THE MAUDSLEY LECTURE

(It is a special honour in psychiatry to be invited to give this Lecture and, on this occasion, it was given by Dr.Cameron in November, 1962.)

THE PROCESSES OF REMEMBERING

BY

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The Processes of Remembering

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By D. EWEN CAMERON

I have been deeply moved by your invitation to deliver this year's Maudsley Lecture. Founded to commemorate so distinguished a man, it has become most properly one of the honours of psychiatry.

Those who have presented this Lecture on earlier occasions have clearly turned to the great themes of their own life work. Each man has found in the writings of Henry Maudsley thoughts and plans already foreshadowing the advances which the lecturer has brought into being more than three-quarters of a century later. For Maudsley had a penetrating mind which struck swiftly and incisively down to the fundamentals of human nature.

In his *Physiology of Mind*, published in 1876, Maudsley had already seized upon the fact of the cardinal position that memory plays in the total behaviour of man. He pointed out that "No mental development would be possible without it. For if a man possessed it not, he would be obliged to begin his conscious life fresh with each impression made upon him and would be incapable of any education." He also foresaw—although the immense range of data which we now possess was lacking to him—that it is not images or ideas of objects that are stored, but rather changes in some organic substrate of the brain. He recognized, in a word, that "coding" takes place and indeed he saw this long before that phrase had been coined. He was clearly and profoundly interested in the process with which many of us are presently concerned, namely the retrieval of stored information.

The word "remembering" covers not one but a multiplicity of functions. They lie in a long range and are varied in nature. First and most commonly thought of as remembering are those functions which serve our needs for precise recovery of information in the exact form in which it was laid down—an address, a formula, a date. Then we pass over to the curious, evolving, moving, changing kind of remembering which is required for the learning of a skill. This kind of remembering allows us to replace one modification by the next and almost always to produce in response to the same cue the most recent modification. An excellent example is furnished by the learning of a new top spin drive in tennis.

Passing on to the far end of the range, we find lying there those memorial functions which permit us to change our recollections of the past so that the past becomes more endurable, more reconcilable with the image of ourselves which we find at least tolerable. These functions appear to be governed by our emotions and by the remoulding powers exercised by our ongoing concept of ourselves and of our world. So we come to forget that we stole from our mother's purse as a child, or we may discover —like Darwin building his theory of the origin of species—that unless we are careful immediately to record as they occur all ideas contrary to the theory, they are remarkably soon forgotten.

Intelligence may be the pride—the towering distinction of man; emotion gives colour and force to his actions; but memory is the bastion of his being. Without memory, there is no personal identity, there is no continuity to the days of his life. Memory provides the raw material for designs both small and great. Thus, governed and enriched by memory, all the enterprises of man go forward.

Last year's distinguished Lecturer spoke on remembering and I make no apology for

returning to the theme, for memory has become within the last few years one of the great areas of intensive study. Promise murmurs from the pioneering laboratories that matters concerning remembering—over which mankind has pondered for 1,500 years by record—may be on their way to solution.

What are these basic problems of remembering? Let me first state them as they were considered by the Greeks. Plato (1) around 354 B.C. was deeply concerned as to how memory traces were formed and stored. He advanced the idea that there is an analogy between this and the process of imparting an impression to a block of wax. He saw the wax impression and the memory trace share a common destiny—in some cases quickly fading —sometimes being preserved throughout a lifetime—or yet again being misplaced for moments, for days or forever. Other Greeks raised the question of how memories are retrieved. Or again, what is the difference, if any, between knowledge when it is first recorded and the same knowledge later recalled?—clearly our own problem, stated in other words, of secondary elaboration. And finally, the Greeks wondered how memory is related to that elusive faculty—our sense of time.

With our vastly increased store of information about the human organism, we have been able, as a first step, to sharpen and reshape these questions. Let me state them in terms of three great areas of enquiry, each containing hardly less important questions within it.

The first is one which in far earlier times could not be set up because of the lack of anatomical knowledge. This is, where in the brain are memory traces recorded and stored? The second great area of enquiry is, what is it that serves as a substrate for memory? What is the substance which, like Plato's wax block, actually receives and holds the memory trace? The third area of search is, how does the machinery of the memorial process work? How do we perform this great range of functions—coding and decoding, precision of recall, evolving recall as required in skills and the greatly modified recall of otherwise unacceptable memory traces?

Within this vast and vastly intricate area there lie the questions of the nature of retrieval, the curious enigma of the differing ease of recognition and recall, the mechanisms of retroactive and proactive inhibition and the intriguing phenomena of anterograde and posterograde amnesia. Here too, lie the fascinating puzzles of how the incoming sensory impulses are coded for recording and how, on retrieval, this coding is converted into the data of consciousness—the process of readout.

Now let us look down on to these three great areas of exploration, follow the men at work in them, see what tools they are using, note what they have now discovered, and trace their plans for further exploration.

In the first area at which we look—the arena where men are working to discover where memory traces are recorded and brought to their final storage areas—there still remains great confusion and contradiction. This confusion is characteristic of a great wide-flung research area in which all the facts have not yet been found; all the connections between the intricate array of findings have not yet been traced out.

A long series of men worked in this field all throughout the 19th century. During this period the clinical neurologists took the lead—men such as Prochaska and Gall who sought to find where memories are stored in the brain chiefly on the basis of their clinical findings. Theory took form largely under the leadership of Flechsig and favoured the localized storage of memories.

These workers were later supported by growing advances made by the conditioned reflex school. The claims of Pavlov and his co-workers, however, were made without actual neurological and neurosurgical experimental evidence. For the Pavlovians, the assumption that memories were stored in association areas served simply to complete the structure of their basic theory.

A beginning sophistication in the concept of the storage of memory traces appeared with the discoveries of Henry Head (3) and Kurt Goldstein (2) who showed that the disturbances found in aphasia and agnosia are not true failures in remembering, but defects in the categorization of ideas. Early in the twentieth

century, the lead in the search for the location of the storage of memory traces was increasingly taken by the animal experimentalists and, in particular, by those who based their experiments upon surgical procedures. For by these means, it was possible to study the function of one part of the brain after another with respect to the memorial process. The work of the animal experimenters reached the point of greatest penetration in the researches of Lashley (4).

In 1950, Lashley summarized his work in an article entitled "In Search of the Engram". This report exercised profound influence upon the thinking of men working in this field, and its effects are still felt. He concluded that it was not possible to demonstrate specific localization of the memory trace anywhere within the nervous system and definitively declared that the association areas are not storehouses for particular memories.

Lashley considered that the memory trace is recorded by means of multiple representations. He postulated that the nervous network may develop a pattern of activity by the spread of excitation much as the surface of a liquid develops an interference pattern of spreading waves when it is disturbed at various points. This, he felt, would result in the neurons being sensitized to react in certain combinations, perhaps in complex patterns of reverberatory circuits reduplicated throughout the area. Furthermore, he gave consideration to the number of cells in the brain and concluded that all of the cells must be in almost constant activity; that there is no excess of cells which can be used for the preservation of special memories. He concluded further that recall involves the synchronized action of a very large number of neurons.

His long series of researches were of particular value in bringing to the fore not only this fundamental conception, but also in making clear that much of what previously had been taken as a disturbance in the storage of memory traces was actually a disturbance in closely linked but not identical functions—such as in failure in shifting from one task to another or in difficulty in maintaining a constant set while endeavouring to remember a task. And he supported the views of Henry Head and Kurt Goldstein who, as we have already pointed out, showed that aphasia and agnosia are to be considered as primary defects in the organization of ideas rather than as representing the loss of memory traces.

Hardly had this monumental and apparently conclusive report been published than it was challenged by evidence brought forward by the neurosurgeons. For with the coming of the mid-century, information derived from operative procedures on the human subject became at once much more abundant and far more reliable. It was more reliable for two reasons: the first is that increasingly refined and efficient techniques permitted operations to be carried out on parts of the human brain into which the neurosurgeons previously could not venture. The second is that part of the evidence was derived from varieties of the lobotomy operation, which was then reaching its acme of application. This operation was carried out on brains which, if they could not be described as entirely healthy, were at least free from massive and pervasive pathologies such as traumatic change, abscesses or tumours.

In 1954, Williams and Pennypacker (5) reported a Korsakoff type of memory deficit occurring in individuals who had lesions in the hypothalamic region. They were followed by a number of workers (Scoville and Milner, 1957 (6); Whitty and Lewin, 1957, 1960 (7); Sweet *et al.*, 1959 (8)) who rapidly defined a specific area which when bilaterally damaged results in a persistent failure of recent memory and an immediate retrograde amnesia of at least several weeks. The area thus defined is the hippocampal-fornix-mammillary system.

A rather interesting light on the possible specificity of localization was thrown by the work of Penfield (9) on electrical stimulation of the temporal lobe. Discussing the memory changes following on bilateral hippocampal lesions, Penfield has suggested that they interfere with memory recording and that already established skills are not interfered with. It is probably premature, however, to come to this conclusion inasmuch as one cannot say to what extent the damage is in the retrieval mechanism rather than in the recording

mechanism. However, it is quite possible to state that there may not be such a discordance between the views of Lashley and the reports of these more recent workers, since this system, namely the hippocampal-fornix-mammillary body circuit, might simply be an essential pathway to the general areas of the brain where memories are recorded and from which they are retrieved.

Another attack on this apparent enigma presented by these contrasting findings of Lashley and the neurosurgeons has been made by those who consider that recording is a two-stage procedure. Teuber (10) for instance has recently stated, "A focal process of initial registration and consolidation precedes a subsequent dispersal involving large portions of the cerebral hemisphere." In the electro-shock procedure, we have a means of producing graduated amnesia, and it is of interest to note that there is a proportional relationship between the number of electroshocks given within a period of time and the extent of the amnesias. It is quite possible, for instance, to produce a long-lasting, probably permanent, amnesia by setting the number of electroshock treatments to be given within a predetermined period. Those of us who have worked on this at the Institute take the view that this phenomenon cannot readily be understood in terms of consolidation, but can be more easily grasped if we consider that the longer a memory trace exists the more connections it develops with other traces. From here we may go on to postulate that those memory traces with numerous, long-established inter-connections are much less easily obliterated than those of recent origin. This criticism of the concept of consolidation leaves intact the possibility that recording may be in the form of a two-stage operation as already described.

We may now leave this first great area, namely, the location where memory traces are recorded and stored, with at least the temporary assumptions that they are widely stored throughout the brain and that the hippocampal-fornix-mammillary system probably plays an important part in the conveying of the neural impulses to and from the storage areas.

We now turn to the second great area of enquiry: what serves as the organic substrate for the memory trace? For a considerable time it has been considered that memories are preserved in the brain in the form of traces which are laid down at the time the experience occurs and which are reactivated at the moment of remembering.

Earlier workers, in attempting to provide on theoretic grounds a substrate for the trace, tended to put forward one of several hypotheses. The first was that the trace is laid down in terms of alteration at the synapse; a modification of this was that it is laid down in terms of the linking together of a network of neurons. The third one, which deviated relatively little from the first two, was that the trace is laid down in terms of altered conductivity.

It was not until 1947 that an entirely new concept arose. This was that the memory trace is laid down in terms of changes in cell protein. This new concept sprang into being with the discovery that the protein structure of neural cells is exceedingly complex and that it also varies from cell to cell. This at last provided what had been sought, namely, a substrate of sufficient complexity to permit the recording of the exceptionally large number of bits of information which the individual possesses in the form of memories.

Katz and Halstead in 1950 (11) stated the concept in these terms: "Neurons involved in memory become fully functional only after chemical structural changes" and they suggested that a neuron becomes operative in virtue of the formation of a new, specifically oriented, protein molecule. They assumed that the molecule was a nucleoprotein and that it acted as a template for the synthesis of protein replicas.

From this point onwards, a number of workers entered this field, of whom the most active has been Hydén (12). He advanced the hypothesis that the substrate is ribonucleic acid and pointed out that in the many combinations permitted by the rearrangement of its four bases, one has a substance which in principle could encode 10^{15} or more bits of information. He set up a theory as to how the pattern of nerve impulses entering the cell could determine

the stability of one of the four bases at a given site on a pre-existing RNA molecule. He was not however able to demonstrate this experimentally.

Interest in this spread rapidly. Morrell (13), using a technique whereby the production of an artificial epileptogenic area in the cortex of one hemisphere could produce a mirror epileptogenic area on the cortex of the opposite hemisphere in the same general area, demonstrated that this resulted in unusually high concentrations of ribonucleic acid in the abnormally discharging mirror focus.

Despite this interest, experimentation on the human subject was strangely absent. In 1956, when we commenced our studies of the role of RNA in the memorial process of aged individuals, so great are the ranges of scientific literature that we were quite unaware of the earlier conjectures of Katz and Halstead. So if the early theorists and microbiochemists seemed unaware of the possibilities offered by human investigation, those of us who were experienced in this field were equally unaware of those stimulating ideas which had grown up in the shadow of larger speculations concerning the structure of proteins and the micrometabolism of cells.

For over 20 years we had been working in an attempt to find some substance which would correct the memory deficit found in the aged. In 1955 Paul Weiss (14) made a report summarizing his work on the neuron in the previous several decades. It was a singularly stimulating report. He pointed out that the neuron—far from being a fixed or relatively static structure—is constantly in action, and that in particular it is continually producing material at the nucleated end which passes along, disappearing as it goes, towards the terminal structure of the axon. In a subsequent review of the work of himself and others (15), using both his axon-damming method and radioactive isotope tracers, he estimated that the flow occurred at the rate of 2–3 millimetres a day. Since there was some evidence that the substances might include the nucleic acids, as suggested by the earlier work of Hydén (16) and Samuels *et al.* (17), it was decided to start exploring the use of the nucleic acids in the human subject.

It seemed reasonable, seeing that DNA is primarily found in the nucleus, to start with it. We used this primarily in oral form but to a limited extent also in intravenous form, and got no results. We then turned to ribonucleic acid (RNA), both in oral and intravenous form, and began at least with the former to get definite although limited evidence of amelioration of memory deficits in the aged individuals we were studying. However, the earlier intravenous solutions were so apt to produce severe shock-like reactions, that they were stopped.

We continued improving oral administration, and as we did so and could give larger and larger amounts, we began to be increasingly certain that in a growing number of cases we were able to produce changes which could be recorded and statistically evaluated by the test instruments which we had devised—notably the counting test (18), certain parameters of the conditioned reflex procedure (19) and the Wechsler Memory Quotient.

In 1961, Dr. S. Sved, who had joined the biochemical side of our investigative team, was able to produce a greatly improved solution of RNA for intravenous use. This solution yielded much more rapid and much more extensive results and we were now able to differentiate between the responsiveness of three categories of patients showing organic brain deficits, namely, presenile, arteriosclerotic and senile (20).

The procedure which we presently follow calls for extensive pre-treatment evaluation, in which we employ the counting test, the Wechsler Memory Quotient and the following parameters of the conditioned reflex procedure which have been developed by Dr. Solyom of our research team into methods for estimation of memory change (21):

(*a*) Rate of extinction of the orienting reflex;
(*b*) Speed of acquisition of a conditioned reflex;
(*c*) Rate of retention of the conditioned reflex;
(*d*) Rate of extinction of the conditioned reflex;
(*e*) Capacity for discrimination between conditioned stimuli;
(*f*) Capacity to delay a conditioned reflex.

We now employ as well two types of a time-estimation test as developed for us by Mr.

Claude Beaulieu of our research group. The first is based on asking the individual to state when 5, 10, 15 and 30 seconds have passed from the time that a given sound was heard and the second is based on presenting the individual with given intervals of time and asking him to estimate how many seconds he feels they represent.

We have also started to explore dichotic memory tests, which involve passing a different signal in simultaneously through each ear and asking the individual to repeat them. This test, originally evolved by Broadbent (22), is based on the fact that one ear habitually shows itself to be dominant and therefore the data passed through the other ear must be held transiently in a memory storage system. The test is essentially one to show the efficiency of this storage system.

Along with the data, we record the electroencephalogram and collect a great deal of reportorial information through the medical staff and the social workers—the material being obtained both from the patient and his relatives. Furthermore, we are in the process of developing an occupational therapy battery to assess memory change.

Once these procedures have gone forward and once the dimensions and nature of the patient's memory deficit are defined, we select only those patients whose deficit is relatively stationary and who are not suffering from mood disorders or any serious physical condition which might in any way disturb the memorial capacity of the individual.

The subject is then given RNA in a 10 per cent. buffered solution, the basic material being obtained from yeast. We have employed a variety of intravenous procedures. First we used a low concentration method whereby 10 grams of RNA in a 10 per cent. solution were added to 1,000 c.c. of normal saline and given by slow drip over 6–8 hours. A second method has been to administer 10 grams of RNA in a 10 per cent. solution undiluted over a period of 50 minutes. These injections were usually given three times per week. A third procedure has been to give 1 gram of RNA in a 10 per cent. solution twice a day. The advantage of the first is that side-effects are kept down to a minimum. The advantage of the second is to secure a high concentration of RNA and its breakdown products in the blood, and the advantage of the third is to provide a more continuous (i.e. daily) administration of RNA and at the same time to avoid the side-effects. Our more recent studies, however, suggest that the first procedure is preferable.

The side-effects referred to consist primarily in nausea and abdominal discomfort, in cramping sensations in the extremities and in a fall in blood pressure. The severity of the side-effects is related to the speed of injection. The fall in blood pressure can be corrected by pressor agents such as aramine.

In 1961 Montanari *et al.* (23), using ribonucleotides in oral form, reported confirmation of our results.

After accumulating a considerable number of cases, we have found it possible to say that the best results are obtained in individuals whose memory disturbance is on an arteriosclerotic basis, the second group is that of the presenile, Alzheimer's and Pick's disease types, and the third group is the senile. In all three categories, the best results are obtained where the cases are treated in the early stages of memory defect.

The results demonstrating the greater effectiveness of intravenous as against oral administration can be seen on Table I. The results in intravenous administration can be seen on Table II and the breakdown of the group into presenile, senile and arteriosclerotic sub-groups can be seen in Tables III, IV and V. The further presentation of the effects upon delayed reflex formation can be seen in Table VI and with respect to discrimination there is a portrayal on Table VII. Changes in the direction of reduction in pathology were found in a majority of the EEG tracings taken after administration of RNA. These can be seen in illustrative cases recorded in Charts I and II.

In the meantime, other types of experimentation were now going forward which brought further evidence to support the hypothesis that ribonucleic acid is the substrate for memory. Certain of these approaches have already been discussed, and of the additional

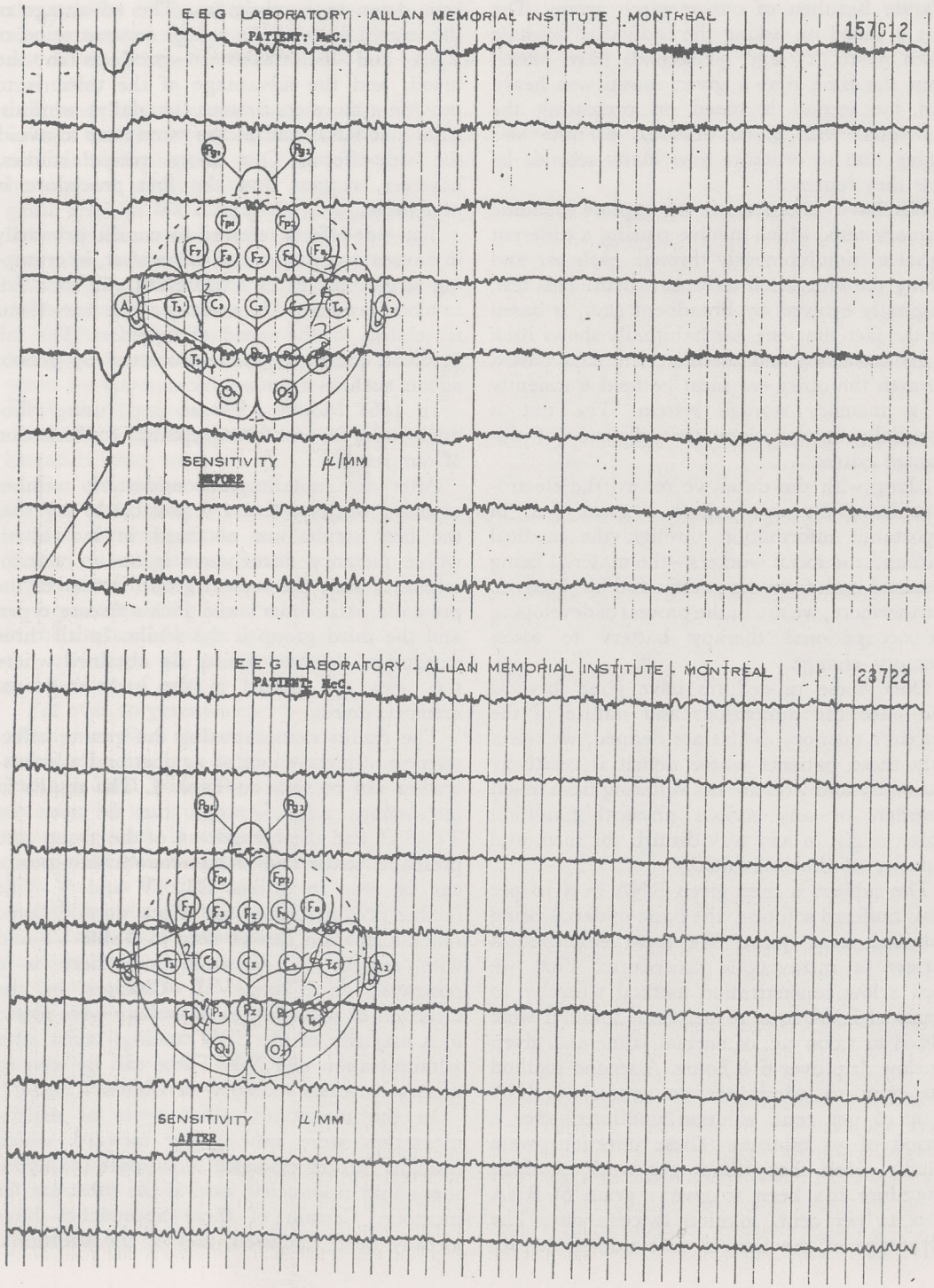


CHART I.—The alpha activity is more organized and regular and there is more alpha activity present after RNA treatment. Moreover, other abnormal activities are decreased.

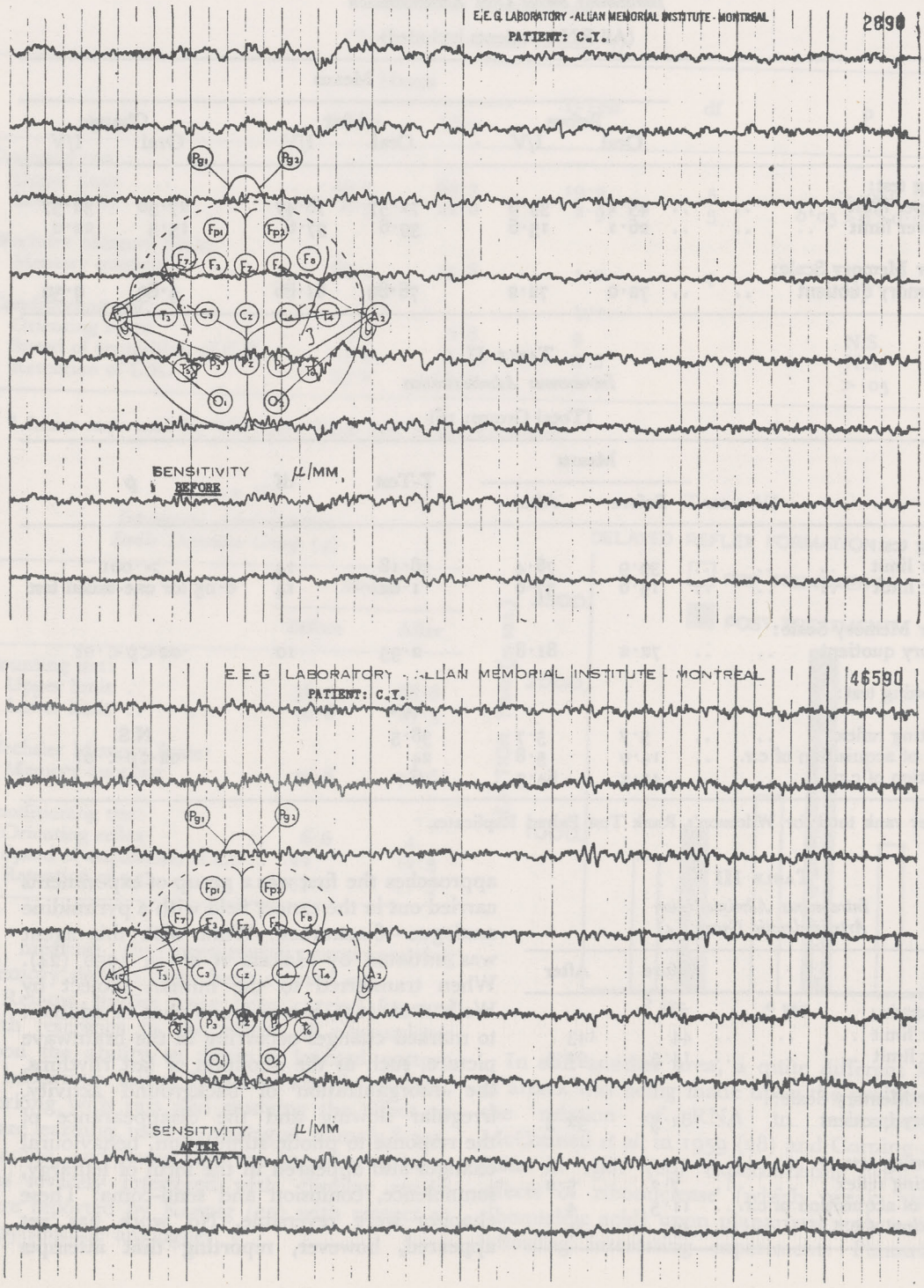


CHART II.—The alpha activity is more regular and of somewhat higher voltage after RNA treatment. The alpha index seems slightly higher.

TABLE I

Intravenous versus Oral Administration

(All RNA patients included)

	Means					
	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 II

Intravenous Administration

(Total Group: 16)

	Means		T-Test	df	p
	Before	After			
Counting test:					
Upper limit	39·9	78·4	38·18	14	>·001
Lower limit	15·6	37·6	1·82	14	0·05 for one-tailed test
Wechsler Memory Scale:					
Memory quotient	72·2	81·8	2·95	10	·02<p<·01
Conditioning test:					
			W*		
Orienting reflex	5·7	5·7	38·5		N.S.
Speed of acquisition of c.r. ..	14·0	5·8	24		·02<p<·01
Retention of c.r.	43·2	64·3	16		·02

* Lesser rank total for Wilcoxon's Rank Test Paired Replicates.

TABLE III

Intravenous Administration
Arteriosclerotic Group (4)

	Before	After
Counting test:		
Upper limit	44	143
Lower limit	14·5	92·5
Wechsler Memory Scale:		
Memory quotient	82·3	92·3
Conditioning test:		
Orienting reflex	7·2	5·2
Speed of acquisition of c.r. ..	11·5	4
Retention of c.r.	49	75

approaches the first was a group of experiments carried out in the cancer field with a pyrimidine analogue—6-azauracil. Work with this agent was initiated by Hakala *et al.* in 1956 (24). When transferred to the human subject by Wells *et al.* (25), it was found that in addition to marked changes occurring in the brainwave picture, such as the abolition of fast rhythms, the disorganization of background activity, irregular slowing and the disappearance of the response to photic stimulation, behavioural changes also appeared in the form of lethargy, somnolence, confusion and semi-coma. These changes were reversible. No work has yet appeared, however, reporting that attempts

TABLE IV

Intravenous Administration

(Presenile Dementia Group: 7)

	Means		T-Test	df	p
	Before	After			
Counting test:					
Upper limit	42·3	69·7	19·9	5	>·001
Lower limit	8·5	22·0	2·91	5	0·05>p>0·02
Wechsler Memory Scale:					
Memory quotient	69·4	75·8	1·0	4	N.S.
Conditioning test:			W*		
Orienting reflex	5·2	6·8	9		N.S.
Speed of acquisition of C.R. ..	14·3	5·14	3·5		N.S.
Retention of C.R.	39·0	69·4	1·5		>·05

* Lesser rank total for Wilcoxon's Rank Test Paired Replicates.

TABLE V

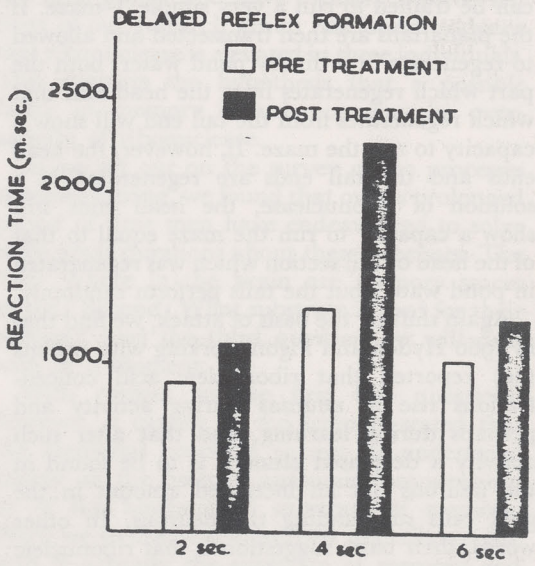
Intravenous Administration
Senile Dementia Group (4)

	Means	
	Before	After
Counting test:		
Upper limit	36·0	88·8
Lower limit	18·8	27·5
Wechsler Memory Scale:		
Memory quotient	70·6	76·6
Conditioning test:		-
Orienting reflex	6·6	4
Speed of acquisition of c.r. ..	22	12·3
Retention of c.r.	39·5	77·3

to measure the presumably accompanying memory deficits have been carried out.

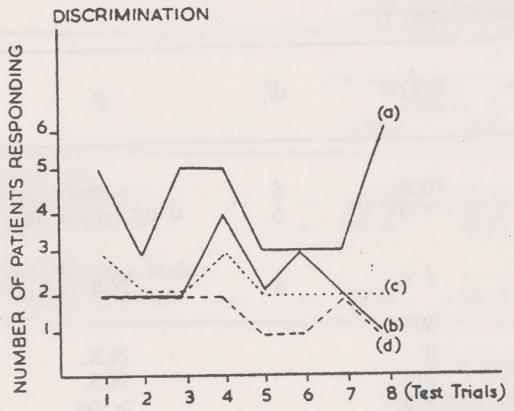
Related studies have been carried forward with reference to the effects of ribonuclease upon the ability to retain a learned pattern of behaviour. Later, Dingman and Sporn (26), working with rats and studying the effect on maze learning, used an analogue, namely 8-aza-guanine, and found that the capacity to learn was severely interfered with. Similar results were reported by Koenig (27) with respect to a pyrimidine analogue.

TABLE VI



In still another area, a quite different kind of attack was being made upon the problem of the relation of RNA to remembering. McConnell *et al.* in 1959 (28) and Corning and John in 1961 (29) experimenting with the effects of ribonuclease (which breaks down ribonucleic acid) upon planarians reported the following interesting experiment: Planarians

TABLE VII



(a) Response to positive stimuli after treatment
(b) Response to positive stimuli before treatment
(c) Response to negative stimuli before treatment
(d) Response to negative stimuli after treatment

can be trained to run a very simple T-maze. If the planarians are then transsected and allowed to regenerate in ordinary pond water, both the part which regenerates from the head and that which regenerates from the tail end will show a capacity to run the maze. If, however, the head ends and the tail ends are regenerated in a solution of ribonuclease, the head ends still show a capacity to run the maze equal to that of the head or tail section which was regenerated in pond water, but the tails perform randomly.

Again shifting the basis of attack, we find that in 1960 Hydén and Pigon working with rabbits (30) reported that ribonucleic acid concentrations rise in neurons during activity and perhaps during learning, and that after such activity a decreased amount is to be found in the neurons but an increased amount in the glial cells surrounding the neurons. In other words, their basic suggestion is that ribonucleic acid increases in amount in neurons during activity, and their second suggestion is that the glial cells possibly play a much more active part in cerebral activity and perhaps in memory than has hitherto been supposed. They consider that these findings give further support to the contention that the substrate of remembering is ribonucleic acid.

This may be the answer to a difficult question, namely, if the contents of the neuron are constantly streaming towards the end of the axon, how is it possible to ensure the maintenance of a fixed memory trace? However, this suggestion that the memory trace may actually be in the glial cells rather than in the neuron should only be taken as highly tentative, since our information concerning the contents of the neuron so streaming is based on evidence supplied by the electron microscope and also on Weiss' extraordinary earlier experiments in constricting the axon.

Still another possibility should be considered in endeavouring to understand the curious phenomenon of the continuing flow of material from the nucleated part to the peripheral end of the axon and the dilemma which this raises in attempting to explain how a trace is maintained. This possibility is that although the basic mass of a substance in the neuron may change both in amount and in identity (although not necessarily in nature), yet nonetheless the trace may remain as a design of organization.

A simple illustration of this can be seen in the skin, which remains relatively constant in location and in texture, but which is constantly being renewed, or again in the eddy and swirl on the surface of a stream, which remain the same although the water which forms them is forever changing.

In a similar manner, it is possible that a memory trace may endure, although the original RNA which was its substrate has been replaced by a new supply. Fluctuations in the amount of RNA, such as the increase which has been described during neural activity, may be linked with working proposals regarding active forgetting. Thus it is possible that when a considerable number of new memory traces are being formed, as when we are actively experiencing, an increased amount of RNA is required, but less will be needed when those memories created by our experiencing are no longer necessary and have been eliminated by a process of active forgetting.

Countless experiments such as those on rote learning, on immediate recall, have shown that while memory traces are endlessly being formed during our waking hours—and apparently to

some degree during our hours of sleep—a vastly greater proportion of them can no longer be recovered a few minutes after they have been formed.

It is moreover a matter of common experience that the number of bits of information which impinge upon the individual and to which he responds by forming temporary memory traces is clearly fluctuating. In turn, the individual shows considerable fluctuation in the extent to which he responds or, as one says in common language, in the extent to which he attends.

Weiss (31) although clearly basically concerned with the presentation of his concept of perpetual neuronal growth, approaches the problem of how fixed or relatively fixed memory traces are maintained in a substratum which may be constantly moving its location and also being broken up or replaced. He points to the high rate of synthesis of proteins and of ribonucleic activity and to the continuous flow of semi-solid materials from the nucleated part of the neuron to the end of its axon. He considers that the fact that the neuronal mechanism is undergoing perpetual renewal permits of adaptive remodelling.

He cites the example of the antigen causing not only the formation of antibody molecules when it is actually present, but resulting in modifying the cells in a lasting manner so that they continue to manufacture the same specific antibodies. He suggests that in a similar way the nuclear production apparatus of the nerve cell might in response to appropriate stimulation henceforth turn to molecules having a particular configuration.

It seems not unreasonable to suggest that nerve impulses evoked by meaningful experience as they pass through the nerve cells may alter the conformation of molecules in a lasting way. One may assume that as these molecules are reproduced they will tend to be identical with those formed by the original impulse. Here one may see the sketched-in outline of a theory serving to explain the preservation of engrams in a field which itself is constantly changing with respect to the substrate.

These things, however, remain highly speculative and we should not close the list of possibilities without pointing to the fact that we are only now beginning to discover the presence in the neuron of a highly complicated inner structure consisting of a great variety of organelles. Among these organelles we should mention the ribosomes which are reported as possessing a particularly high RNA content. The role of the various membranes which exist within the cells is still largely unknown. Among these membranes is the endoplastic reticulum which, while located in the cytoplasm, is thought possibly to have direct communication with the nuclear membrane. These organelles, of which reference is being made only to two, constitute what Brachet has termed the "cytoskeleton" (32).

Finally, quite recently we ourselves have made a further step forward in so far that we have begun to examine ribonuclease in the blood of normals and of various individuals in the aged group who have memory defects. Dr. Sved of our research group has found evidence that ribonuclease is elevated in these individuals. This suggests the hypothesis that a possible factor in memory disturbance may be overactivity of ribonuclease.

As we set out on the survey of the processes of remembering, we found that over a prolonged period of time men have endeavoured to solve three great questions about these processes. The first: Where in the brain are memory traces stored? Second: What substrate is used for their storage? And the third question we will deal with in a moment.

With respect to the first two questions, however, it cannot be too strongly stated that the memorial processes cannot be understood purely on the basis of anatomical connections or of the biochemical substrate of memory. Were we to discover tomorrow that ribonucleic acid is actually the substrate of memory and were we able to demonstrate how this substrate is used for the coding of memory, we would still be confronted with the vastly intricate matter of the total functioning of the memorial process—a matter which no doubt will concern coming generations of researchers. How does the incoming stimulus produce the memory trace? What is the nature of coding? How is the trace held? What is the role of the

emotional response? How does the retrieval mechanism find with such remarkable speed, and in most cases with such extraordinary accuracy, the tiny datum of information laid down in a day now far off. How are memory traces once coded then read out again?

Our third question then to which we now address ourselves is by far the most comprehensive and difficult. It is—placing to one side the question of the location of the storehouse of memory and the nature of the substrate—how do we remember and forget? The questions here are numerous, complex and far from solution. They include one that is outstanding in its complexity and in its fundamental nature. For, as we consider the intricate chain which runs from perception through recording of the memory trace and back through decoding of that trace to actual conscious recall, there breaks in time and again to face us that most profound of enigmas, namely, the conversion of neurochemical events into the events of consciousness.

It is in a sense well that we should be thus confronted, since undoubtedly some of our difficulties in understanding remembering arise from our having tended to explore the anatomical, biochemical and psychological aspects of this function separately. Whereas, if the process is taken as a whole, leads developed in any one part can be of assistance in others. For instance, it is well known that a stimulus situation must last for a given time for the individual to respond by developing a memory trace. This suggests that the necessary neurochemical mechanism requires a certain period of time to operate. This in turn means that we can eliminate from our questioning any neurochemical mechanisms which take appreciably longer to complete operation.

Or, again, we may point out that repetition serves to stabilize the memory trace as does the intensity of the meaning of the stimulus reaction. This raises conjectures as to the nature of the coding and storage procedures.

Finally, we may point to something that we shall shortly discuss in more detail, namely, that recognition is better preserved than is recall in organic memory deficits. This again makes one ask questions and perhaps serves to point our questions in given directions as to the nature of the storage of the memory trace.

In the course of our work on remembering, we have developed a working concept of the various stages of the memorial process as they occur at the behavioural level. It should be pointed out that this is a purely provisional picture and probably bears no more relationship to the final portrayal of the stages of remembering than do the architect's initial sketches to the finally completed building. This working concept is shown on Figure 1.

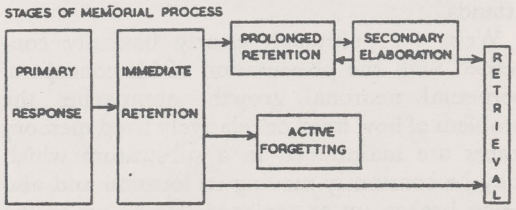


FIG. 1.

I shall not attempt to deal with the links separately, but shall make some overall observations and also deal with one or two points in the process which seem particularly promising for study.

The primary response is of course an organismal event. It is based upon psychological, neurophysiological and biochemical happenings. Nonetheless, when we describe its duration, this is most easily stated in terms of its neurophysiological events. Thus we may say that the primary response is in operation during that period when the inflow of neural impulses from some stimulus commences to the point where their encoding as a memory trace is completed. Here is at once an unanswered question. Is this the course of all incoming information or does some become held in a highly transitory form for perhaps a few seconds? . . . or up to a minute or two, according to some workers, in reverberatory circuits? . . . or for periods as long as half to one hour as suggested by John (33)?

Broadbent (22), and Inglis and Sanderson (34), on the basis of the former's dichotic testing procedure, have advanced a most explicit statement of memory as a two-stage procedure. And there is now a widely held belief that

memory is a two-stage procedure and hence in the Figure I have at least recorded a link for immediate retention and another link for prolonged retention.

The link dealing with active forgetting is more contentious, and there are those who claim, as you know, and to my mind quite absurdly, that nothing ever experienced and recalled no matter how briefly is ever forgotten, so that, theoretically, you should be able to remember the fifth poached egg that you ate in your life, the third person you met entering the railroad station in your home city 31 years ago, as well as the colour of the tie you wore on 16 August, 1952. Moreover, quite apart from these relatively discrete events, such a theory postulates recording of every conversation heard, the frequency of lightning flashes and thunderstorms which one has endured since birth, the structure and content of every reverie, all the songs you have heard and the order of every fleeting cloud formation ever seen and noted.

Quite clearly the burden of proof is on those who assert such a concept. Nature is well known to be most parsimonious, though if the end demands it prodigal in the extreme. But no such comprehensive and indeed total remembering of experience is required. What is valuable and useful for the individual to retain—beyond the brief retention necessary to afford continuity—is strictly limited. All evidence from a great many investigators using a very considerable variety of testing procedures suggests strongly that storage space in the brain is reserved for the memory traces of matters set there under the urgency of their special emotional significance for us and maintained there because of the frequency with which such memory traces are called upon—in a word, because they are especially meaningful or they are continually useful to us.

Indeed we have some evidence of this in studies we have carried on in the last two years on perseveration. The term "perseveration" is used here in the sense that has been employed by Bumke, Jaspers and Solder (35, 36, 37), namely, to designate a phenomenon which is particularly apt to appear in the organic brain syndrome. This consists in the patient tending to respond to a question by means of an answer which he has just given in reply to a quite different question. Using the counting test, we found that perseveration tended to interfere with retention, that it usually appeared at the upper limits of retention, and that it could only be overcome by means of massive reinforcement of the stimulus, as where one uses multiple modalities in attaining initial registration. We considered that there are grounds for thinking that perseveration is due to a failure in the process of forgetting; in other words, that the previous question and answer had not been removed from immediate retention.

Somewhere, and probably in the section described as prolonged retention, encoding takes place. Encoding and the formation of the trace appear to us at least at the present time to be functions which are difficult to separate. As is well known, men are at this moment in the process of breaking the genetic code which employs DNA as its substrate, but we are still without a lead as to how to break the memory code which we presume is based upon RNA. It is here that the use of analogues for the bases may be of great value.

A rapidly lengthening series of reports is appearing on how encoding takes place. Most of them, however, are derived from studies of mechanical and sometimes purely theoretical information. It would also appear that those attempting these approaches are handicapped by lack of direct experience with behavioural phenomena.

May I lastly pass on to a brief consideration of what also suggests a good lead—this time to the understanding of decoding or recollection. This lead lies within the section of retrieval and consists in the comparison of the process of recall and recognition. Here one may point to the very interesting phenomenon that if one after another one puts before a patient a series of numbers, it is quite easy to demonstrate the time interval beyond which he cannot recall. If one puts before him four numbers of which one is that in quest, he will be able to recognize the correct one over a much more extended period than he can recall correctly. It would seem that in the case of recall the stream of ingoing impulses derived from the question is

unable to reactivate the trace, but the trace is still there, for if this stream of ingoing impulses contains a pattern derived from the number which is being sought, it is possible to reactivate the trace. This clearly brings us to the question of how the trace is reactivated and opens the way for a series of interesting experimental approaches.

And so we complete our review of the great questions with which men have struggled from the earliest of times concerning this amazingly powerful cord which holds together all the days of our lives. Thus armed and supported, our powers infinitely amplified by all the scientific devices of our time, we draw near to the discovery of the answers to these ancient questions. We must in all humility pay tribute to the extraordinary penetration of those men who pondered these questions thousands of years ago with no devices to aid them, but fortified by the fact that if they had but one tool, it was and remains the most powerful of all—the mind of man.

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