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Recent Advances in Biological Psychiatry

JOSEPH WORTIS, M.D., *Editor*

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Contents

Part IV: STUDIES ON LSD

Part V: LABORATORY RESEARCH REPORTS

Part VI: DEVELOPMENTAL STUDIES

Part VII: A. E. BENNETT AWARD PAPERS

Chapter 1

Evolving Concepts of Memory

PRESIDENTIAL ADDRESS

D. Ewen Cameron, M.D., F.R.C.P.(C), D.P.M. (Lond)

The last few decades have changed our concepts of memory beyond recognition. It is true that some of the older designations remain. But the mechanisms we now recognize—the conceptual framework which we use for thinking about memory—and the means which we are working out and putting together with such rapidity to control the various mechanisms of memory are profoundly different from those of 30 years ago. In 1936 R. D. Gillespie [1] was using the blueprint shown in Fig. 1 to describe his concept of the memorial process. It is almost identical with that which Plato used over 2000 years ago. From this has begun to evolve an advanced idea that there is not simply one memory system, but many. Our current working diagram of the various mechanisms of the memorial process is depicted in Fig. 2. The memorial process is not a biochemical system, and it is just as assuredly not a pattern of behavior. It is essentially an organismal system.

Still more recently, the extraordinary vistas opened up by our growing knowledge of DNA as the carrier of the genetic code seem to be bringing us to the end of the search which man has carried on for 2500 years, namely, the search for the substrate which carries day-to-day information. Great though the prospects to be seen as we stand on the present heights of our knowledge of the genetic code, the possibilities implied by the suggestion that RNA or its derived proteins may be the substrate for the maintenance of day-to-day information hold even greater promise—greater for the simple reason that the thoughts and acts of men in the here and now have an infinitely greater potentiality than do the long slow shifts which at least hitherto have been the expression of genetic change.

Our conception of memory function is advancing on an exceptionally wide front. Groups of workers are discovering new mechanisms. Some are working on the various kinds of coding used—from the time that the tympanic membrane first vibrates in response to a question to the time the answer receives its final coding into words. Others are exploring the matter of the substrate whereby the memory trace is held. Still others are investigating whether memory can actually be transferred in biochemical form from animal to animal and, indeed, from species to species. Yet another group is reconsidering the old concept in the light of our knowledge of information processing.

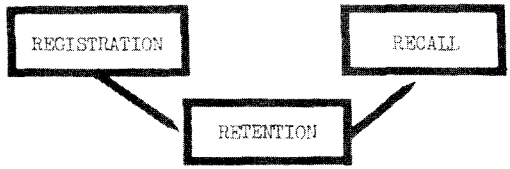

Fig. 1. 1936 model of memorial function.

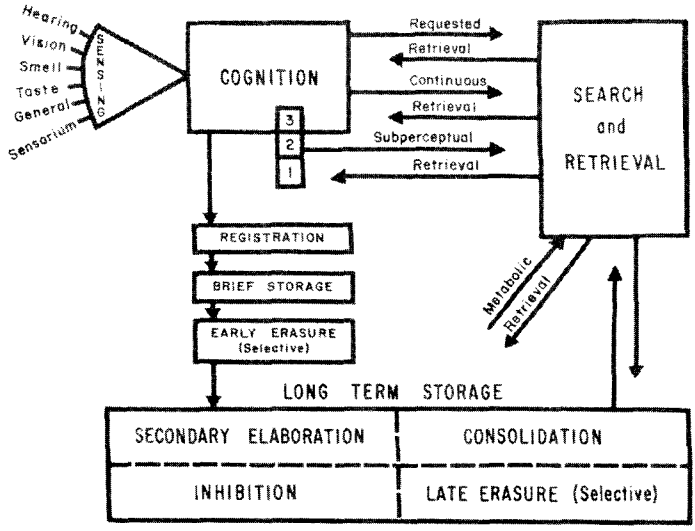

Fig. 2. General schema of memorial processes (April 1966).

This paper is concerned with one particular area, namely, the definition of the substrate for the holding of the memory trace.

A crucial forward step was taken ten years ago, when a macromolecule was first administered for the purpose of rectifying memory deficits in man. The time was ripe for this. Our knowledge of the nucleic acids goes back to Miescher's original account in 1871. As in the case of the genetic theory itself, almost 80 years passed from the discovery of the nucleic acids until we began to realize their capacity to carry information.

In 1955, before the Association for Research in Nervous and Mental Disease, in New York City, Paul Weiss [2] gave a stimulating account of the activities of the neuron. He pointed out that instead of the fixed, static, structure which we had previously considered it to be, it is actually continually in motion, forming new dendritic connections with the neuronal network which stretches throughout the brain, withdrawing from them, expanding, contracting, in constant reaction to the demands being made upon the organism. In particular, he demonstrated that at the nuclear end there is continuous production of material, which moves steadily down toward the peripheral end organs. At the same time

some evidence had appeared that the material thus formed at the nuclear end might be comprised of nucleic acids.

In early 1956 a start was made with the intravenous administration of DNA, chosen because it is the template and hence seemed reasonably certain to be the controlling substance. Moreover, it is produced primarily in the nucleus. No favorable effect on memory was obtained, but when RNA was used intravenously in humans, an effect was observed at once. In this we were fortunate, since the solutions available at that time were extremely crude, and the amounts given were in milligrams, whereas subsequently, amounts ranging up to 30 g daily were administered.

As our solutions improved, we expanded our explorations. Table I shows our major findings, Table II the contrast between oral and intravenous RNA, and Table III the contrast between the large-fragment type of RNA and the small-fragment type.

Following our return to Albany in September 1964, we were unable to continue RNA investigations in humans. However, our laboratories then received a request from the Abbott Research Laboratories to carry out the human testing of an agent with which their research group in North Chicago had been working, and which was said to stimulate the

Table I. Major Findings Regarding Ribonucleic Acid and Memory

1. Increased speed of trace formation (animal and man)
2. Increased capacity for discrimination (animal and man)
3. Increased resistance to extinction (animal and man)
4. Intravenous administration is more effective than oral administration
5. Large-fragment solutions are more effective than small-fragment solutions
6. Uridine given intravenously is without effect
7. ATP given intravenously is without effect
8. Hydrolyzed RNA is less effective than whole RNA
9. DNA has very limited effect on memory
10. DNA and RNA is about the same as RNA
11. Ribonuclease given intravenously is without effect in humans

Table II. Intravenous Versus Oral Administration (All RNA patients included) (Means)

Test	Before		After		Change	
	Oral	I/V	Oral	I/V	Oral	I/V
Counting Test						
Upper limit	45.27	39.9	72.57	78.47	27.30	38.57
Lower limit	26.1	15.6	39.6	37.6	13.5	22.0
Wechsler Memory Scale						
Memory quotient	72.0	72.2	76.89	81.86	4.89	9.59

Table III. Results of Wechsler Memory Scale

	Sved group mean (X)	Schwarz group mean (X)	Between-group comparison
Before RNA	74.3	72.8	N.S.
After RNA	85.7	75.6	
Mean difference (D)	+11.4	+2.8	8.60
N	10	20	30
t	3.44	2.44	3.72
p	0.01	0.05	0.001

synthesis of RNA. This substance was variously known as magnesium pemoline and *Cylert*, the latter being the Abbott designation. Its chemical formula and chemical designation are shown in Fig. 3.

The history of the parent substance, pemoline, is interesting. It was discovered as far back as 1913 by Traube and Ascher [3], but nothing further was done with it until 1956 when Schmidt [4] was exploring the properties of a number of agents and, for reasons which he describes as accidental, tested pemoline and found a stimulant action. He recommended its use in the treatment of fatigue states, states of debility, and exhaustion. It has been marketed for this purpose in Europe under several names, such as Pio, Tradon, and others. In 1962, W. E. Lange [5] and his co-workers discovered that if the drug was combined with magnesium hydroxide its efficiency was increased. Finally, in 1965, Glasky and Simon [6], whose interest had been aroused by the reports of the action of RNA on memory, started a systematic search for a substance which would facilitate the synthesis of RNA in the brain in animals and man. They reported that magnesium pemoline had a capacity to facilitate the synthesis of RNA in the brain. Behavioral studies of the effects of this drug upon the memorial process in animals were carried out by N. Plotnikoff [7]. He showed that the drug did affect the speed with which memory traces were acquired and their durability.

In December 1965 we set up an experimental group of 24 patients, using a double-blind, cross-over study. The experiment had two aims: to determine whether or not the agent had an effect on memory; and to

PEMOLINE (2-IMINO-5-PHENYL-4-OXAZOLIDINONE)
+ MAGNESIUM HYDROXIDE = CYLERT

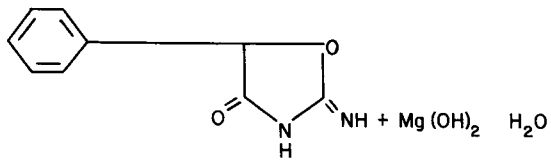

Fig. 3

determine whether it had a progressive effect. Related to this, of course, was the question of which of the mechanisms of the memorial process the drug affected.

The instruments we used to measure the effects are listed below:

1. Wechsler Memory Scale
2. Counting Test
3. Cinemanalysis
4. Memory Inventory
5. Fluency Test
6. Voice Analysis
7. Flicker Fusion
8. Reflex Reaction Time
9. Urinalysis
10. Uric Acid, BSP, SGOT
11. RBC, WBC, Hgb., Sedimentation Rate

Only the first five deal directly with memory. The voice analysis was used to obtain information on speed of talking. Flicker fusion and reflex reaction time tests were carried out because of the previously described stimulant effects of the drug in these tests.

It is often very difficult to convey data concerning behavioral change from the laboratory to the audience. It can be put in the form of tables, curves, and statistical analysis, with their appropriate notations of degrees of validity. Somehow this often fails to carry the true flavor of change. Hence, we have set up in film form a test which we carried out before, during, and after the administration of magnesium pemoline; this we call cinemanalysis. The patient is placed behind a glass screen facing

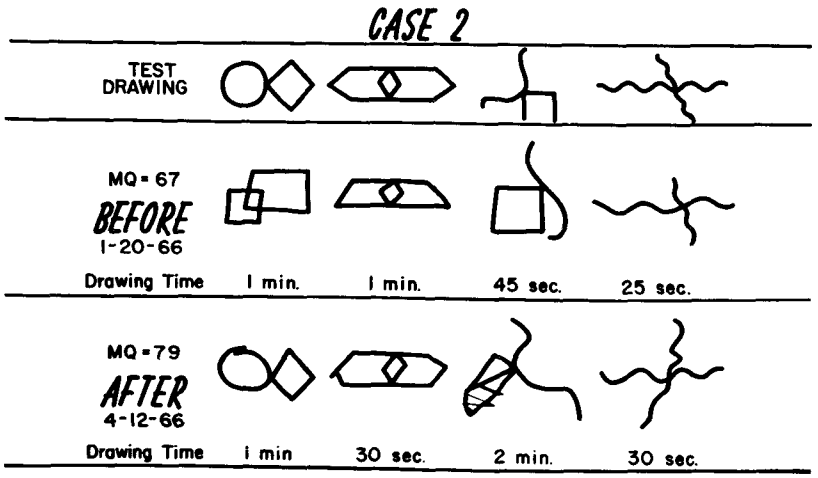

Fig. 4