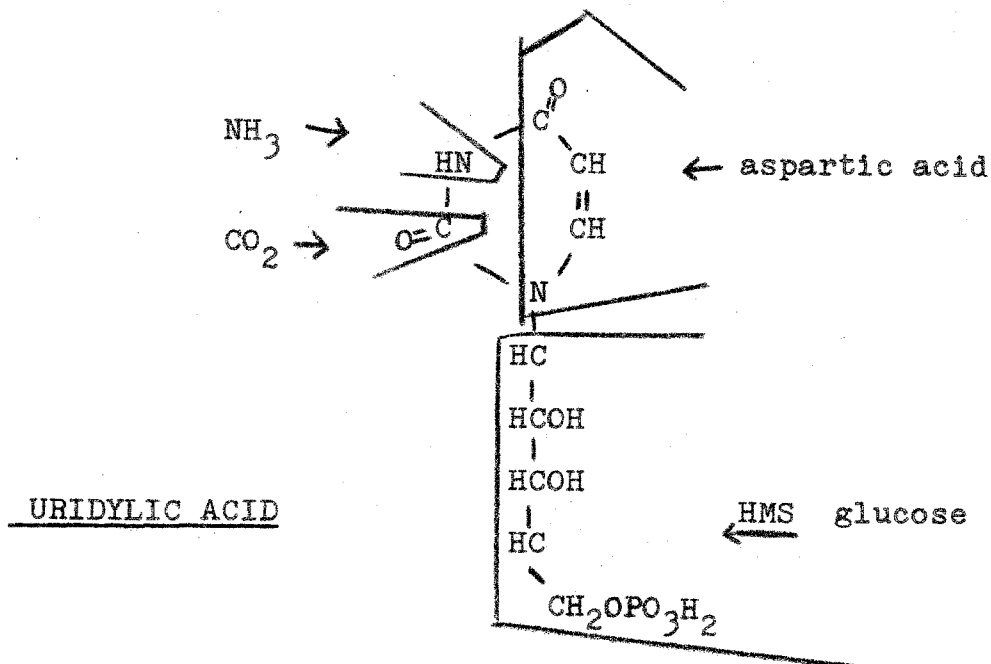
The formation of new molecules of RNA biochemically is very complicated. It can be divided into three main stages: 1) the formation of purine and pyrimidine nucleotides, 2) their phosphorylation to trinucleotides, and 3) their

polymerization to polynucleotides.

The formation of purine and pyrimidine nucleotides can occur two ways: 1) by ingestion of highly cellular foods which contain these bases and/or 2) endogenous biosyntheses. For adenylic and guanylic acid the basic structure is inosinic acid. This is formed as follows:



For cytidylic and uridylic acid the basic structure is uridylic acid. This is formed endogenously as follows:



The purine and pyrimidine nucleotides are phosphorylated by ATP to form the corresponding trinucleotides. These four: ATP, CTP, GTP, and UTP are then reacted by RNA polymerase in an unknown way to form polynucleotides. These may form separate chains or may add on to existing chains.

Since RNA is believed to be the transmitter of the genetic code in protein synthesis, it may be responsible for nearly all aspects of life. Specific enzymes for general metabolism are synthesized using RNA as a template. Enzyme deficiency diseases have begun to be traced to an error in the RNA coding device. The general scheme of protein biosynthesis will be explored below.

RNA exists in the cells in three different states:

1) Nuclear RNA which remains in the nucleus (probably in the nucleolus), 2) m-RNA which is formed by DNA and becomes the template for protein biosynthesis at the site of the ribosome, and 3) s-RNA (t-RNA) which is cytoplasmic RNA which transports amino acids to the ribosome. These interact to form proteins.

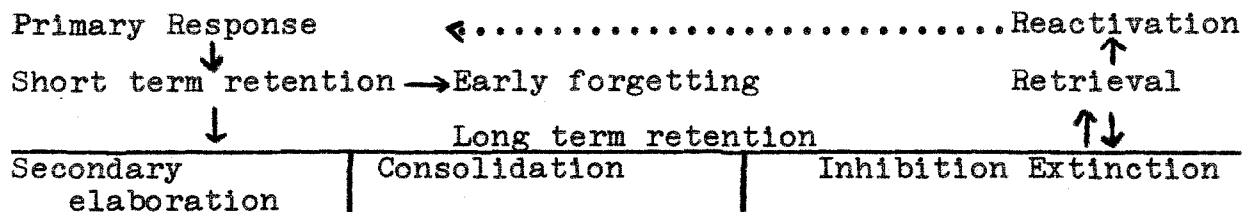
In the nucleus a DNA molecule forms a complement which splits off as m-RNA. This single-stranded chain then attaches itself to a ribosome. The bases are in a specific order on the ribosome and are responsible for the proteins that are synthesized. In the cytoplasm s-RNA picks up a specific amino acid. This mechanism is not clearly understood, but requires the energy found in ATP. The s-RNA then transfers the amino acid to the site of the m-RNA and attaches itself

so that the amino acid is away from the m-RNA. The m-RNA codes for specific molecules of s-RNA which in turn code for specific amino acids. This has been shown because amino acid s-RNA complexes have been isolated and a different amino acid has been put on the complex with no change in site of attachment to m-RNA. This occurs until several amino acids are attached. They then form peptide bonds and are split off as long chains of amino acids. The s-RNA molecules return to the cytoplasmic pool.

The proteins thus formed are determined by the genetic code. This code describes the way in which a sequence of twenty or more things (amino acids) is determined by a sequence of four things of a different type (nitrogenous bases). This code has theoretically been determined as a triplet code. This is called a codon (Crick, 1963). This is a set of three bases which codes for a given amino acid. It could not be a set of two bases because this would only code for sixteen amino acids. Although a codon consists of three specific bases the sequence of these bases can vary; also, there are some sequences which do not code for amino acids at all. Simple variations in the codon can lead to the synthesis of the wrong protein which can cause any number of biological disorders.

The possible role of RNA in memory and/or learning enhancement¹

Not only is RNA thought to be the template for the formation of body proteins but it is also thought to be the substrate for memory. The latter with more reservation than the former. The subject of memory has long been one of darkness with many hidden facets. The idea of registration, retention, and reproduction has been revised for a mechanism drafted in 1964.



Carl Pribram (Gaito, 1966) believes that in order to understand memory we must get away from the idea of storage of information. This old concept leads to the idea of memory having only the quality of duration; memory however, is multi-dimensional. Recognition is an instantaneous event. Also, memory seems to be a two-fold process. Within two hours after a memory impression has been made, it can be completely forgotten; however, if the protein-configuration idea is assumed, some change in configuration must take place during this time. There needs to be a change in neural

1. Only the major or pertinent literature is incorporated into the present discussion and reference list. The minor or less pertinent references are included, for completeness of review, in a special appended reference list.

connectivity to account for a more permanent registration of the memory experience.

Whether or not RNA is the substrate for memory is the significant question. If RNA is the substrate for memory it can then be regarded as intimately connected with learning and performance. Drugs have been used in an attempt to determine the basis of these mechanisms. The problems encountered in these investigations have been whether or not the drugs affect the actual seat of memory and learning, or whether they affect them through indirect effects on the central nervous system. The hypothesis that RNA is the basis of memory and learning has been explored with the use of experimental animals and drugs. Experiments have been conducted along the following lines (Gaito, 1966): 1) Examination of RNA content of various parts of the brain after work requiring memorization; 2) use of agents to prevent protein and RNA synthesis, used both in animals, and humans; 3) use of agents to break down RNA; 4) administration of RNA to animals and humans with pre- and post-administration memory testing; and 5) use of agents to promote RNA synthesis (Table 1).

The RNA used for injection into a human or animal is derived mostly from yeast. DNA and m-RNA are species specific, but t-RNA and r-RNA are believed to be transferrable between species. It is believed that the RNA administered orally or intravenously is broken down quickly, but that its action occurs from stimulation of the synthesis of new RNA.

Most of the past work on administering RNA to humans has

been conducted at the Allen Memorial Institute of Psychiatry on aged patients since 1956 (Cameron, 1961, 1963, 1964). The patients were chosen on a basis of severe memory defect, and those with other psychotic or neurotic problems or recent cerebral accidents were not used. RNA was administered both orally and intravenously, but the oral method was more favorable because the intravenous method produced shock-like side effects. Later in 1963, they developed a greatly improved solution which in high concentrations caused side effects in 100% of patients and 20% with low concentrations (Cameron, 1963). The intravenous method permits the administration of five to ten times as much RNA as the oral method. Before the administration of RNA the patients were examined as to their previous memory defects. They were tested on the Wechsler memory scale and the counting test. Also several parameters of the conditioned reflex procedure were recorded. The patients were placed in three groups: arteriosclerotic group, presenile dementia group, and senile dementia group. These groups were administered RNA orally and intravenously and the tests were repeated. The results of these tests are as follows:

	<u>Counting test</u>	<u>IV</u> <u>Means</u> <u>Before</u>	<u>After</u>	<u>Chg.</u>	<u>Oral</u> <u>Means</u> <u>Before</u>	<u>After</u>	<u>Chg.</u>
Highest scores (most damaged patients)	Upper limit	82.2	119.3	37.0	136.3	174.5	38.3
	Lower limit	31.5	42.3	10.8	86.8	106.8	20.0
	<u>Wechsler Memory Scale</u>						
	Memory Quotient	85.0	96.25	11.25	105.0	118.0	13.0
Lowest scores	<u>Counting test</u>						
	Upper limit	9.8	37.0	27.2	6.0	10.5	4.5
	Lower limit	4.3	11.3	7.0	6.0	7.8	1.8
	<u>Wechsler Memory Scale</u>						
	Memory Quotient	60	64.0	4.0	52.8	56.8	4.0

The administration of RNA to the aged patients showed positive results and the results were better for mildly disturbed patients. Cameron (1963) suggested the following implications of his experiments: 1) RNA acts on a mechanism for retention, 2) there is probably an unrecognized mechanism for the storage of data by classification and 3) there is another unrecognized mechanism apart from retention which is favorably affected by RNA.

Agents known to prevent protein and RNA synthesis have been used by researchers to examine effects on decreased RNA synthesis on memory and learning. Wells (Gaito, 1966) used 6-azauracil, a purine and pyrimidine analogue, and produced in his patients "lethargy, somnolence, confusion, semi-coma, with abolition of fast rhythms and disorganization of background activity accompanied by irregular slurring and disappearances of response to photic stimulation in brain wave". Dingman and Sporn (1961), using 8-azaguanine, found that the ability of rats to learn a maze was impaired but that there was no effect on previously learned mazes. This leads to the assumption that the capacity to learn was interfered by the drug's action on brain RNA metabolism. Flexner (1963) used puromycin injected into the hippocampal gyrus to demonstrate loss of recent memory in mice. This was shown through a process known as reversal learning. In this, a mouse is trained to run in the left arm of a Y maze. Three weeks later he is trained to run in the right arm. Twenty-four

hours later he is injected with puromycin and retested. It was found that the mouse ran back in the left arm. This agrees with the hypothesis that recent memory was lost by curbing the RNA synthesis in this region.

Perhaps the most useful and most promising method of investigation is the use of agents to promote RNA synthesis.. Hydén and Hartelius (1948) discovered that malononitrile stimulated large nerve cells in the central nervous system to produce more nucleic acid. Experiments done with malononitrile (U-9189) have indicated an enhancement of retention. Solyom has shown an increased number of bar presses in rats injected intraperitoneally with U-9189 (Gaito, 1966).

A relatively recent approach in this area was reported by Plotnikoff (1966) and Glasky and Simon (1966), at Abbott Laboratories with magnesium pemoline. They developed and studied this drug and reported that it increased the brain biosynthesis of RNA. Magnesium pemoline has a stimulant action on the central nervous system but is reportedly devoid of sympatho-mimetic activities. By increasing the activity of brain RNA polymerase, learning and memory capacity would increase. Plotnikoff (1966) conducted experiments with magnesium pemoline on rats. Over a period of time the rats were trained in a chamber where a shock was followed by a buzz. One group was given magnesium pemoline orally and the other group was given a saline solution for control. The jump-out time was measured for each group. This was the criterion for learning. The drugged rats escaped within three

to eight seconds. The control group failed to even remember their previously learned responses and rapidly showed a decline from thirteen to twenty-three seconds escape time over ten retention trials. Thus, magnesium pemoline enhances the acquisition and retention of a conditioned avoidance response in rats. Whether or not the enhancement of learning and memory by magnesium pemoline in rats is causally related to the biochemical effects of magnesium pemoline, cannot be established from these experiments. The potential for possibly enhancing learning and memory in humans (especially mentally retarded children) by increasing brain RNA biosynthesis will be discussed later.

Experiments in which agents are used to break down RNA have been moderately successful. Corning and John (1963) conditioned planaria, then cut them in half, and allowed them to regenerate in pond water and pond water with ribonuclease (0.07 to 0.10 milligrams per milliliter). Regenerated heads learned faster than regenerated tails and the sections regenerated in pond water relearned faster than those regenerated in the enzyme. The investigators found that some degree of experience was left even after treatment with ribonuclease, but that the tails could not transmit this residual information to the regenerated heads.

Hyden (1962), the Swedish neurobiologist, developed a technique which has contributed greatly to the hypothesis that RNA is the substrate for learning and memory. By micro-dissecting

single nerve cells in Deiter's nucleus of rats, and analyzing their RNA content, he found a definite increase with a learning and memory experience. He, himself, interprets the results as follows: 1) during learning, the adenine-uracil ratio of nuclear RNA increases significantly. This indicates that a synthesis of fraction(s) of nuclear RNA with highly specific base ratios occurs during learning. 2) The failure to detect an altered base ratio in the cytoplasmic RNA does not exclude the possibility that the specific nuclear RNA produced during learning is influencing or incorporated in small amounts into the r-RNA. It suggests characteristics of m-RNA. 3) The amounts of RNA per cell increased. 4) Controlled experiments excluded possibilities that the chemical changes observed in the nuclear RNA of the nerve cell were due to demands on the neuro-function per se. 5) The nuclear RNA changes during learning were interpreted as an activation of regions on the chromosomes to produce nuclear (chromosomal) RNA with highly specific base ratios. The significance of the changes in amount of RNA and in what proportions according to bases will be great when attempts are made to change the body concentration of RNA by direct administration or by increased biosynthesis.

The work with RNA and magnesium pemoline prompted many investigators to enter this area of study. The results with magnesium pemoline were generally disappointing, but it is encouraging to see further investigations being conducted along these lines. The experiments by Plotnikoff (1966) were encouraging. Bowman (1966), however, did a concise analysis

of the Plotnikoff data with a different interpretation. He believed that the difference in retention (control rats/magnesium pemoline) may simply be a consequence of the difference in the level of acquisition--which the drug is known to affect. He also believed that the difference in retention time between the pemoline controls and the methylphenidate and metamphetamine and their controls throws some doubt on the reliability tests. Bowman (1966) further believed that if pemoline affects RNA synthesis, one might expect to see more long-term memory effects in terms of behavior and lesser, if any, effects on acquisition--short memory.

Later in 1966, Plotnikoff (1966) conducted another study with rats. In this study he found that rats, previously determined to be intelligent by conditioning experiments, showed interesting changes when given both magnesium pemoline and electro-convulsive therapy. The rats were tested, given the drug, retested, shocked, and then retested. When finally retested, the pemoline rats were seen to have faster escape times than the controls and all eventually returned to pre-shock escape time, except for the control groups which never did. He believed this to be an indication of memory enhancement.

Other investigators attempted to show positive memory effects with human subjects. Smith (1967) found that pemoline in 25 mg. dosages had no effect on facilitation of learning, memory, or performance in normal adult men and actually got

poorer performance from those on 37.5 mg. dosages. He admitted that he was only looking for a short-term effect from the drug because the data with the rats was based upon short-term effects.

Another group reported on the effects of magnesium pemoline and dextroamphetamine on human learning (Burns, Hause, Fensch, and Miller, 1967). They found that in a normal population of intellectually above average subjects, pemoline did not facilitate learning and dextroamphetamine interfered with it. They stated that amphetamines increase arousal and that high levels of arousal are detrimental to the acquisition of complex new associations.

In a more recent work with magnesium pemoline (Cylert, Abbott Laboratories), the memory enhancing effects seemed to be due to general stimulant properties (Tolland, Hagen, and James, 1967), (Tolland and McGuire, 1967). These supported the findings of other studies with magnesium pemoline. It is interesting to note that this agent was used as a stimulant in Europe in the 1950's.

The most recent breakthroughs in the area of memory and learning have not been in agents designed to enhance them, but in the biochemical mechanism by which they work. McGaugh (1966) published a study dealing with memory storage. He found that there is evidence for long-lasting neural changes due to experiences but not that a specific experience produces a specific neural change. He also believed that memory is not only the capacity to repeat, but also the

capacity to vary. In his studies he found a protein basis for long-term memory. Puromycin (a known inhibitor of protein synthesis) was found to wipe out retention in test subjects but not to affect acquisition.

McGaugh (1966) has also worked with several agents known to facilitate memory. These include CNS stimulants such as strychnine, picrotoxin, metrazol, amphetamines, nicotine, and magnesium pemoline. He could not correlate their actions with any common mechanisms for increasing memory. He did, however, establish that the consolidation of any piece of information into memory is time-dependent. He postulates three memory trace symptoms: 1) immediate memory, 2) short-term memory, and 3) long-term consolidation.

This idea was expanded by Krech (1968). He envisioned short-term memory as a physiological process with the main process occurring as electrochemical changes in neural synapses. On the other hand, long-term memory required chemical changes with the synthesis of new protein. These conclusions were based on experiments where short-term memory was interfered with by electric current producing high levels of neural activation.

Summary

In this paper I have attempted to review the recent status of research in the area of memory and learning. I have emphasized the more prominent pharmacological agents

which have been thought to be enhancers of memory and learning. The experiments with glutamic acid were many, but the only conclusion that can be reached is that a more scientific and better controlled experiment needs to be conducted. There is probably good evidence that the amphetamines function as neural stimulants without any direct enhancement of memory and learning.

The most promising, and exciting, work with memory and learning has been concerned with protein synthesis, DNA, and RNA. Unfortunately, the results have been equivocal and, in many cases, unable to be repeated. The thought of increasing protein synthesis by increasing precursor intake, increasing enzyme action, and blocking metabolic by-product pathways is intriguing. At present, this seems to be the major emphasis for memory and learning enhancement.

The implications of this research for the mentally retarded are boundless. Since one's ability to remember and to learn is the basis of his intelligence, enhancement of this ability would mean increased intelligence. I am convinced that the road to enhancing memory and learning through pharmacological agents is long. I believe, however, that better understanding of neural functioning on a molecular basis will shorten that road.

TABLE 1

Synoptic Review of Hypothesized Pharmacological Views
on RNA, Memory, and Learning

1. Nerve cell analysis (Hyden, 1959, 1961)
learning and memory tasks examine cells
by
(vestibular conditioning) ----->
micro-dissection
(rats) increased content
of RNA, change in
base ratios:
uracil + adenine
cytosine + guanine

increases

2. Protein synthesis blocking agents
 - a) Wells (Gaito, 1966)
RNA
6-azauracil----->(blocks RNA synthesis)-->semi-coma, confu-
analogue sion, lethargy,
(humans) slow and dis-
organized EEG with
abolition of response
to photic stimula-
tion

 - b) Dingman and Sporn (1961)
RNA
8-azaguanine----->(blocks RNA synthesis)-->affected recent
analogue learning of maze
(rats) performance (not
old performance.)

 - c) Flexner (1962).
injected into
puromycin ----->(blocks RNA synthesis)-->causes
hippocampal gyrus reversal of learn-
(mice) ing in rats -
loss of recent
memory (Y maze
trained; old
pattern to right
replaces newly
learned pattern
to left after
puromycin

3. Agents breaking down RNA

a) Corning and John (1963) regenerated normally in pond water
 conditioned planaria $\xrightarrow{\text{cut in half}}$ pond water
 \downarrow
 impaired when regenerated in ribonuclease (RNA catabolic agent)

b) Cameron (unpublished - see Gaito, 1966, p. 144)

ribonuclease $\xrightarrow{\text{IV}}$ inconclusive results
 Humans

4. Administration of RNA (Cameron et al, 1960, 1961, 1963, 1964)

RNA $\xrightarrow{\text{orally}}$ stimulates body synthesis of new RNA
 \downarrow IV
 shock-like effects
 \downarrow
 hypothetical - becomes substrate for new memory \rightarrow increased ability/capacity for memory and learning
 \downarrow
 increased and more organized alpha activity in EEG (1963)

Source: commercial yeast (sodium ribonucleate)

5. Trained planaria $\xrightarrow{\text{transection}}$ retain conditioned responses (to a degree) on regeneration
 McConnell (1962) \downarrow
 sacrificed; RNA extracted and fed to untrained planaria \rightarrow partial transfer of conditioned response to untrained planaria

Comment:

1. Can planaria be trained?
2. Can RNA produce "transfer of learning?" (Luttges, et al, 1966)

6. Agents promoting RNA synthesis

a. Hyden and Hartelius (1948)

malononitrile-->Stimulates RNA production --> enhances
in large nerve cells retention
activity in rats

Comment: Mendelson, Fax, and Grenell (1954) suggested that results were secondarily caused by a reaction product.

b. Plotnikoff (1966)

magnesium pemoline ---> increased the < increases the biosyn-
activity of RNA thesis of RNA
polymerase enhances capacity for
learning (acquisition
rate and retention of
conditioned avoidance
performance - rats)

Comment: Author reports that methamphetamine and methylphenidate do not have this effect.

c. Glasky and Simon (1966)

magnesium pemoline-->increases the---->proportionately great-
activity of RNA er stimulation of RNA
polymerase polymerase than metham-
phetamine, methyl-
phenidate, trimetha-
dione, imipramine,
and pipradol..

d. Frey and Polidora (1957)

magnesium pemoline-->enhances avoidance-->authors have diffi-
conditioning culty in inter-
(shock) in rats preting their study:
CNA stimulatory
effect? Learning?

7. Recent Clinical Trials (Humans)

a. Burns, House, Fensch and Miller (1957)

magnesium pemoline---initial report of ----Well-designed
acute single dosage double-blind
administration to study. No
30 male University facilitation of
students learning with
magnesium pemoline
Indeed, placebo
subjects learned
faster than
subjects on mag-
nesium pemoline
and/or amphetamine

b. No other reports concerning human trial are available
at the time of this writing

REFERENCES

- Albert, K., Koch, P., Waelsch, H., Glutamic acid and mental deficiency, Journal of Nervous and Mental Disease, 114, 471-491, 1951.
- Astin, A.W., Ross, S., Glutamic acid and human intelligence, Psychological Bulletin, 57, 429-434, 1960.
- Babich, F.R., Jacobson, A.L., Bubash, S., Jacobson, A., Transfer of a response to naive rats by injection of RNA extracted from trained rats, Science, 149, 656-657, 1965.
- Bernhard, R., Crisis in biology, Scientific Research, 1:10:33, October, 1966.
- Bowman, R., Magnesium pemoline and behavior, Science, 153:902, August 19, 1966.
- Burns, J.T., Hause, R. F., Fensch, F. C., and Miller, J. G., Effects of magnesium pemoline and dextroamphetamine on human learning, Science, 155:849, February, 17, 1967.
- Byrne, W., Samuel, D., Bennett, E., Rosenweig, M., Wasserman, E., Wagner, A., Gradner, R., Galambos, R., Berger, B., Margules, D., Fernichel, R., Stein, L., Carson, J., Enesco, H., Chorover, S., Holt, D., Schiller, P., Chiapetta, L., Jarvils, M., Leaf, R., Dutcher, J., Horority, F., Carlson, P., Memory transfer, Science, 153: 658-659, August 5, 1966.
- Cameron, D. E., Remembering in the aged, Excerpta Medica, (XX) 2: 467-469, 1959.
- Cameron, D. E., Solyom, L., Effects of ribonucleic acid on memory, Geriatrics, 16: 74-81, 1961.
- Cameron, D. E., Sved, S., Solyom, L., Wainrib, B., Barik, H., Effects of ribonucleic acid on memory defect in the aged, American Journal of Psychiatry, 120: 320-325, October, 1963.
- Cameron, D. E., The processes of remembering, British Journal of Psychiatry, 109: 325-340, May, 1963.
- Cattell, R. B., The effects of alcohol and amphetamine on intelligence, British Journal of Medical Psychology, 10: 20-33, 1930.
- Cavalleri, L. F., Rosenberg, B. H., On the transient template for in vivo DNA synthesis, Proceedings of the National Academy of Science of the United States of America, 51: 826-834, May, 1964.

- Clausen, J., Fineman, M., Henry, C. E., Wohl, N., The effect of deaner (2-dimethylaminoethanol) on mentally retarded subjects, Training School Bulletin, 57: 3-12, 1960.
- Connors, C. K., Eisenburg, L., Barcai, A., Effect of dextro-amphetamine on children. Studies on subjects with learning disabilities and school behavior problems, Archives of General Psychiatry, 17: 478-485, 1967.
- Corning, W. C., John, E. R., Effect of ribonuclease on retention of conditioned response in regenerated planarians, Science, 134- 1363-1365, 1961.
- Crick, F. H., On the genetic code, Science, 139: 461-464, 1963.
- Cutter, M., Little, J. W., The effect of benzidrine on mentally deficient children, American Journal of Mental Deficiency, 45: 59-65, 1940.
- Dingman, W., Sporn, M. B., The incorporation of 8 azaguanine into rat brain RNA and its effect on maze-learning by the rat: an inquiry into the biochemical basis of memory, Journal of Psychiatric Research, 1: 1-11, 1961.
- Doty, P., Boedther, H., Fresco, J. R., Hall, B. D., Haselkorn, R., Configurational studies of polynucleotides and ribonucleic acid, Annals of the New York Academy of Sciences, 81: 693-708, 1959.
- Flexner, J. B., Flexner, L. B., Steller, E., DeLa Haba, G., Roberts, R. B., Inhibition of protein synthesis in brain and learning and memory following puromycin, Journal of Neurochemistry, 9: 595-605, 1962.
- Flexner, J. B., Flexner, L. B., Steller, E., Memory in mice as affected by intracerebral puromycin, Science, 141: 57-59, 1963.
- Flory, C. D., Gilbert, J., Effects of benzidrine sulfate and caffeine citrate on the efficiency of college students, Journal of Applied Psychology, 27: 121-134, 1943.
- Fresco, J. R., Helical arrangements in synthetic and natural polynucleotides, Transaction of the New York Academy of Science, 21: 653-658, 1959.
- Frey, P. W., Polidora, V. J., Magnesium pemoline: effect of avoidance conditioning in rats, Science, 155: 1281-1282, 1967.
- Gaito, J., Macromolecules and Behavior, New York: Appleton-Century-Crofts, 1966.
- Glasky, A. J., Simon, L. N., Magnesium pemoline: enhancement of brain RNA polymerases, Science, 151: 702-703, February, 1966.

- Hebb, D. O., The Organization of Behavior, New York, Wiley, 1949.
- Hyden, H., Behavior, neural function, and RNA, Progress in Nucleic Acid Research, 6: 187-218, 1967.
- Hyden, H., Egyhozi, E., Changes in RNA content and base composition in cortical neurons of rats in a learning experiment involving transfer of handed-ness, Proceedings of the National Academy of Science of the United States of America, 52: 1030-1035, October, 1964.
- Hyden, H., Egyhozi, E., Changes in the base composition of nuclear ribonucleic acid of neurons during a short period of enhanced protein production, Journal of Cellular Biology, 15: 37-44, 1962.
- Hyden, H., Egyhozi, E., Nuclear RNA changes of nerve cells during a learning experiment in rats, Proceedings of the National Academy of Science of the United States of America, 48: 1366-1373, 1962.
- Hyden, H., Hartelius, H., Acta psychiatrica et neurologica scandinavica, Suppl. 48, 1948.
- Hyden H., Lange, P. W., A differentiation in RNA response in neurons early and late during learning, Proceedings of the National Academy of Science of the United States of America, 53: 946-952, May, 1965.
- Hyden, H., Macromolecular Specificity and Biological Memory, M.I.T. Press, 55-69, 1962.
- Hyden, H., Quantitative assay of compounds in isolated, fresh, nerve cells and glial cells from control and stimulated animals, Nature, 184: 433-435, 1959.
- Krech, David, The chemistry of learning, Saturday Review, January 20, 1968.
- Laufer, M. W., Denhoff, E., Hyperkinetic behavior syndrome in children, Journal of Pediatrics, 50 (4): 463-474, April, 1957.
- Luttges, M., Johnson, T., Buck, C., Holland, J., McGaugh, J., An examination of "transfer of learning" by nucleic acid, Science, 151: 834-837, February 18, 1966.
- McConnell, J. V., Memory transfer through cannibalism in planarians, Journal of Neuropsychiatry, 3 (suppl. 1): 542-548, 1962
- McGaugh, James, Time dependent processes in memory storage, Science, 153: 1351, September 16, 1966.

- Morris, J. W., MacGillwray, R. C., Mathieson, C. M., The results of the experimental administration of amphetamine sulfate in oligophrenia, Journal of Mental Science, 101: 131-140, 1955.
- Plotnikoff, N., Everett, G. M., Potentiation of evoked cortical responses in the rabbit by methamphetamine and antidepressants, Life Sciences, 4: 1135--1147, June 1965.
- Plotnikoff, N., Magnesium pemoline: Enhancement of memory after ECS in rats, Life Sciences, 5: 1495-1498, August, 1966.
- Plotnikoff, N., Magnesium pemoline: enhancement of learning and memory of a conditioned avoidance response, Science, 151: 703-704, February, 1966.
- Plotnikoff, N., Meekma, P., Pemoline and $Mg(OH)_2$ versus pemoline: enhancement of learning and memory of a conditioned avoidance response in rats, Journal of Pharmacology, Sciences, 56: 290, February, 1967.
- Pond, D. A., Pond, M. H., Glutamic acid and its salts in epilepsy, Journal of Mental Science, 97, 663-673, 1951.
- Pond, Virginia, personal communication from Smith, Kline and French Laboratories, August 15, 1966.
- Smith, R. G., Magnesium pemoline: lack of facilitation in human learning, memory and performance tests, Science, 155: 603, February 3, 1967.
- Tolland, G., Hagen, D., James, M., Performance tests of amnesiac patients with cylert, Journal of Nervous and Mental Disease, 144: 421-429, May, 1967.
- Tolland, G., McGuire, M., Tests of learning and memory with cylert, Psychopharmacologica, 10: 445, 1967.
- Vogel, W., Broverman, D. M., Draguns, J. G., Klaiber, E. L., The role of glutamic acid in cognitive behaviors, Psychological Bulletin, 65: 6: 367-382, 1966.
- Weil-Malberbe, H., Studies on brain metabolism: mechanisms of glutamic acid in brain, Biochemical Journal, 30, 665-676, 1936.
- Weiss, B., Laties, V. G., Enhancement of human performance by caffeine and the amphetamines, Pharmacological Reviews, 14: 1-36, 1962.
- Zimmerman, F. T., Ross, S., Effect of glutamic acid and other amino acids on maze learning in the rat, Archives of Neurology and Psychiatry, 51, 446-451, 1944.

APPENDED REFERENCES

- Barondes, S. H., Jarvik, M. E., The influence of actinomycin on brain RNA synthesis and on memory, Journal of Neurochemistry, 11: 187-195, March, 1964.
- Barondes, S. H., Relationship of biological regulatory mechanisms to learning and memory, Nature, (London, 205: 18-21, January 2, 1965.
- Benoit, E., Mental Retardation, Jerome Rothstein (ed.), New York: Holt, Rinehart, and Winston, 155-162, 1961.
- Brain Function, Volume 2, Editor: Mary Brazier, University of California Press, 1964.
- Cook, L., Davidson, A., David, D., Green, H., Fellows, E., Ribonucleic acid: effect on conditioned behavior in rats, Science, 141: 268-269, 1963.
- Egyhazi, E., Hyden, H., Biosynthesis of rapidly labeled RNA in brain cells, Life Sciences, 5: 1215-1223, July, 1966.
- Egyhazi, E., Hyden, H., Experimentally induced changes in the base composition of the ribonucleic acids of isolated nerve cells and their oligodendroglial cells, Journal of Biophysical and Biochemical Cytology, 10: 403-410, 1961.
- Egyhazi, E., Hyden, H., RNA with high specific activity in neurons and glia, Brain Research, 2: 197-200, August, 1966.
- Egyhazi, E., Microchemical fractionation of neuronal and glial RNA, Biochimica et biophysica acta, 114: 516-526, March 21, 1966.
- Furth, J.J., Hurwitz, J., Krug, R., Alexander, M., The incorporation of adenylic and cytidylic acids into ribonucleic acid, Journal of Biological Chemistry, 236: 3317-3322, 1961.
- Gaito, J., DNA and RNA as memory molecules, Psychological Review, 70: 471--480, September, 1963.
- Gaito, J., Zavala, A., Neurochemistry and learning, Psychological Bulletin, 61: 45-62, January, 1964.
- Harris, H., The breakdown of ribonucleic acid in the cell nucleus, Proceedings of the Royal Society, Biological Science, 158: 79-104, 1963.
- Halstead, W. C., Brain and Intelligence, Chicago, University of Chicago Press, 1947.
- Hurwitz, J., Furth, J. J., Anders, M., Ortiz, P. J., August, J. T., The enzymatic incorporation of ribonucleotides with RNA and the role of DNA, Symposia on Quantitative Biology, 26: 91-100, 1961.

- Hurwitz, J., Furth, J. J., Messenger RNA, Scientific America, 206: 41-49, 1962.
- Kartry, A. L., Keith-Lee, P., Morton, W. D., Planaria: memory transfer through cannibalism reexamined, Science, 146: 274-275, October 9, 1964.
- Landauer, T. K., Two hypotheses concerning the biochemical basis of memory, Psychological Review, 71: 167-179, May, 1964.
- Lawson, H., Wall Street Journal, May 23, 1966.
- McGaugh, J. L., Petrinovich, L. F., Effects of drugs on learning and memory, International Review of Neurobiology, 8: 139-196, 1965.
- McPherson, M. W., Mental Retardation, Jerome Rothstein (ed.) New York: Holt, Rhinehart, and Winston, 138-149, 1961.
- Morrell, F., Electrophysiological contributions to the neural basis of learning, Physiological Review, 41: 443-494, 1961.
- Peterson, L. R., Short-term memory, Scientific American, 215: 90--95, July, 1966.
- Peterson, L. R., Short-term verbal memory and learning, Psychological Review, 73: 193-207, May, 1966.
- Robinson, H. B., Robinson, N., The Mentally Retarded Child: A Psychological Approach, New York: McGraw-Hill, 316-327, 1965.
- Scientific Research, Controversy grows over molecular basis of memory, 1: 6: 19-22, 1966.
- Time, A molecule of memory?, 66, January 7, 1966.
- Time, Memory pills, 56, July 24, 1966.
- Wall Street Journal, Memory-improvement drug shows promise in first human tests, 1, June 15, 1966.
- Zimmerman, F..T., Bergemeister, B. B., A controlled experiment of glutamic acid therapy, Archives of Neurology and Psychiatry, 81: 639-647, 1959.