

Neurosciences Research Program Bulletin

Volume 4 (Supplement)

Published July 15, 1966

C O N T E N T S

Page

CORRELATIONS BETWEEN SPECIFIC HUMAN BRAIN LESIONS AND MEMORY CHANGES

A Critical Survey of the Literature by
Robert G. Ojemann 1 ✓

HYSTERESIS AND MACROMOLECULAR MEMORY

A Discussion Paper (based on a Presentation
at the NRP Seventh Stated Meeting) by
Aharon Katchalsky and Abraham Oplatka 71 ✓

N 67-22581 N 67-22583

FACILITY FORM 802

(ACCESSION NUMBER)
97
(PAGES)
CR-83422
(NASA CR OR TMX OR AD NUMBER)

(THRU)
1
(CODE)
04
(CATEGORY)

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N 67-22582

CORRELATIONS BETWEEN SPECIFIC
HUMAN BRAIN LESIONS AND MEMORY CHANGES

A Critical Survey of the Literature,
Dated June 15, 1966*

by

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*In June 1964, the NRP Bulletin (Vol. 2, No. 3, Pp. 77-144) published a critical survey of studies in the literature that correlate specific loss or absence of brain tissue with memory deficit. Since demand for this survey far exceeded supply - it has been out of print for well over a year - we decided to publish an updated and re-edited version that would include new material published during the two years since the first edition.

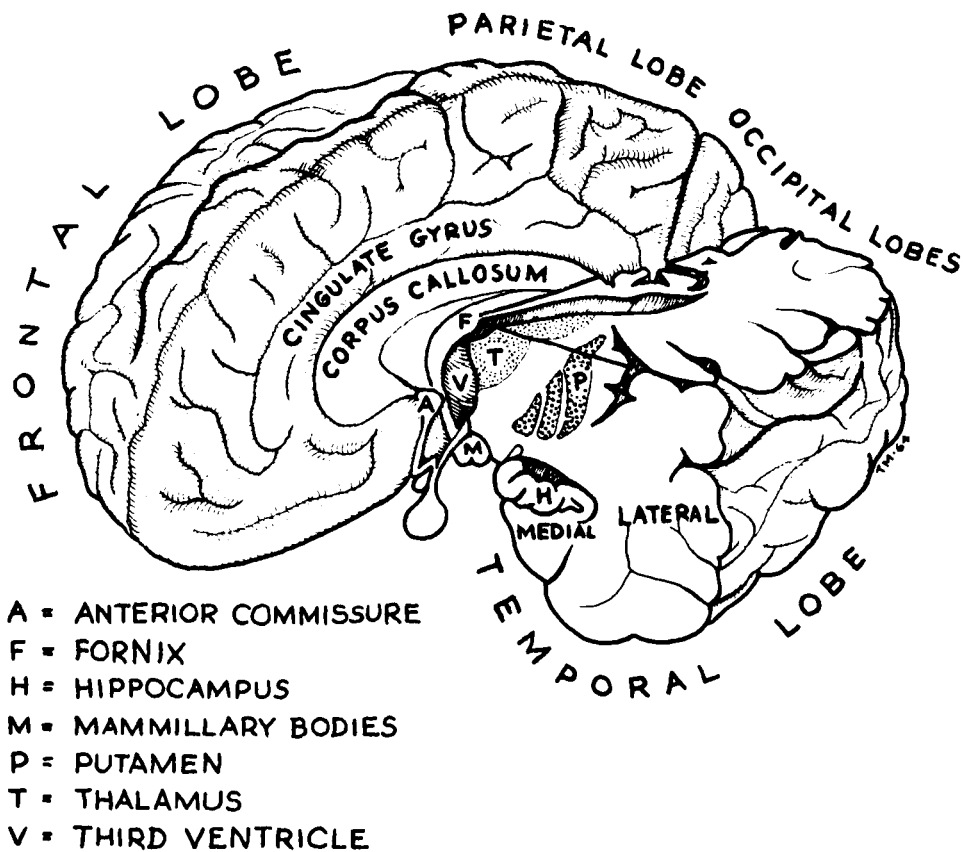
Accordingly, Dr. Ojemann, though no longer a member of the NRP Resident Scientist group, agreed to undertake the revision and updating of this review which had such great practical and theoretical interest for our interdisciplinary audience in its earlier form.

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Figure 1. Cut-away perspective drawing of a human brain, showing the spatial relationships of most of the regions and structures thought to be related to general memory function. (The putamen is shown only as a landmark for readers familiar with the brain.) [Ojemann - Melnechuk]



INTRODUCTION

Certain specific areas of the human brain are known to be important to mechanisms in the recording, storage and retrieval of information. (1-9) This report is a critical survey of the literature that correlates a specific loss of brain tissue, resulting from surgical removal, disease or congenital absence, with the details of the memory deficit, or lack of deficit, recorded for each case. Some of the literature, however, is of limited value, since in some cases general terms

(1) Jasper, H., Gloor, P. and Milner, B. (1956): Higher functions of the nervous system. Ann. Rev. Physiol. 18:359-386.

(2) Adams, R.D. (1959): Concerning certain psychological principles which have been derived from clinico-pathologic study. Trans. & Studies College of Physicians of Phila. 27(I): 1-11.

(3) Victor, M., Angevine, J.B., Jr., Mancall, E.L. and Fisher, C.M. (1961): Memory loss with lesions of hippocampal formation. Arch. Neurol. 5:26-45.

(4) Brierley, J.B. (1961): Clinico-pathological correlations in amnesia. Gerontol. Clinica 3:97-109.

(5) Whitty, C.W.M. (1962): The neurological basis of memory. In: Modern Trends in Neurology. Williams, D., ed. Washington: Butterworth, Pp. 314-335.

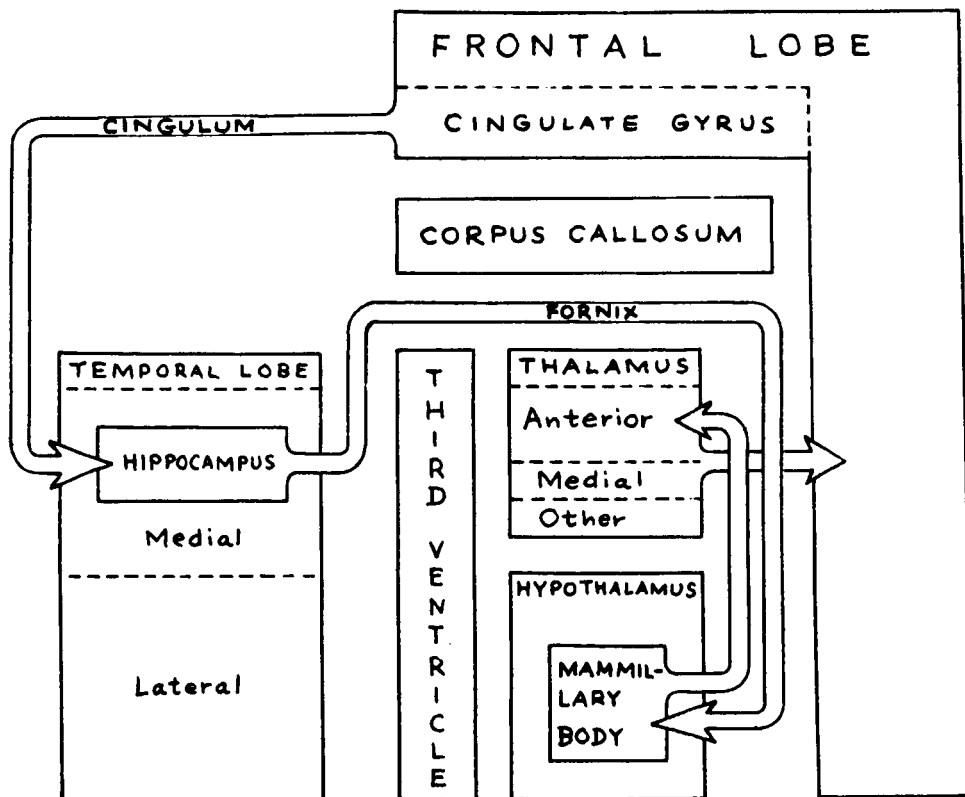
(6) Barbizet, J. (1963): Defect of memorizing of hippocampal - mammillary origin: A review. J. Neurol. Neurosurg. Psychiat. 26:127-135.

(7) Drachman, D.A. and Ommaga, A.K. (1964): Memory and the hippocampal complex. Arch. Neurol. 10:411-425.

(8) Adams, R.D., Collins, G.H. and Victor, M. (1961): Troubles de la mémoire et de l'apprentissage chez l'homme. Leurs relations avec des lésions des lobes temporaux et du diencéphale. In: Physiologie de L'Hippocampe. (Colloques Internationaux du Centre National de la Recherche Scientifique. No. 107.) Paris:C.N.R.S. Pp. 273-295.

(9) Piercy, M. (1964): The effects of cerebral lesions on intellectual function: A review of current research trends. Brit. J. Psychiat. 110:310-352.

Figure 2. Schematic diagram of human brain structures and connections thought to be related to general memory function. Coverage in the text begins with the medial temporal lobe and generally follows the course of the outflow circuit from the hippocampus as shown below. [Ojemann - Melnechuk]



are used without qualification to describe the memory deficit, and in other cases the specific tests utilized in determining a lack of memory loss are not recorded. We can have absolute proof of the exact boundaries of the lesions only in those cases where direct examination of the brain is possible; still, localized surgical lesions can give us valuable information.

This report is intended to be an easily accessible summary of this information, together with an appropriate bibliography for use by all scientists, particularly those with non-medical backgrounds who are interested in this field. We hope that new questions may be provoked and areas of investigation synthesized or guided in the light of the known relationships compiled here.

The regions of the brain thought to be most important in general memory function are shown in Fig. 1. We begin the discussion with the hippocampal region and adjacent structures because of the emphasis placed on this region in recent years and its reported relationships to memory function. The anatomic pathway of the major outflow from the hippocampus will be followed (see Fig. 2), and then attention will be given to the remaining cortical regions. Each lesion will be illustrated by an anatomic drawing.

It has been stated by Adams⁽⁸⁾ that "the neocortex itself is involved in the mechanisms of all special auditory, visual, tactile, and other learning and memories as well as those for words, mathematical figures, etc.; for lesions here abolish specific memories and prevent relearning of that type of material." Brain damage associated with aphasia, agnosia and apraxia has been the subject of a number of reviews (see Nielsen⁽¹⁰⁾). Lesions causing these disorders do involve these special types of memory function but do not alter memory as a whole and will not be considered in this review.

Changes in memory will be described in three general categories: First, a loss of ability to store recent memory, as measured by inability to learn or record ongoing day-to-day events. Second, amnesia for events immediately prior to the loss of brain tissue; this period may vary from less than a day to several months. Third, memory for events from the distant past, that is several years before the lesion. Changes

(10) Nielsen, J.M. (1962): Agnosias, apraxias, speech and aphasia. In: Clinical Neurology. Baker, A.B., ed. New York: Harper. Pp. 433-459.

in affect will also be indicated, because this aspect may be an integral part of the memory mechanism or may alter the testing of memory function. Lewis(11) has stated that "closer examination of false memories suggests that much of what is remembered and even more of what is forgotten depends on emotional forces."

The results of psychological tests will be presented when available. Descriptions of the various tests used are given in the Appendix. To evaluate immediate-memory measurements by psychological tests is complicated in that the tests vary with respect to the nature of the content, the sensory modality carrying the test stimuli, the use of recall or recognition as the measure, and the type of response scored.

Heilbrun(12) attempted to determine the effect on memory test results of patients' loss of verbal skill following left hemisphere injury and loss in spatial skill following right hemisphere injury. Caution was indicated in drawing conclusions about a patient's memory function from a single type of test. However, for a large group of "brain damage" patients, tests indicated that differential impairment in verbal and spatial tasks did not produce substantial specific decline in memory.

I. MEDIAL TEMPORAL LOBE

A. Bilateral Infarction

The first report to associate a memory disturbance in the human being* with an alteration in temporal lobe structure

* In 1888 Brown and Schafer(13) described an apparent disturbance of memory in monkeys after the partial or total removal of both lobes.

(11) Lewis, A. (1961): Amnesic syndromes. Proc. Roy. Soc. Med. 54:955-961.

(12) Heilbrun, A.B., Jr. (1960): Specificity of immediate memory function associated with cerebral cortex damage. J. Ment. Sci. 106:241-245.

(13) Brown, S. and Schäfer, E.A. (1888): An investigation into the functions of the occipital and temporal lobes of the monkey's brain. Philos. Trans. Roy. Soc. (London): 179:303-327.

was by von Bechterew⁽¹⁴⁾ in 1900. This was a brief summary of a patient who had shown an extraordinary degree of memory disturbance, as well as considerable apathy, for many years. Examination of the brain revealed bilateral softening of the cortex and underlying structures of the medial temporal area.

In 1952 Glees and Griffith⁽¹⁵⁾ reported a case with a severe retentive memory defect. Victor and co-workers⁽³⁾ summarized this case: "They described the case of a 58-year-old woman who was hospitalized in a state of disorientation and agitation, and who showed a marked disorder of memory, more profound for recent events than for those of the remote past. Two months after admission she lapsed into an automatic and vegetative way of life, in which she was quiet and withdrawn. The impairment of recent and remote memory was said to progress until her death 15 years later. The patient's mental state prior to the onset of her illness was not recorded, nor was the disorder in cognitive function clearly delineated. Pathologically, destructive bilaterally symmetrical cyst-like lesions limited to the hippocampal and fusiform gyri were described. The number of fibers in the fornix was markedly reduced, but the mammillary bodies were considered normal."

B. Bilateral Surgical Resection

The medial temporal-lobe lesions to be described below are diagrammed in Fig. 3.

1. Uncus, Amygdala, Anterior Two-Thirds of Hippocampus (8 cm. from Tip of Temporal Lobe)

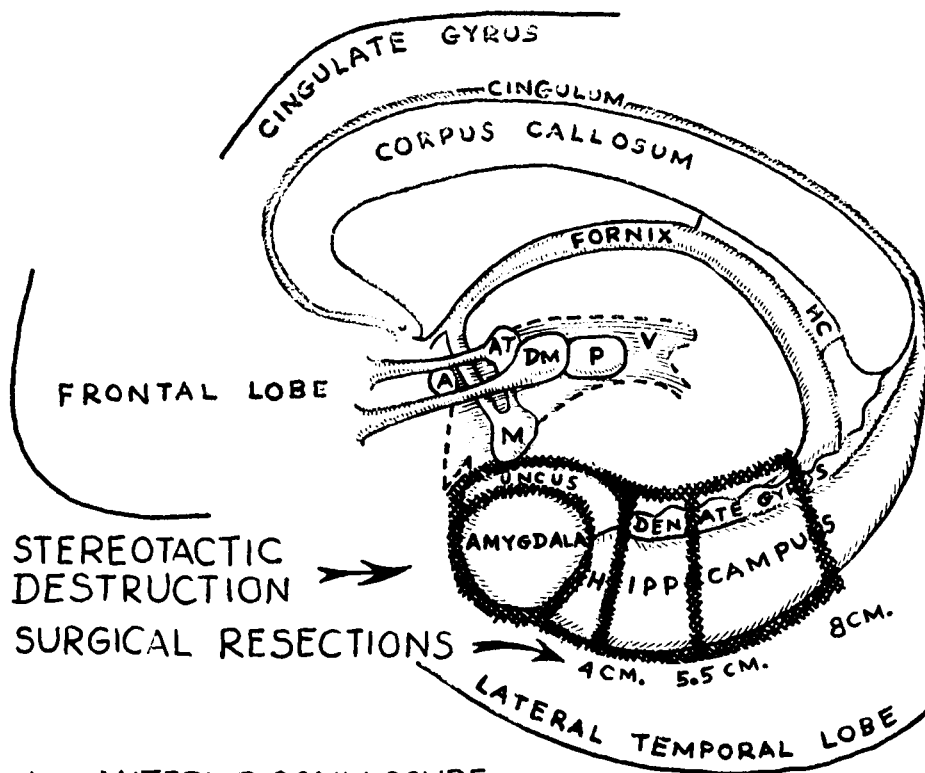
In 1954, Scoville⁽¹⁶⁾ briefly reported two cases in which this resection caused "very grave recent memory loss." The detailed report of these deficits was presented by Scoville

(14) von Bechterew, W.V. (1900): Demonstration eines Gehirns mit Zerstörung der vorderen und inneren Theile der Hirnrinde beider Schläfenlappen. Neurol. Cbl. 19:990-991.

(15) Glees, P. and Griffith, H.B. (1952): Bilateral destruction of the hippocampus (cornu ammonis) in a case of dementia. M Schr. Psychiat. Neurol. 129:193-204.

(16) Scoville, W.B. (1954): The limbic lobe in man. J. Neurosurg. 11:64-66.

Figure 3. Schematic diagram of lesions in the medial temporal lobe. [Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
 AT = ANTERIOR THALAMIC NUCLEUS
 DM = DORSAL-MEDIAL THALAMIC NUCLEUS
 HC = HIPPOCAMPAL COMMISSURE
 M = MAMMILLARY BODY
 P = PULVINAR THALAMIC NUCLEUS
 V = THIRD VENTRICLE

and Milner⁽¹⁷⁾ in 1957 and later amplified by Milner.⁽¹⁸⁾ No lateral temporal or frontal cortex was resected, since the surgical procedure was to elevate the frontal lobes to expose the medial temporal areas.

Case 1. A 29-year-old male high school graduate with intractable seizure. The EEG showed diffuse abnormality. Prior to operation there was no memory deficit and no seizure aura. After surgery the following deficits were permanent:

(1) Recording of ongoing events: He could recall nothing of day-to-day events.

(a) Examples in activities: He could not keep in mind where objects in continual use were kept; would do the same puzzles or read the same magazine repeatedly without showing any evidence of learning; thirty minutes after lunch could not remember eating; could not learn a new home address or find his way to a new house.

(b) Examples in specific tests: On the Wechsler Memory Scale*, immediate recall fell far below average. On "associate learning," he scored zero on hard words and very low on easy words. He failed to improve with practice, and a few minutes after the test he had no memory of it. If not disturbed, he could retain a three-figure number or a pair of unrelated words for several minutes; but as soon as his attention was diverted there was no recollection of the figures or words. For example, he was able to retain the number 584 for at least 15 minutes in the following way: "It's easy. You just remember 8. You see, 5, 8 and 4 add to 17. You remember 8, subtract it from 17, and it leaves 9. Divide 9 in half and you get 5 and 4, and there you are. 584. Easy." Psychological tests revealed good motivation, and no deficits of perception, abstract thinking or reasoning. IQ = 112.

(2) Amnesia: He could not recall any portion of the period of hospitalization prior to operation; could not recog-

*See Appendix for a description of this test.

(17) Scoville, W.B. and Milner, B. (1957): Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiat. 20:11-21.

(18) Milner, B. (1959): The memory defect in bilateral hippocampal lesions. NLM Psychiat. Res. Rep. 11:43-52.

nize the hospital staff; did not remember the death of a favorite uncle three years before; but could recall some minor events that had occurred just prior to his admission.

(3) Distant memory: No impairment.

(4) Personality and emotion: No change.

Case 2. A 55-year-old woman, former clerical worker, with manic-depressive psychosis. Prior to operation, recent memory was normal. There had been no seizures. After operation the following deficits were apparently permanent:

(1) Recording of ongoing events: Twenty-eight months after the operation she had no memory for any event since surgery. Immediate recall was inaccurate, and delayed recall, impossible. Vocabulary, attention and comprehension were normal.

(2) Amnesia: She could not recall the one-year period of hospitalization prior to operation.

(3) Distant memory: Probably fairly good.

(4) Personality and emotion: "Neater and more even-tempered and is held to be greatly improved."

2. Uncus, Amygdala, Anterior Hippocampus (5-5.5 cm. from Tip of Temporal Lobe)

Three cases with this resection were reported by Scoville and Milner.⁽¹⁷⁾ In the first case, amplified by Milner,⁽¹⁸⁾ the memory loss was similar to that described in those patients with an 8 cm. removal; so, although only a 5.5 cm. resection was recorded, it is possible that the effects of the surgical removal could have extended further posteriorly.

Case 1. A 47-year-old physician with paranoid schizophrenia. Apparently memory was normal prior to operation although this is not definitely stated. The EEG at operation showed spiking bilaterally from the medial temporal regions.

(1) Recording of ongoing events: He could not recall any events following the operation; was unable to learn the name of the hospital or examiner; could not recognize his own drawings. Immediate recall was poor; once a new task was

introduced, previous tests were completely forgotten. IQ = 122.

(2) Amnesia: He did not recall hospitalization of six months prior to the operation.

(3) Distant memory: He could give minute details of early life and medical training.

(4) Personality and emotion: Now friendly with no return of aggressive behavior, but paranoid ideas continued.

In Cases 2 and 3, a persistent memory defect was present, but not of such a severe degree. Memory deficits in three additional patients, whose operations were combined with a frontal lobotomy, were similar.

Case 2. A 35-year-old woman with paranoid schizophrenia. The status of her memory prior to surgery is not recorded. She had had "extensive" electro-shock therapy. Three and one-half years after surgery there was persistent difficulty with memory.

(1) Recording of ongoing events: This was impaired but not completely absent.

(a) Examples of activities: She could give the address of the house where she had worked for only two days and could describe the furnishings, although she had not learned the name of her employer. She could give a brief description of a new doctor who had spoken to her briefly several hours before, but could recall little of the conversation.

(b) Examples from psychological testing:
IQ = 96. Immediate recall of stories was normal, but going on to the next story was enough to wipe out most of the first story. Visual and verbal tests showed some impairment. She could not learn unfamiliar word associations.

(2) Amnesia: Retrograde amnesia for the entire period of her illness (over three years).

(3) Distant memory: No evaluation reported.

(4) Personality and emotion: Dramatic improvement in her psychotic state with remission of delusions, anxiety and paranoid behavior.

Case 3. A 44-year-old schizophrenic woman. No comment is made about memory prior to her operation. Testing was reported to be difficult because she was "too distractable."

(1) Recording of ongoing events: Only partial impairment was noted.

(a) Examples from activities: She knew where she had been working in the hospital and what she had done several hours before.

(b) Examples from psychological testing: Deficits were reported to be the same as in Case 2.

(2) Amnesia	}	No evaluation reported.
(3) Distant Memory		
(4) Personality and Emotion		

3. Uncus, Amygdala (4 cm. from Tip of Temporal Lobe)

Scoville and Milner⁽¹⁷⁾ reported one case of bilateral removal of the uncus and amygdala. No change in memory function was noted either in activities or in detailed psychological tests. Other reports of bilateral ablation of the amygdala, summarized by Terzian,⁽¹⁹⁾ include Williams,⁽²⁰⁾ Walker,⁽²¹⁾ and Sawa.⁽²²⁾ An alteration in general memory function as part of the postoperative clinical picture was not recorded.

(19) Terzian, H. (1958): Observations of the clinical symptomatology of bilateral partial or total removal of the temporal lobes in man. In: Temporal Lobe Epilepsy. Baldwin, M. and Bailey, P., eds. Springfield, Ill.: C.C. Thomas. Pp. 510-529.

(20) Williams, J.M. (1953): The amygdaloid nucleus. A clinical study of its ablation and a theory as to its function. Confin. Neurol. 13:202-221.

(21) Walker, A.E. (1953): Res. Publ. Ass. Nerv. Ment. Dis. 31:370-371.

(22) Sawa, M., Ueki, Y., Arita, M. and Harada, T. (1954): Preliminary report on the amygdaloidectomy on the psychotic patients, with interpretation of oral-emotional manifestation in schizophrenics. Folia Psychiat. Neurol. Jap. 7:309-329.

C. Sterotactic Lesion: Amygdala

Sixty patients with temporal lobe epilepsy or behavior disorders, in some cases associated with mental retardation, were treated by stereotactic destruction of the amygdaloid nucleus (Narabayashi and co-workers⁽²³⁾). In 21 of these cases the lesions were made bilaterally. No evidence of signs of the Klüver-Bucy syndrome^(24,25) was observed including disturbances in memory functions. It was noted, however, that some observations were limited because of pre-existing mental deficiency in these patients.

D. Other Lesions

Drachman and Arbit⁽²⁶⁾ compared six patients with memory defects due to bilateral lesions of the hippocampal complexes with a group of 20 normal patients. The type and extent of the pathologic process was not defined.

"Two new behavioral tasks were used in which memoranda of gradually increasing length were presented. The memoranda in the first task consisted of series of numbers from 5 to 20 digits in length; in the second, memoranda consisted of series of light patterns using from 3 to 10 pairs of lights. In each task, the shortest series was presented first, and the subject attempted to recall the memorandum after a single presentation. Successively longer memoranda were then presented; the longest memorandum recalled on single trial represented the subject's immediate memory span (IMS) for that task. Longer (supra-span)

(23) Narabayashi, H., Nagao, T., Saito, Y., Yoshida, M. and Nagahata, M. (1963): Stereotaxic amygdalotomy for behavior disorders. Arch. Neurol. 9:11-26.

(24) Klüver, H. and Bucy, P.C. (1939): Preliminary analysis of functions of the temporal lobes in monkeys. Arch. Neurol. Psychiat. 42:979-1000.

(25) Klüver, H. (1951): Functional differences between the occipital and temporal lobes with special reference to the interrelations of behavior and extracerebral mechanisms. In: Cerebral Mechanisms in Behavior. Jeffress, L.A., ed. New York: Wiley, pp. 147-182.

(26) Drachman, D.A. and Arbit, J. (1966): Is memory a multiple process? An experimental study of patients with hippocampal lesions. Neurology 16:312-313.

memoranda were then presented in succession, allowing up to 25 trials for the learning of each memorandum. The longest series of numbers recalled within 25 trials was considered the subject's digit storage capacity (DSC); the longest series of paired lights was the paired light storage capacity (PLSC).

Patients with hippocampal lesions showed no impairment of IMS compared with normal controls, indicating that lesions of the hippocampal complexes do not interfere with immediate memory mechanisms. With supra-span memoranda, however, DSC and PLSC were severely impaired in the patients; all six patients had lower scores than any of 20 normal controls. Further, patients with hippocampal lesions failed to show improvement of performance on successive trials, while normals achieved higher numbers of correct responses with repetition."

II. LATERAL TEMPORAL LOBE

A. Surgical Resection

Adams (8) has noted that some special memory deficits are related to the temporal neocortex. (See Introduction, page 5) Milner, (27) in discussion of this paper, reported visual memory deficits following right temporal lobectomy where the hippocampus was spared (Fig. 4). These abnormalities were made worse when the hippocampus was added to the resection. Details of these cases are not given.

In four cases of extensive bilateral ablation of the temporal cortex sparing the medial aspect (Fig. 4), Baily et al., (19,28) did not observe a gross alteration in memory function.

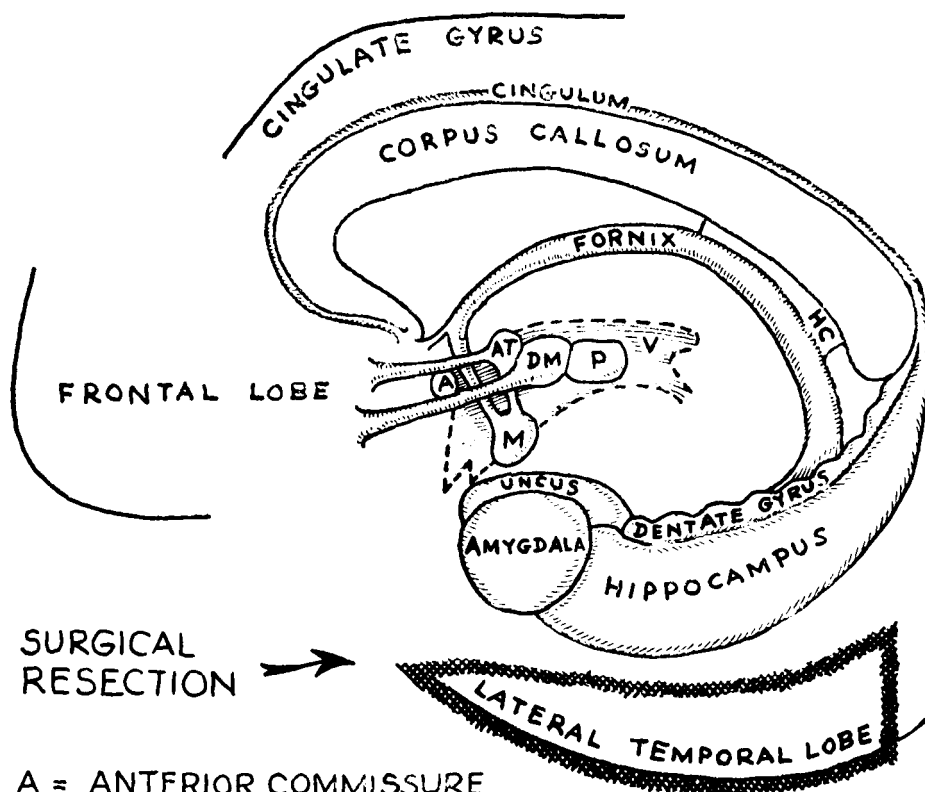
Petit-Dutaillis et al., (29) have reported a patient with frequent psychomotor seizures and a psychotic syndrome. First a right anterior temporal lobectomy was carried out with removal of the uncus. Five months later a left lateral lobectomy, not including uncus or hippocampus, was performed. Following this second operation there was confusion in the initial postoperative period; but one month later it was apparent that there was a retrograde amnesia for a period of months preceding the hospitalization, and this was apparently a permanent deficit. A transient inability to retain the sense of a phrase that he had just read correctly was also noted.

(27) Milner, B. (1961): Discussion, p. 292. In: Adams, R.D., et al., ref. 8.

(28) Baily, P., Green, J.R., Amador, L. and Gibbs, F.A. (1953): Treatment of psychomotor states by anterior temporal lobectomy. A report of progress. Res. Publ. Assoc. Nerv. Ment. Dis. 31:341-346.

(29) Petit-Dutaillis, D., Christophe, J., Pertuiset, B., Dreyfus-Brisac, C. and Blanc, C. (1954): Lobectomie temporale bilaterale pour epilepsie. Evolution des perturbations fonctionnelles postoperatoires. Rev. Neurol. (Paris) 91:129-133.

Figure 4. Schematic diagram of lesion in the lateral temporal lobe. [Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
 AT = ANTERIOR THALAMIC NUCLEUS
 DM = DORSAL-MEDIAL THALAMIC NUCLEUS
 HC = HIPPOCAMPAL COMMISSURE
 M = MAMMILLARY BODY
 P = PULVINAR THALAMIC NUCLEUS
 V = THIRD VENTRICLE

III. ENTIRE TEMPORAL LOBE

The temporal-lobe lesions to be described below are diagrammed in Fig. 5.

A. Bilateral Resection

Terzian and Ore⁽³⁰⁾ reported a case where each temporal lobe was resected to a point 7 cm. from the tip, in an attempt to treat a seizure and psychic disorder. In addition to the memory deficit, the patient showed disorientation, loss of recognition of people, alexia, agraphia, increased sexual activity and remarkable changes in dietary habits and emotional behavior, which resembled the syndrome of Klüver and Bucy^(24,25) described in monkeys.

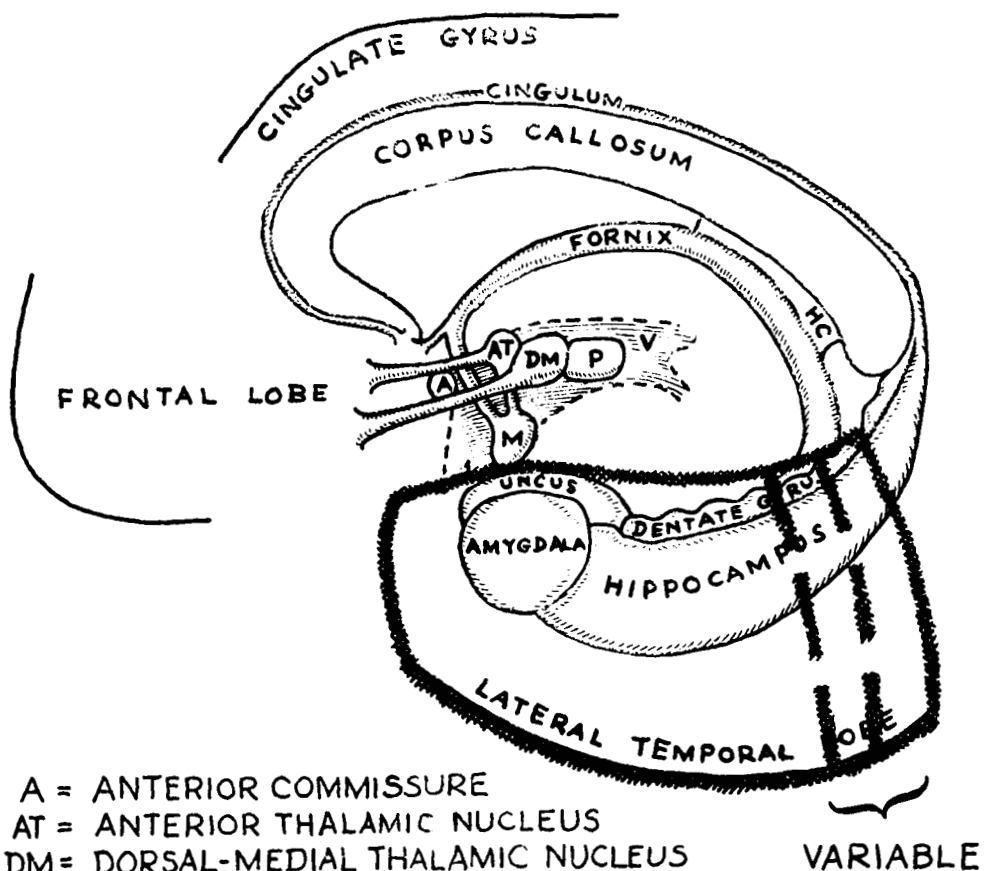
The memory deficit was described as follows: "There was a serious disorder in his memory. Not only did he not remember at all what had recently happened, he did not remember anything of his past. Even when we insisted on knowing something about his house, his family, the city he lived in, the patient did not even seem to understand these questions, as if their object was entirely unknown to him. It was not possible to analyze his memory functions, but we can affirm that the patient felt completely isolated, without a past to remember and consequently without any future whatever." Four years after operation "grave memory defects persist, although some improvement of fixing attention was noted."⁽¹⁹⁾ Unfortunately, the complexity of the syndrome and the inability to do detailed testing leave us in doubt as to the exact status of memory function.

Terzian⁽¹⁹⁾ has discussed two cases reported by Paillas⁽³¹⁾ where a bilateral temporal lobectomy, including uncus and part of the hippocampus, was performed for epilepsy. After removal of the second temporal lobe a disturbance of memory for recent events was noted, with no impairment of remote memory.

(30) Terzian, H. and Ore, G.D. (1955): Syndrome of Klüver and Bucy. Reproduced in man by bilateral removal of the temporal lobes. Neurology 5:373-380.

(31) Paillas, J.E. (1952,1953): Cited by Terzian, H., in reference 19.

Figure 5. Schematic diagram of lesions in the entire temporal lobe. [Ojemann - Melnechuk]



A bilateral temporal lobectomy was performed in one case by Falconer.⁽³²⁾ The patient "had profound disturbance of memory." Details of this alteration in memory are not recorded, and the patient died six months after surgery from status epilepticus.

B. Unilateral Resection

Penfield and Milner⁽³³⁾ note that unilateral operations do not usually cause a generalized memory disturbance. A mild difficulty in learning and retention of verbal material is seen in most patients with epileptogenic lesions of the dominant temporal lobe prior to operation, and this may be accentuated slightly by removal of the lesion. In over 80 cases with unilateral partial temporal lobectomy including hippocampus and hippocampal gyrus, psychological tests have failed to show any generalized memory loss.

Serafetinides and Falconer⁽³⁴⁾ reported resection of the right anterior temporal lobe for seizures. A transient impairment in memory was noted in only two of 27 patients. Postoperative EEG in all cases did not reveal any evidence of focal disease in the contralateral temporal lobe. In a series of 60 patients with subtotal temporal lobectomy, Baldwin⁽³⁵⁾ recorded six cases where removal of one temporal lobe, including uncus, amygdala and anterior hippocampus, was associated with a transient memory deficit.

Removal of the inferior non-dominant right temporal lobe (9 cm. from temporal tip) was reported by Scoville and Milner⁽¹⁷⁾ in a patient with cerebral edema following resection

(32) Falconer, M.A. (1955): Treatment of temporal-lobe epilepsy by temporal lobectomy. A survey of findings and results. Lancet 1:827-835.

(33) Penfield, W. and Milner, B. (1958): Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch. Neurol. Psychiat. 79:475-497.

(34) Serafetinides, E.A. and Falconer, M.A. (1962): Some observations on memory impairment after temporal lobectomy for epilepsy. J. Neurol. Neurosurg. Psychiat. 25:251-255.

(35) Baldwin, M. (1956): Modifications psychiques survenant après lobectomie temporale subtotale. Neurochirurgie 2:152-195.

of a brain tumor. For several weeks a disturbance of recent memory, similar to that noted in the bilateral medial resections, was present; but sixteen months later the deficit had disappeared. This temporary loss of memory might have been related to disturbed function in the opposite (left) temporal lobe from compression and edema. Another case took a similar course after removal of the non-dominant temporal lobe because of cerebral edema associated with subarachnoid hemorrhage and a temporal-lobe hematoma from an aneurysm.(16)

Walker(36) reported a lasting memory defect in four patients following abolition of one temporal lobe; but Victor,(3) with whom I agree, thought that in only one of these cases could one be fairly certain that the lesion was confined solely to the operative area.

In this case, (a 40-year-old housewife), the left temporal lobe was resected at 5 cm. to expose an aneurysm of the left internal carotid artery. There was no clinical or EEG evidence of damage to the opposite temporal lobe, but with this disease a "silent" area of infarction might be missed. Eleven months after the operation the patient's memory was characterized by inability to record ongoing events, such as being unable to follow a story on television and even a short paragraph. Memory for distant events was good.

Kimura(37) noted that patients with right temporal resection did not recognize previously presented visual designs nearly as well as those with left temporal removal. Since the ability to recognize material immediately after presentation is unimpaired, the defect is not perceptual.

Meyer and Yates(38) reported on six cases in which the dominant temporal lobe had been removed at distances of 5 cm. to 9 cm. by Falconer to treat seizures. Immediately after the

(36) Walker, A.E. (1957): Recent memory impairment in unilateral temporal lesions. Neurology 78:543-552.

(37) Kimura, D. (1963): Right temporal-lobe damage. Perception of unfamiliar stimuli after damage. Arch. Neurol. 8:264-271.

(38) Meyer, V. and Yates, A.J. (1955): Intellectual changes following temporal lobectomy for psychomotor epilepsy. Preliminary communication. J. Neurol. Neurosurg. Psychiat. 18:44-52.

operation, tests showed significant impairment in new-word learning, associate learning and retention.* One year after the operation, four patients showed no deficit on standard intelligence tests, but were "incapable of learning unfamiliar verbal-auditory material." This deficit in auditory-verbal learning ability was confirmed in a larger series of cases by Meyer.(39)

Dimsdale, Logue and Piercy(40) have recently recorded a case where a right temporal lobectomy, performed for focal epilepsy, resulted in a persistent memory deficit. There was no evidence at any time, from electroencephalography, air encephalography, angiography, or clinical examination, of abnormality in the opposite cerebral hemisphere. Absolute proof of this fact, of course, cannot be determined; but, the immediate postoperative course suggests to me that there may have been interference with function in the opposite temporal lobe which could have been followed by a "silent" permanent lesion.

Case report: A 53-year-old woman with depression, paranoid ideas and epilepsy. At operation, a 7 cm. resection of the right temporal lobe was performed. Immediately post-operatively, "she was drowsy and with no spontaneous conversation although she was easily aroused and co-operative and replied to questions and commands. She was variably orientated for time but usually correctly orientated for place. Memory was not otherwise tested at this stage. On the third postoperative day she was pyrexial and complaining of headache. Lumbar puncture revealed blood-stained C.S.F. This was interpreted as a secondary haemorrhage into the cavity and was treated with repeated lumbar puncture."

Five weeks before surgery IQ was 100, and memory quotient on the Wechsler Memory Scale was 80. The MQ was particularly poor in the areas of learning and immediate memory of verbal material. There was no difficulty in record-

* See Appendix for a description of this test.

(39) Meyer, V. (1959): Cognitive changes following temporal lobectomy for relief of temporal lobe epilepsy. AMA Arch. Neurol. Psychiat. 81:299-309.

(40) Dimsdale, H., Logue, V. and Piercy, M. (1964): A case of persisting impairment of recent memory following right temporal lobectomy. Neuropsychologia 1:287-298.

ing ongoing events. Three weeks after operation IQ was 102 and MQ 101. However, tests involving retention of material over a time span (ten minutes or longer) revealed impairment, and the deficit persisted on repeat testing 14 months later. There also "appeared to be a profound retrograde amnesia extending over a period of years."

Stepien and Sierpinski⁽⁴¹⁾ have reported an unusual case of a 15-year-old girl with temporal-lobe seizures. Prior to operation, memory testing using auditory and visual compound stimuli* revealed impairment in recent memory. "She was able to perform the task only when the interval between two signals was 60 seconds (normal, over 120 sec.) and when she was permitted to keep her attention upon it." There was no difficulty with memory for distant events. The EEG showed bilateral temporal abnormality, occurring initially on the right side. On performing a 7 cm. resection of the right temporal lobe, sclerosis of the hippocampal region was found.⁽⁴²⁾ After operation, no abnormality was found in tests of recent memory. It was assumed that the epileptogenic focus in the right temporal lobe was causing bilateral hippocampal discharge which interfered with recent memory function.

C. Unilateral Resection with EEG Evidence of Damage in Opposite Temporal Lobe

Penfield and Milner^(18,33,43) have reported two cases of persistent memory loss following this unilateral operation. It was thought that an initially unsuspected, but destructive,

* See Appendix for a description of this test.

(41) Stepien, L. and Sierpinski, S. (1960): The effect of focal lesions of the brain upon auditory and visual recent memory in man. J. Neurol Neurosurg. Psychiat. 23: 334-340.

(42) Earle, K.M., Baldwin, M. and Penfield, W. (1953): Incisural sclerosis and temporal lobe seizures produced by hippocampal herniation at birth. AMA Arch. Neurol. Psychiat. 69:27-42.

(43) Milner, B. and Penfield, W. (1955): The effect of hippocampal lesions on recent memory. Trans. Amer. Neurol. Assn. 80:42-48.

lesion in the opposite hippocampal zone, combined with the operative resection effectively eliminated hippocampal function bilaterally. The presence of the second lesion was documented by subsequent EEG studies.

Case 1. A 29-year-old glove-cutter with seizures. Memory recall was not part of the aura. Prior to operation he complained of being "forgetful" and unable to reassemble a machine he had taken apart for repair. However, he easily remembered daily events. According to memory tests, associate learning and visual recall were normal; but there was definite inability to recall two stories in the logical memory test. The EEG revealed bilateral abnormality, worse on the left side. The operative resection was 6.5 cm. along the inferior temporal surface, and incisural sclerosis was found. (42)

Two and one-half years after operation a definite residual EEG abnormality was present in the right temporal region, and the following deficits were noted.

(1) Recording of ongoing events: Severe, but not absolute loss of recent memory with some indication of improvement with time.

(a) Examples from activities: In the first year following surgery he could recall some things that particularly interested him (TV wrestling program and being usher at brother's wedding). Two and one-half years post-operative he could remember two hours after supper most of what he had eaten. On the other hand, after being interviewed for several hours, he denied the event later the same day. He could not learn the way to his bed.

(b) Examples from psychological testing: IQ = 109 (preoperative, 106). Distraction of his attention was very important. He could retain a three-figure number or an unfamiliar word association for many minutes; but, if distracted, he completely lost the memory. Immediate recall of geometric designs was fragmentary and had not improved. Delayed recall was severely impaired, and there was difficulty in recognition. Verbal recall was much worse than before the operation.

(2) Amnesia: Retrograde amnesia for the four years prior to operation. The example given was that he no longer recognized a girl who had been a close friend for eighteen months before surgery.

(3) Distant memory: Intact. No loss of old skills.

(4) Personality and emotion: No change in behavior. Attention, concentration and reasoning were not impaired.

Case 2. A 46-year-old civil engineer with seizures. Five years before admission he had had a partial temporal lobectomy (4 cm.) which did not include the hippocampal zone. There had been no difficulty with memory postoperatively.

He returned to the hospital because of continued seizures. The EEG showed a left temporal abnormality without transmission to the right side, except with a metrazol-induced seizure. Psychological examination revealed no gross memory disturbance. At the second operation the uncus and hippocampus were removed. One month later the following deficits in memory were noted:

(1) Recording of ongoing events: He could recall very little of what was happening around him.

(a) Examples in activities: He was unable to remember whether his wife visited him on any given day; could not identify members of the staff; but could remember something about what he had had to eat.

(b) Examples from psychological testing: IQ remained at 120. Memory of verbal and nonverbal material was impaired. He could repeat nine digits forward and seven backward and carry out complicated mental arithmetic with speed and accuracy. However, after a lapse of five minutes or less, particularly if attention was diverted, he was unable to reproduce four of seven patterns on the Benton Visual Retention Test.* In drawing a plan of his house and garden he made a 90-degree error in garage position. He was unable to recall any details of short stories read to him. He could not learn an unfamiliar association of words.

(2) Amnesia: Partial retrograde amnesia for three months

(3) Storage of distant events: Not altered.

(4) Personality and emotion: No change noted. Attention, Concentration and reasoning were normal.

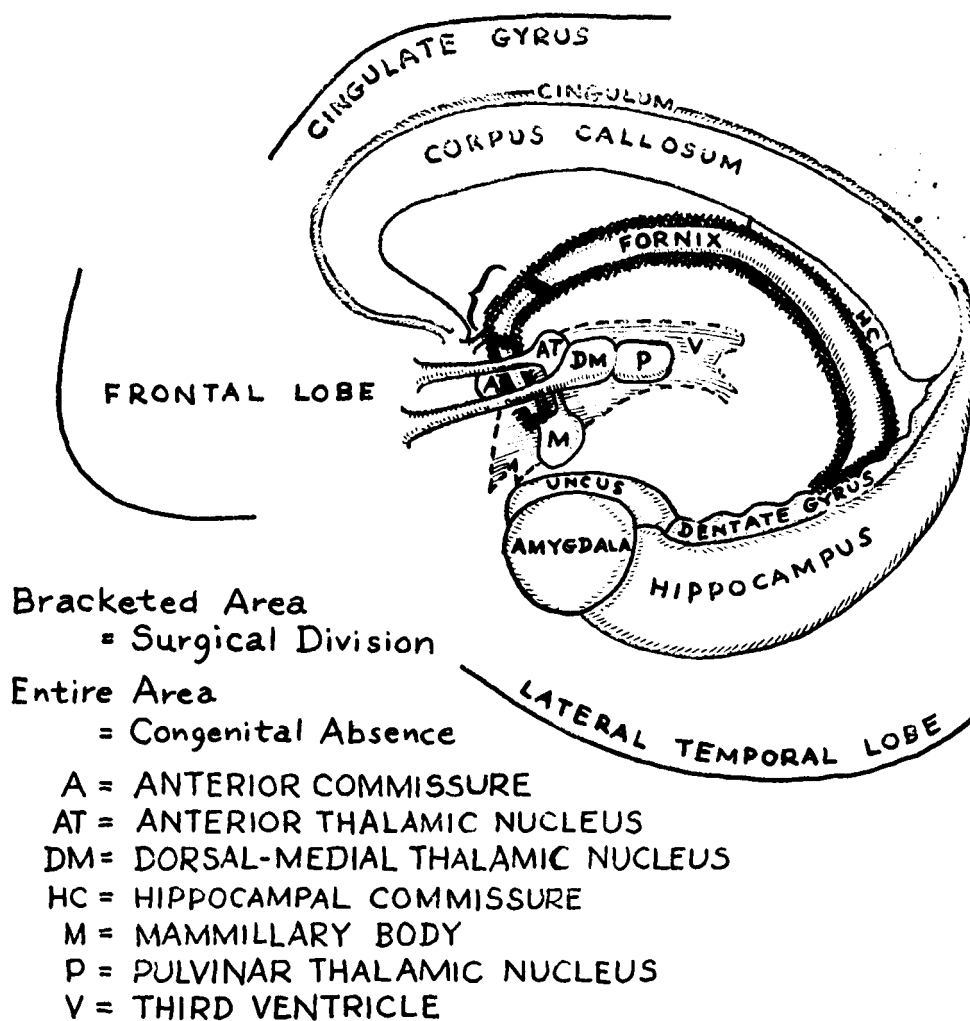
* See Appendix for a description of this test.

Three months after the operation an attempt to recover "some of the forgotten material" was completely unsuccessful. Four years after the operation an EEG made during a seizure revealed suppression of activity over the right temporal region followed by sharp waves from the right hemisphere, indicating an abnormal region in the right temporal lobe. At that time his memory had improved (but most of this had occurred in the first year). He still was unable to learn anything new in his work. He was able to recall a few outstanding associations, but nothing about small day-to-day events.

Serafetinides and Falconer⁽³⁴⁾ removed the right temporal lobe in seven seizure patients who postoperatively showed an EEG focus in the opposite temporal lobe. Six of these patients had persistent impairment of memory and in four, a preoperative memory deficit was worsened. Detailed testing was not reported, and the assessment was a clinical judgment which "did not correlate with more formal psychological tests."

On the other hand, Walker⁽³⁶⁾ stated that several unilateral lobectomy patients showing bilateral temporal EEG spikes had no memory defect. The location and extent of damage within the temporal region and the extent of the EEG abnormality are undoubtedly the determining factors.

Figure 6. Schematic diagram of lesions in the fornix.
[Ojemann - Melnechuk]



IV. FORNIX

The lesions to be described below are diagrammed in Fig. 6.

A. Bilateral Surgical Section

In 1938 Dott⁽⁴⁴⁾ described two cases where removal of a tumor necessitated section of the fornices. No defect in memory function was reported. Garcia-Bengochea and co-workers⁽⁴⁵⁾ reported 14 patients on whom this operation had been carried out for the treatment of severe epilepsy. No "unfavorable neurological or psychiatric sequelae" were noted. Cairns and Mosberg⁽⁴⁶⁾ sectioned the fornix bilaterally in eight cases to remove a colloid cyst of the third ventricle. No change in memory was reported. Section of the fornix bilaterally with complete division of the corpus callosum was reported by Akelaitis.⁽⁴⁷⁾ There was apparently no change in memory function. Unfortunately, no mention was made of specific or detailed psychological tests on which these statements were based.

On the other hand, Sweet, Talland and Ervin⁽⁴⁸⁾ found a marked change in memory following this section, which was done to facilitate removal of a tumor (colloid cyst) from the third ventricle.

(44) Dott, N.M. (1938): Surgical aspects of the hypothalamus. In: The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects. Clark, W.E. Le Gros, Beattie, J., Riddoch, G. and Dott, N.M., eds. Edinburgh: Oliver and Boyd. P. 131.

(45) Garcia-Bengochea, F., De La Torre, O., Esquivel, O., Vieta, R. and Fernandez, C. (1954): The section of the fornix in the surgical treatment of certain epilepsies. A preliminary report. Trans. Amer. Neurol. Assn. 79:176-178.

(46) Cairns, H. and Mosberg, W.H., Jr. (1951): Colloid cyst of the third ventricle. Surg. Gynec. Obstet. 92:545-570.

(47) Akelaitis, A.J. (1943): Studies on the corpus callosum. VII. Study of language functions (tactile and visual lexia and graphia) unilaterally following section of the corpus callosum. J. Neuropath. Exp. Neurol. 2:226-262.

(48) Sweet, W.H., Talland, G.A. and Ervin, F.R. (1959): Loss of recent memory following section of fornix. Trans. Amer. Neurol. Assn. 84:76-82.

Case Report. The patient was a 36-year-old woman. Prior to operation there was no gross memory deficit. The smooth postoperative course supported the impression of minimal trauma to hypothalamic structure. Little, if any, injury to the walls or floor of the third ventricle should occur since this tumor arises superiorly and laterally from the roof of the ventricle.

(1) Recording of ongoing events: She was permanently (2 years) unable to record recent events except when highly motivated, and then a shift in attention would cause even that information to be lost.

(a) Example from activities: She was unable to remember any events happening around her.

(b) Example from psychological testing: Immediate recall was normal as tested by Wechsler digit span, but became severely impaired if there was a shift in attention. The result for nonsense syllables was zero. After one year IQ was 103, and memory quotient 90.

(2) Amnesia: Permanent retrograde loss of memory for several weeks prior to hospitalization, and subjective complaint of amnesia for events during the preceding four to five years.

(3) Storage of distant events: Temporary inability to recognize or know what to do with a box of candy or to use a knife and fork. These faculties recovered rapidly. Memory for more remote events was intact.

(4) Personality and emotion: Loss of spontaneity and some indifference.

In discussion of this presentation, Milner⁽⁴⁹⁾ reported a similar operation performed by Welch, on a 44-year-old geologist of high professional skill. One year after surgery he could achieve, with effort, a fairly good performance on formal memory tests by attempting to link the current event with something from his distant memory. On formal testing IQ was 120, and memory quotient 105. When he made no effort to retain an event he did show some memory impairment. In contrast, none of the patients she had studied with bilateral hippocampal

(49) Milner, B. (1959): Discussion, pp. 78-79. In: Sweet, W.H., et al., ref. 42.

lesions could overcome the memory deficit in this fashion. Possibly the more severe disturbance in Sweet's case was caused by the reduction in motivation.

B. Congenital Absence

Nathan and Smith⁽⁵⁰⁾ have reported the case of a 34-year-old man who died from a chondrosarcoma of the ileum. No defect in memory or intellectual function had been noted during his life.

The most striking finding in examination of the brain was a complete absence of the fimbria (formed by fibers from the hippocampal formation) and fornix. In addition there was an abnormal cingulate gyrus. The hippocampus and dentate gyrus were present on gross pathological examination, but appeared small. Microscopic study, however, revealed that the cells had a normal appearance and arrangement. The two hippocampal complexes joined posteriorly beneath the corpus callosum. This bridge seemed to represent the only efferent path from the hippocampus. Nuclear groups of the mammillary bodies, which usually receive the fibers of the fornix, were normal, as was the major outflow tract from this structure, the mammillothalamic tract.

(50) Nathan, P.W. and Smith, M.C. (1950): Normal mentality associated with a maldeveloped "rhinencephalon." J. Neurol. Neurosurg. Psychiat. 13:191-197.

V. HIPPOCAMPUS, FORNIX, AND COMMISSURES

A. Bilateral Infarction

Victor, Angevine, Mancall and Fisher⁽³⁾ reported in detail the clinical and pathologic findings in a case with occlusion of both posterior cerebral arteries and a serious disorder in memory function.

Case Report: A 54-year-old man was described as "completely normal" prior to the onset of his first stroke. Clinically the first stroke involved the area of distribution of the left posterior cerebral artery. There was no evidence of memory disturbance although he was somewhat withdrawn and indifferent. Approximately two years later, he developed evidence of a less severe lesion in the distribution of the right posterior cerebral artery and an associated memory deficit which remained unchanged for the remaining three years of his life.

(1) Recording of ongoing events: For the most part, he could not recall any event that occurred after the second stroke, but there were a few exceptions.

(a) Examples from activities: He would spend hours watching baseball on television, but as soon as the game was over he could not remember the score or details of the game. He could not remember if he had recently smoked a cigarette, would forget simple instructions left by his wife, could not learn any new card games. One exception was the memory of a visit by his niece who came to visit for several days but stayed on for two months. For many months he could recall the event and appreciate its humorous aspect. On the other exceptional occasion he briefly recalled inspecting some heavy equipment several days before.

(b) Examples from psychological tests: IQ = 117. Although he could not learn any difficult word associations, simple ones were well retained. Tests of digit retention, particularly repeating digits backwards, indicated impairment.

(2) Amnesia: There was retrograde loss of memory except for isolated events occurring during the two years preceding the second stroke.

(3) Storage of distant events: Not impaired.

(4) Personality and emotion: Affect was generally flat, with persistent inactivity, indifference and loss of initiative. This has also been observed in patients with infero-medial frontal lobe lesion and intact memory.

Pathologic study revealed the following chronic changes (see Fig. 7): On the left side, the uncus, amygdaloid body and anterior hippocampus were intact. Immediately posteriorly the hippocampal gyrus was partially destroyed. Further posteriorly the destruction became more extensive and involved the hippocampus dentate gyrus, subiculum, the inferior portion of the splenium of the corpus callosum, and the commissure of the fornix. Examination of the fornix revealed secondary degeneration. This lesion extended into the inferomedial portion of the occipital lobe and occipital pole, destroying striate cortex.

On the right side, the uncus, amygdaloid body and anterior hippocampus were also intact. There was a patchy loss of pyramidal cells and severe necrosis of the white matter of the hippocampal gyrus. There was a separate lesion partially interrupting the fibers of the fornix, in effect, then, giving the patient a bilateral lesion of the hippocampal formation. There was also extensive destruction in the inferior medial aspect of the occipital lobe.

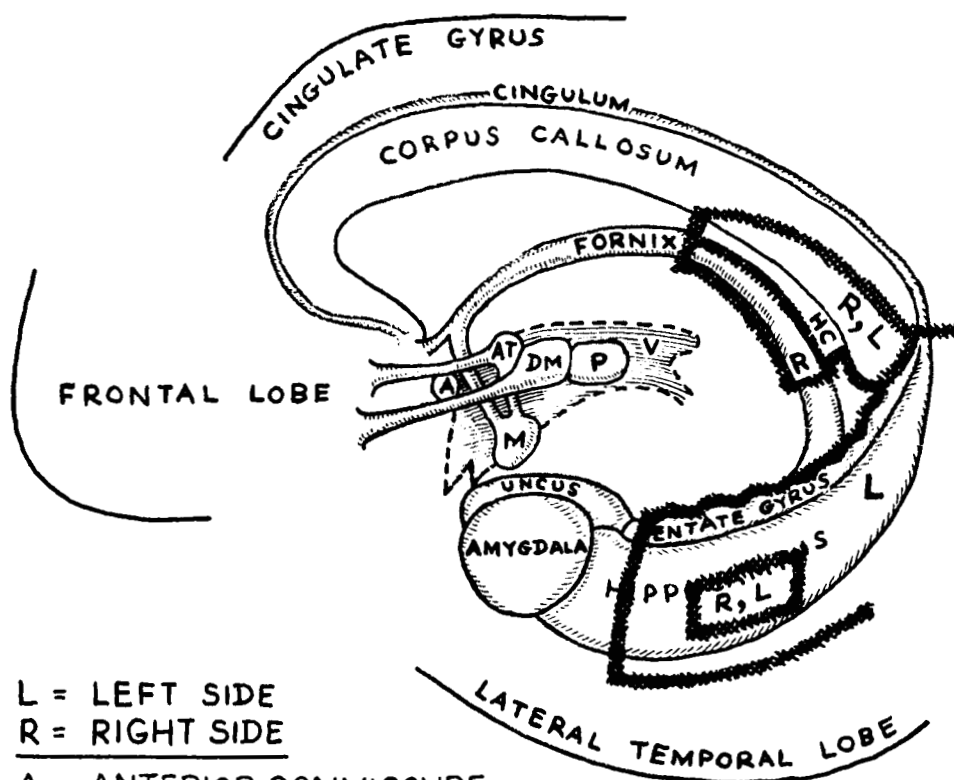
Both mammillary bodies were reduced in size (left more than right) due to marked nerve cell loss probably from trans-synaptic degeneration. There were a few small infarcts scattered in the frontal and parietal lobe, which were thought to be insignificant. Death was due to acute infarction of the midbrain, pons and cerebellum from basilar artery occlusion.

B. Lesions Due to Tumor

Smith and Smith⁽⁵¹⁾ have reported a case which they believe is supporting evidence for the fact that memory impairment may result from a unilateral temporal-lobe lesion. This was described as a disturbance in memory for recent events with no loss for events prior to the illness. Their patient had a malignant astrocytoma which at postmortem examination involved not only the posterior portion of the

(51) Smith, R.A. and Smith, W.A. (1966): Loss of recent memory as a sign of focal temporal lobe disorder. J. Neurosurg. 24:91-95.

Figure 7. Schematic diagram of lesions in the hippocampus-fornix. [Ojemann - Melnechuk]



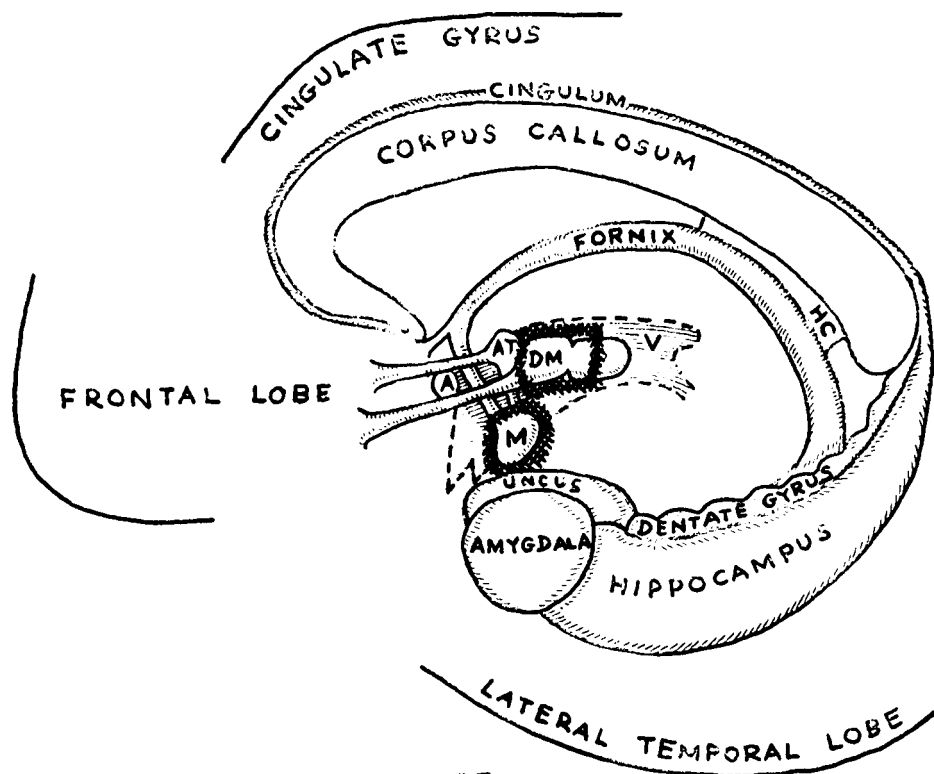
L = LEFT SIDE
R = RIGHT SIDE

A = ANTERIOR COMMISSURE
 AT = ANTERIOR THALAMIC NUCLEUS
 DM = DORSAL-MEDIAL THALAMIC NUCLEUS
 HC = HIPPOCAMPAL COMMISSURE
 M = MAMMILLARY BODY
 P = PULVINAR THALAMIC NUCLEUS
 V = THIRD VENTRICLE

left hippocampus, hippocampal gyrus, fornix and occipital lobe, but also extended across the splenium of the corpus callosum and included the hippocampal commissure. Detailed serial sections of the brain are not reported, but, from the one section illustrated, pressure or invasion in the right fornix is also suspected.

The report of Stepień and Sierpiński⁽⁴¹⁾ is discussed in detail in the section on multiple brain lesions. In only one case of temporal-lobe tumor was there an impairment in recent memory. This was an infiltrating tumor of the left temporal lobe; involvement of the opposite medial temporal area could not be excluded.

Figure 8. Schematic diagram of lesions in the thalamic-hypothalamic region. [Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
- AT = ANTERIOR THALAMIC NUCLEUS
- DM = DORSAL-MEDIAL THALAMIC NUCLEUS
- HC = HIPPOCAMPAL COMMISSURE
- M = MAMMILLARY BODY
- P = PULVINAR THALAMIC NUCLEUS
- V = THIRD VENTRICLE

VI. THALAMUS AND HYPOTHALAMUS

The lesions to be described below are diagrammed in Fig. 8.

A. Korsakoff's Psychosis

Several reports have considered the mammillary bodies to be critical in memory function because of the defects noted in Korsakoff's psychosis.⁽⁶⁾ This disease is usually associated with chronic alcoholism, but may be encountered in a variety of other disorders.^(4,5) It is thought to be due to a critical degree of thiamin chloride deficiency.*

The disease is characterized by a severe memory defect, disproportionate in comparison to minor deficits in cognitive function.^(52,53) There is almost complete inability to record ongoing events, only isolated facts being retained, and these in an incorrect chronological order. Amnesia for some events preceding the illness is noted, and at times even remote memory is defective.

Detailed pathologic study by Adams, Victor and Collins^(3,8,54) revealed that lesions in the mammillary bodies were but one part of the pathologic process. In fact, the

* Ervin⁽⁴⁸⁾ has emphasized the phylogenetic fact that the Indian elephant and dolphin, both of which have excellent behavioral memory, have no mammillary bodies.

(52) Victor, M. and Adams, R.D. (1962): Nutritional disorders of the nervous system. In: Principles of Internal Medicine. Harrison, T.R., ed. New York: McGraw-Hill. P. 1841.

(53) Victor, M. and Yakovlev, P.I. (1955): S.S. Korsakoff's psychic disorder in conjunction with peripheral neuritis. A translation of Korsakoff's original article with brief comments on the author and his contribution to clinical medicine. Neurology 5:394-406.

(54) Collins, G.H., Victor, M. and Adams, R.D. (1961): Neuropathological study of Wernicke's disease and Korsakoff's psychosis. J. Neuropath. Exp. Neurol. 20:289.

most striking feature was the constant lesions found in the medial thalamus (dorsal medial and medial pulvinar nuclei). At times the disease also involved other areas of the medial hypothalamus, periaqueductal gray matter of the midbrain and floor of the fourth ventricle. The hippocampi were intact. It is evident that some part of the medial thalamus and hypothalamus is necessary for memory function.

B. Hemorrhage: Mammillary Bodies

Jasper(55) has briefly noted a case of bilateral destruction in the region of the mammillary bodies due to hemorrhage. For seven years prior to death not a single memory was recorded.

C. Stereotactic Lesions

1. Dorsal Medial Nucleus of Thalamus

In a series of patients with stereotactically placed lesions in the dorsal medial nucleus, Spiegel et al., (56) noted a temporary deficit characterized by temporal disorientation, lack of spontaneity, decreased responsiveness to sensory stimuli and a memory defect for recent and past events. Orchinik(57) has reported in greater detail the effects of these lesions in patients with various types of psychosis.

Using the Wechsler Memory Scale, 12 of 17 cases showed a decline in the memory quotient after operation (tests done within two months). All seven subtest scores declined, with the orientation test (requiring synthesis of old and new material) and the current information test showing the most significant decrease. The changes suggested a deficit both in acquisition of new material and retention of previously learned information. This decline in the memory tests was

(55) Nauta, W.J.H. (1964): Some brain structures and functions related to memory. Neurosciences Res. Prog. Bull. 2(5):14.

(56) Spiegel, A., Wycis, H.T., Orchinik, C.W. and Freed, H. (1955): The thalamus and temporal orientation. Science 121: 771-772.

(57) Orchinik, C.W. (1960): Some psychological aspects of circumscribed lesions of the diencephalon. Confin. Neurol. 20: 292-310.

more marked than that noted in other components of the Wechsler Intelligence Scale.

Repeat tests given three months to one year after operation in eight of these patients still showed some decline in memory scores, but the statistical significance was less. Although these lesions are presumed to be in the dorsal medial nucleus of the thalamus, anatomic confirmation is lacking.

2. Other Thalamic Nuclei

Stereotactic lesions have been placed in the thalamus in order to treat severe pain due to malignant disease. Mark and Hackett⁽⁵⁸⁾ reported that in four of 13 patients there was "transient disorientation in place and time with recent memory loss lasting 1 - 10 days after initial radiofrequency lesions." Three of these patients were reported in detail (Cases 11, 12, and 13).^(59,60) A pronounced change in affect was also observed. Pathologic studies have been carried out in two. In Case 12 the lesion involved the posterior ventral and medial thalamus near the posterior commissure with secondary infarction of the medial thalamus.⁽⁶⁰⁾ In Case 13 the destructive lesion was in the dorsal aspect of the dorsal medial nucleus and in the anterior ventral nucleus.⁽⁶¹⁾ The exact location of the lesion was also determined in 10 other brains.⁽⁶¹⁾ When the principal area of destruction was in the sensory nucleus (nucleus ventralis posteromedialis), parafascicular nucleus or intralaminar nucleus memory disturbance was not reported.

(58) Mark, V.H. and Hackett, T.P. (1959): Surgical aspects of thalamotomy in the human. Trans. Amer. Neurol. Assn. 84: 92-94.

(59) Mark, V.H., Ervin, F.R., and Hackett, T.P. (1960): Clinical aspects of stereotactic thalamotomy in the human. Part I. The treatment of chronic severe pain. Arch. Neurol. 3:351-367.

(60) Mark, V.H. (1964): Personal Communication.

(61) Mark, V.H., Ervin, F.R. and Yakovlev, P.I. (1963): Stereotactic thalamotomy. III. The verification of anatomical lesion sites in the human thalamus. Arch. Neurol. 8:528-538.

Levita and Riklan⁽⁶²⁾ have reported detailed testing in 22 patients with Parkinson's disease treated by unilateral stereotactic thalamotomy. From X-ray measurement, all lesions were thought to be in the ventrolateral nucleus of the thalamus. Using a portion of the Wechsler Memory Scale, no defect in memory function was observed in the postoperative testing.

Patients with Parkinsonism treated by unilateral lesions in the posterior ventral thalamic-subthalamic region have also been studied by Jurko and Andy.⁽⁶³⁾ No impairment in digit span, information, arithmetic, and vocabulary was found. However, impairment in all visual-motor tests, including drawing of designs from memory after a 5-second exposure, was noted in the immediate postoperative period as well as 1 1/2-2 years later.

(62) Levita, E. and Riklan, M. (1965): Cognitive and perceptual functions and lesion location in basal ganglia surgery. J. Clin. Psychol. 21:367-369.

(63) Jurko, M.F. and Andy, O.J. (1964): Psychological aspects of diencephalotomy. J. Neurol. Neurosurg. Psychiat. 27:516-521.

VII. THIRD VENTRICLE AND ADJACENT STRUCTURES

A. Lesions Due to Tumor

Several papers have reported disturbances in memory function caused by tumors that compress or invade tissue adjacent to the third ventricle.^(3,64,65) These lesions are obviously of limited value in making a detailed clinical-pathological correlation because of diffuse boundaries, involvement of multiple structures, and the distant effects of increased intracranial pressure. (See Fig. 9.)

Foerster and Gagel⁽⁶⁶⁾ noted that the mental symptoms, including amnesia, cleared up as soon as a craniopharyngeal cyst compressing the floor and walls of the third ventricle was removed.

Williams and Pennybacker⁽⁶⁴⁾ have attempted to correlate memory disturbance with third-ventricle tumors. In four cases, a well-defined memory disturbance could be correlated with a specific lesion involving the floor and sides of the third ventricle. In two of the cases there was no evidence of pressure on other areas of the brain. Although initially the other two patients had increased intracranial pressure, a return to normal pressure did not alter the memory disturbance. The memory defect consisted of: "(a) inability to retain new impressions for any length of time, (b) inaccessibility of memory for past experiences, (c) distortion and fractionation of recent memory, (d) inability to learn new sensory-motor habits. Immediate memory span, as measured by repetition of digits or sentences was comparatively well maintained."

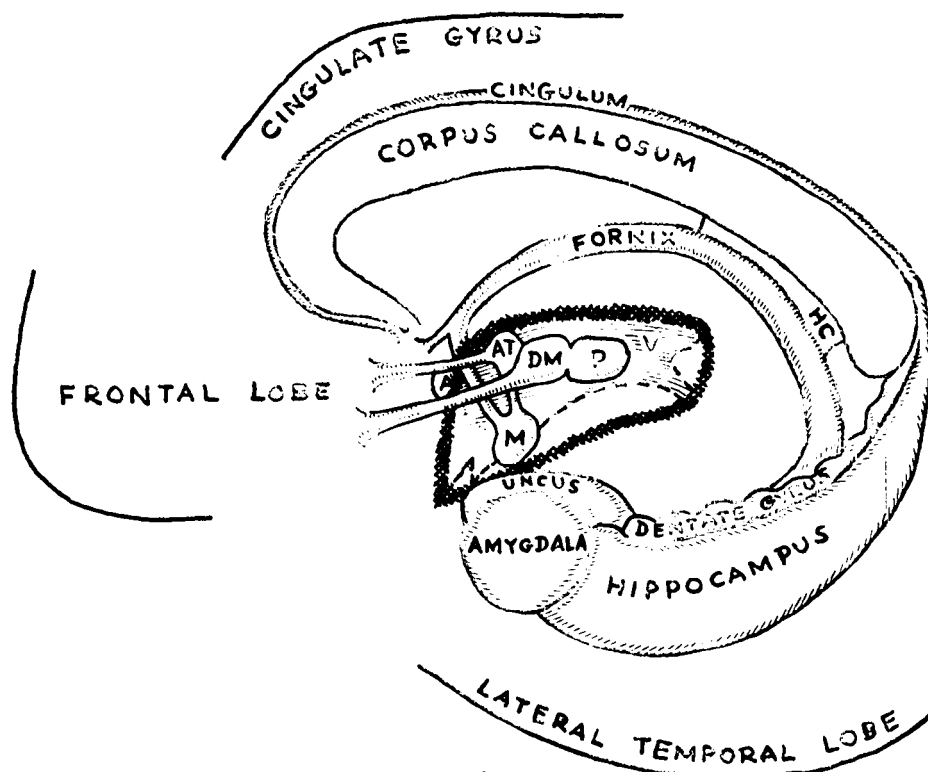
These authors also attempted to analyze the incidence of memory defects in patients with third-ventricle lesions

(64) Williams, M. and Pennybacker, J. (1954): Memory disturbances in third ventricle tumours. J. Neurol. Neurosurg. Psychiat. 17:115-123.

(65) White, J.C. and Cobb, S. (1955): Psychological changes associated with giant pituitary neoplasms. Arch. Neurol. Psychiat. 74:383-396.

(66) Foerster, O. and Gagel, O. (1933): Ein Fall von Ependymcyte des III Ventrikels. Ein Beitrag zur Frage der Beziehungen psychischer Störungen zum Hirnstamm. Z. Ges. Neurol. Psychiat. 149:312-344.

Figure 9. Schematic diagram of lesions in the region of the third ventricle. [Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
- AT = ANTERIOR THALAMIC NUCLEUS
- DM = DORSAL-MEDIAL THALAMIC NUCLEUS
- HC = HIPPOCAMPAL COMMISSURE
- M = MAMMILLARY BODY
- P = PULVINAR THALAMIC NUCLEUS
- V = THIRD VENTRICLE

and also with tumors involving other areas of the brain. Although detailed testing was not done, of 21 patients with tumors (craniopharyngioma) involving the floor and the sides of the third ventricle, 72 percent had some degree of memory impairment, whereas in 11 tumors located 1 cm.-2 cm. anterior to this area there was no memory deficit.

In another group of 24 cases with no lesion in the region of the third ventricle, but with increased pressure caused by a posterior fossa tumor, 45 percent had a memory disturbance. It is presumed that this might be related to the increased pressure within the third ventricle.

Twenty-six other tumors were associated with a definite memory impairment, but the extent of the lesions was unknown.

VIII. FRONTAL LOBE

A. Surgical Lesions1. Unilateral Resection

Rylander(67) carefully studied 32 patients following frontal-lobe resection, comparing each with an intact subject. Although there was impairment in abstract thinking and in the intelligence test, no difference was found in tests of immediate memory and "the ability to fix new impressions in the mind with the help of associates (word associate test)." However, in reference to these impressions "it seems as if the patients forgot more than the control subjects after 3 hours."

2. Bilateral Resection

Hebb(68,69) evaluated a patient after bilateral removal of the frontal lobes. In this case the resection was carried out to remove scar tissue causing seizures. There was therefore no effect on adjacent brain tissue from compression. No change in intellectual or memory function was noted. Malmo(70) studied a patient with bilateral removal of the orbited surface of the frontal lobe (by Penfield) using the Wechsler Memory Scale and "other tests of immediate memory." No deficit was noted.

(67) Rylander, G. (1939): Personality changes after operations on the frontal lobes. Clinical study of 32 cases. Acta Psychiat. Neurol. Suppl. 20:269-274.

(68) Hebb, D.O. and Penfield, W. (1940): Human behavior after extensive bilateral removal from the frontal lobes. Arch. Neurol. Psychiat. 44:421-438.

(69) Hebb, D.O. (1945): Man's frontal lobes. A critical review. Arch. Neurol. Psychiat. 54:10-24.

(70) Malmo, R.B. (1948): Psychological aspects of frontal gyrectomy and frontal lobotomy in mental patients. In: The Frontal Lobe. Fulton, J.F., Aring, C.D. and Wortis, S.B., eds. Baltimore: Williams and Wilkins. Chapt. XXIII, Pt. 3, p. 5510.

3. Cingulotomy

Whitty and Lewin⁽⁷¹⁾ performed a bilateral removal of the anterior 5 cm. of the cingulate gyrus in a group of 10 patients with obsessional states (see Fig. 10). Eight of these individuals were found to have a transient inability to organize remembered events in their correct temporal sequence.

Foltz and White⁽⁷²⁾ placed stereotactic lesions in the cingulum bilaterally in 11 and unilaterally in five patients having various types of pain associated with a significant emotional component. In three cases the site of the lesion has been verified by pathologic study. No change in memory function is reported, although detailed tests were apparently not performed.

4. Leucotomy

The reader is referred to the review by Struckett⁽⁷³⁾ for a summary of the conflicting reports of changes in intellectual function following prefrontal leucotomy (interruption of a varying percentage of the fiber tracts from the anterior frontal lobe). She studied the effect of this procedure on patients with chronic schizophrenia. No significant alteration was found in the memory quotient of the Wechsler Memory Scale or the Benton Visual Retention Test. Barbizet⁽⁷⁴⁾ has discussed the inability to recall complex notions earlier acquired in patients with extensive lobectomies. Smith⁽⁷⁵⁾ has reviewed a series of patients who had varying degrees of bilateral frontal-lobe excisions for mental disease. Initial

(71) Whitty, C.W.M. and Lewin, W. (1960): A Korsakoff syndrome in the post-cingulectomy confusional state. Brain 83:648-653.

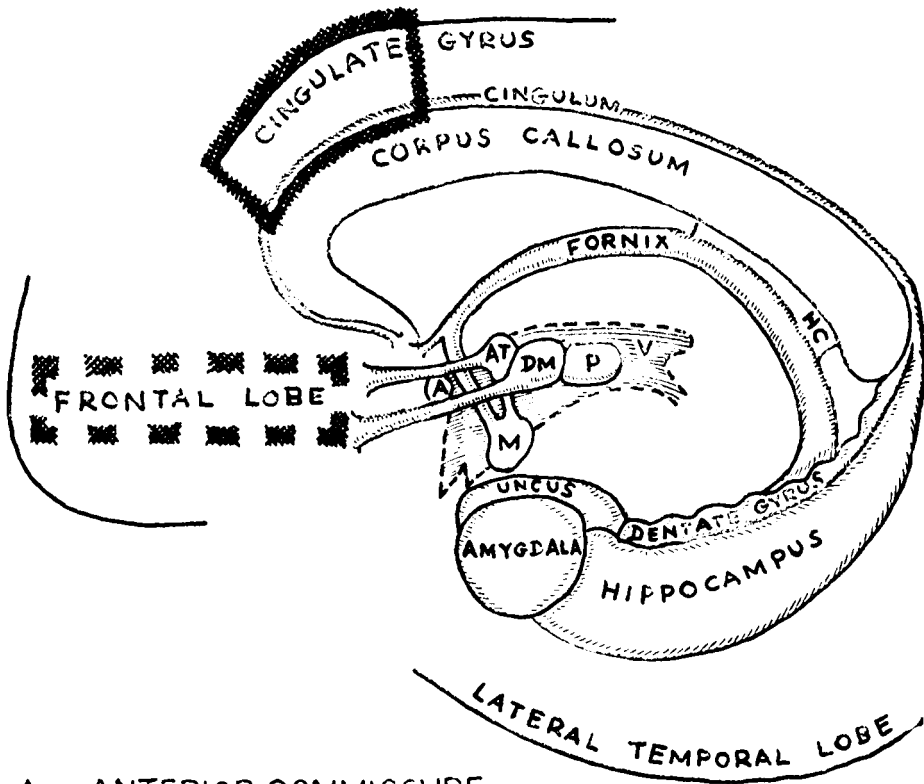
(72) Foltz, E.L. and White, L.E., Jr. (1961): Pain "relief" by frontal cingulumotomy. J. Neurosurg. 19:89-100.

(73) Struckett, P.B.A. (1953): Effect of prefrontal lobotomy on intellectual functioning in chronic schizophrenia. Arch. Neurol. Psychiat. 69:293-304.

(74) Barbizet, J. (1965): Lobe frontal et mémoire. Ann. Medico-Psychol. 2:289-302.

(75) Smith, A. (1964): Changing effects of frontal lesions in man. J. Neurol. Neurosurg. Psychiat. 27:511-515.

Figure 10. Schematic diagram of lesions in the frontal lobe.
[Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
- AT = ANTERIOR THALAMIC NUCLEUS
- DM = DORSAL-MEDIAL THALAMIC NUCLEUS
- HC = HIPPOCAMPAL COMMISSURE
- M = MAMMILLARY BODY
- P = PULVINAR THALAMIC NUCLEUS
- V = THIRD VENTRICLE

evaluation had revealed recovery of mental function to pre-operative levels one year after operation. His follow-up study, 10-12 years later, revealed deficits in mental function; but, from the data presented, memory did not appear to be greatly affected.

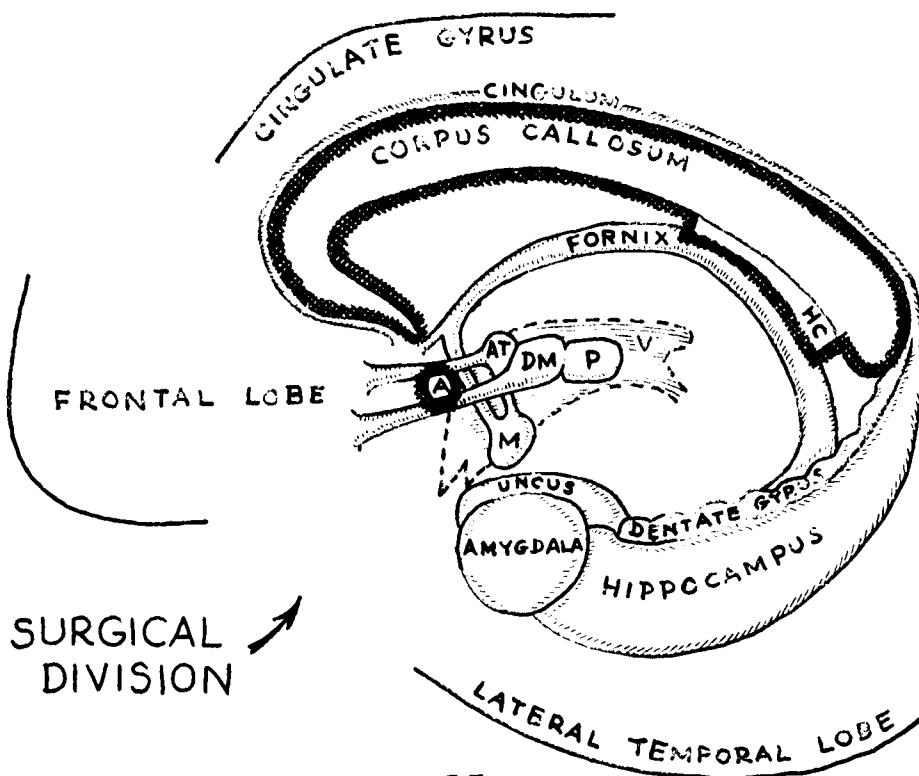
B. Traumatic Lesions (see Fig. 10)

Ghent, Mishkin and Teuber⁽⁷⁶⁾ examined in detail 24 veterans who had sustained penetrating frontal-lobe injuries eight to ten years prior to testing. To test short-term memory, these authors devised several tasks "in which the stimulus material could not be categorized readily with reference to verbal or other framework."* Conventional memory tests using a recall of sequences of digits and visual forms were also utilized. Short-term memory was not impaired.

* See Appendix for a description of this test.

(76) Ghent, L., Mishkin, M. and Teuber, H.-L. (1962): Short-term memory after frontal-lobe injury in man. J. Comp. Physiol. Psychol. 55:705-709.

Figure 11. Schematic diagram of lesions in the corpus callosum and cerebral commissures. [Ojemann - Melnechuk]



- A = ANTERIOR COMMISSURE
 AT = ANTERIOR THALAMIC NUCLEUS
 DM = DORSAL-MEDIAL THALAMIC NUCLEUS
 HC = HIPPOCAMPAL COMMISSURE
 M = MAMMILLARY BODY
 P = PULVINAR THALAMIC NUCLEUS
 V = THIRD VENTRICLE

IX. CORPUS CALLOSUM AND CEREBRAL COMMISSURES

A. Surgical Division

In 1962 Bogen and Vogel⁽⁷⁷⁾ reported the complete sectioning of the corpus callosum and anterior commissure for epilepsy. The massa intermedia was said to be absent (but the hippocampal commissure is not discussed). There was pre-existent brain damage which had an undetermined, but probably insignificant, effect on the postoperative finding. Gazzaniga⁽⁷⁸⁾ evaluated this patient in detail and stated that the hippocampal commissure was also divided. Sperry⁽⁷⁹⁾ has recently summarized the results of these tests and referred to a second patient who had a similar operation. (See Fig. 11 for a diagram of the lesions.)

The first patient was a 40-year-old man with above-average intelligence. The following were found in the post-operative evaluation:

Functions of the right side of the body (controlled by the left hemisphere) were not altered.

Functions of the left side of the body requiring information normally processed in the left hemisphere, i.e., interpretation based on language, and reading in the left visual field, were impaired.

Nonverbal activities performed by the left hand and perceived in the right hemisphere could not be recalled by the left hemisphere. For example, a visual stimulus card could be identified by the left hand after it had been perceived in the visual field of the right hemisphere. If the card was then removed and presented in the visual field of the left hemisphere, it could not be described or designated as previously having been seen.

(77) Bogen, J.E. and Vogel, P.J. (1962): Cerebral commissurotomy in man. Preliminary case report. Bull. Los Angeles Neurol. Soc. 27:169-172.

(78) Gazzaniga, M.S., Bogen, J.E. and Sperry, R.W. (1962): Some functional effects of sectioning the cerebral commissures in man. Proc. Nat. Acad. Sci. 48:1765-1769.

(79) Sperry, R.W. (1964): The great cerebral commissure. Sci. Amer. 210:42-52.

While a task requiring left hemisphere control was being performed, any event being perceived by the right hemisphere might not be noticed or recorded.

Both partial and complete divisions of the corpus callosum were performed by Van Wagenen and reported by Akelaitis⁽⁴⁷⁾ in 1943. No reference to any alteration in memory function is recorded.

X. MULTIPLE BRAIN REGIONS

Stepień and Sierpiński⁽⁴¹⁾ carefully examined 50 patients with a variety of brain lesions (tumor 44, traumatic lesion 3, abscess 2, and incisural sclerosis 1) involving frontal lobe in 15 (12 left, 3 right); parietal lobe in 15 (7 left, 8 right); temporal lobe in 15 (11 left and 4 right); occipital-parietal junction in 4; entire hemisphere in one. The visual and auditory tests used compound stimuli, each stimulus consisting of two signals separated by a short interval. The second signal, tone or light brightness, was compared with the first stimulus.

An impairment in recent memory was found in only three patients. In one, the left side of the brain had been almost entirely removed because of malignant glioma. Involvement of the opposite hippocampal area could not be excluded, and there was also evidence of severe intellectual impairment. The second case, an infiltrating tumor in the left temporal lobe, is discussed on page 35. The third case, the one patient with incisural sclerosis, is discussed on page 24.

Nielsen⁽⁸⁰⁾ has reported three patients in whom the removal of an occipital lobe for tumor was followed by a memory deficit. Few details of these cases are given. Unfortunately, as with any tumor case, the boundaries of the lesion are not clear, and alterations in brain function may be widespread due to the effects of increased pressure. The same problems were emphasized by Williams and Pennybacker⁽⁶⁴⁾ and apply to the reports of Conrad and Ule,⁽⁸¹⁾ Sproffkin and Sciarra,⁽⁸²⁾ Allison,⁽⁸³⁾ and Selecki.⁽⁸⁴⁾

(80) Nielson, J.M. (1956): Presidential address. Studies in memory and amnesia. Trans. Amer. Neurol. Ass. 81:1-7.

(81) Conrad, K. and Ule, G. (1951): Ein Fall von Korsakow-Psychose mit anatomischen Befund und Minischen Betrachtungen. Deutsch. Z. Nervenheilk. 165:430-445.

(82) Sproffkin, B.E. and Sciarra, D. (1952): Korsakoff's psychosis associated with cerebral tumors. Neurology 2:427-434.

(83) Allison, R.S. (1961): Chronic amnesic syndromes in the elderly. Proc. Roy. Soc. Med. 54:961-965.

(84) Selecki, B.R. (1965): Intracranial space-occupying lesions among patients admitted to mental hospitals. Med. J. Australia 1:383-390.

A group of 58 patients with various intracranial tumors and other pathology was examined by McFie and Piercy.(85) Impairment of retention and learning was thought to be related to the size of the lesion rather than location. Again, the extent of the pathology was not definitely known, and many patients had increased intracranial pressure. This conclusion was supported by Chapman and Wolff,(86) but the majority of reports, reviewed earlier in this paper, indicate that a relatively small lesion located in the hippocampal - fornix - mammillary body system will alter memory function.

Enlargement of the lateral ventricles, particularly the frontal horns and third ventricle, with compression of the surrounding tissue, is associated with hydrocephalus. In the syndrome of "normal pressure hydrocephalus" where there is apparently no other loss of brain tissue, immediate, recent, and remote memory loss have all been recorded in association with psychomotor retardation and unsteady gait. Recovery of this function is found after the cerebrospinal fluid pressure is lowered.(87)

Several authors have described memory deficits in patients with viral encephalitis(3,4,88,89) Clinico-pathologic correlations have revealed that destructive lesions were most prominent in the medial temporal lobes, "limbic system," or mammillary bodies, but abnormalities were not limited to these areas.

(85) McFie, J. and Piercy, M.F. (1952): Intellectual impairment with localized cerebral lesions. Brain 25:292-311.

(86) Chapman, L.F. and Wolff, H.G. (1959): The cerebral hemispheres and the highest integrative function of man. Arch. Neurol. 1:357-424.

(87) Adams, R.D., Fisher, C.M., Hakim, S., Ojemann, R.G. and Sweet, W.H. (1965): Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. New England J. Med. 273:117-126.

(88) Rose, F.C. and Symonds, C.P. (1960): Persistent memory defect following encephalitis. Brain 83:195-212.

(89) Drachman, D.A. and Adams, R.D. (1962): Herpes simplex and acute inclusion-body encephalitis. Arch. Neurol. 7: 45-63.

Certain cases of senile dementia which are characterized mainly by a loss of memory show lesions which are most prominent in the hippocampal formation, although not limited to that region.^(3,4) In other patients, however, the changes are most prominent in the cortex.⁽⁵⁾ The memory defect is variable. Both recent and distant memory may be impaired, although the former is usually more severely involved.

A large number of reports have discussed the retrograde amnesia and defects in memory following head trauma.^(6,90,93) Unfortunately, good clinico-pathologic correlations have not been reported in reference to the loss of memory function following head injury. In a series of war injuries, Russel and Espir⁽⁹¹⁾ found that small wounds in the left temporal lobe cause a period of post-traumatic amnesia which is longer than for similar wounds in other areas of the brain, including the right temporal area. (Also see Frontal Lobe, page 44.)

Other reports by Ule⁽⁹⁴⁾ and Grünthal^(95,96) describe various diseases associated with a memory deficit where the lesions were most prominent in the medial portions of the temporal lobe but were not limited to this region.

(90) Williams, M. and Zangwill, O.L. (1952): Memory defects after head injury. J. Neurol. Neurosurg. Psychiat. 15:54-58.

(91) Russel, W. and Espir, M.L.E. (1961): Traumatic Aphasia: A Study of Aphasia in War Wounds of the Brain. London: Oxford University Press. P. 144.

(92) Luria, A.R. (1963): Restoration of Function after Brain Injury. (Transl. B. Haigh; Transl. edited by O.L. Zangwill). New York: Macmillan. Pp. 240-241.

(93) Walker, A.E. and Jablon, S. (1961): A Follow-up Study of Head Wounds in World War II. (VA Medical Monograph) Washington, D.C.: U.S. Government Printing Office. Pp. 46-53.

(94) Ule, G. (1958): Pathologisch-anatomische Befunde bei Korsakow-Psychosen und ihre Bedeutung für die Localisationslehre in der Psychiatrie. Artztl. Wschr. 13:6-13.

(95) Grünthal, E. (1947): Über das klinische Bild nach umschriebenem beiderseitigen Ausfall der Ammonshornrinde. Ein Beitrag zur Kenntnis der Funktion des Ammonshorns. Mschr. Psychiat. Neurol. 113:1-16.

(96) Grünthal, E. (1961): Cited by Victor, M., et al., in reference 3.

SUMMARY AND DISCUSSION

It has been demonstrated that specific brain regions are necessary for certain aspects of general memory function.

Surgical removal, destruction by a disease process, or electrical abnormality of the two hippocampal areas will cause a permanent alteration in memory. What is the deficit produced? Memory of events from the distant past remains intact. The hippocampus is not the storage area and is not necessary for recall of these events. The individual is presented with an event in his environment and is able to record this event and retain it for up to several minutes if his attention is not distracted or the event is not too long or complex. Once attention is altered, even momentarily, the event is forgotten. The ability to retain information even for this brief period also depends to a great degree on the complexity of the event. The impairment therefore is one of inability to permanently record and store the incoming information. Temporary recording (recent memory) is not completely abolished.

How does the bilateral function of the hippocampus interact with new information? Is it necessary in order to maintain the storage of the engram in the primary perceptual system prior to delocalization? Or does the hippocampus maintain some temporary control over the recently delocalized engram -- a "stamping in" or a "booster" mechanism? The varying period of amnesia for events of the past, often accompanying bilateral loss of hippocampal function, would be consistent with these mechanisms. Jasper⁽⁹⁷⁾ has reported that amnesia following stimulation in the medial temporal regions does not occur until the after-discharge has spread to the neocortex.

On the other hand, as Sweet et al., (48) have noted: "one can...utilize the model of a probabilistic 'cell assembly' as suggested by Hebb for the memory trace. Its availability to recall then depends on the complexity of its interrelationships with other significant memories or concepts (i.e., on its 'embeddedness'). Within such a model, the hippocampal - fornix - mammillary system (which is increasingly implicated in 'motivational' or 'emotional' states), might operate in parallel to the primary perceptual system to add 'significance'

(97) Nauta, W.J.H. (1964): Some brain structures and functions related to memory. Neurosciences Res. Prog. Bull. 2(5):15.

to a perception and determine its 'embedding.' Such an hypothesis might also account for occasional shifts in performance under states of high motivation."

The amygdala, adjacent to the anterior portion of the hippocampus, does not seem to be necessary for memory function.

The role of the fornix in memory has not been settled. It would appear, however, from the two cases studied in greatest detail, that intact bilateral function of this structure is necessary for recording ongoing events. The impairment is not as severe as that noted with bilateral loss of hippocampal function. One of these cases was able, by concentrated effort, to link ongoing events with distant memory and thereby recall the recent event. This could not be done by the patients with bilateral hippocampal lesions. In the absence of the fornix from birth some compensatory mechanism appears to have taken over its function.

The classical statement that mammillary bodies alone are essential in memory function (based on effects of the lesions in Korsakoff's psychosis) has been altered by the constant finding of pathologic lesions in the thalamic dorsal medial nucleus and medial portion of the pulvinar nucleus. It is apparent that a lesion in this region will also cause a permanent deficit in memory function with both hippocampal areas being intact.

Destruction of the mammillary bodies due to hemorrhage has been associated with a severe deficit in recording of ongoing events. Stereotactic lesions presumed to be located in the dorsal medial nucleus of the thalamus may also interfere with acquisition of new material as well as retention of previously learned information. Although this nucleus does not receive direct projection from the hippocampal - fornix - mammillary system, it does integrate visceral and somatic impulses with other thalamic and hypothalamic nuclei and connects with the frontal cortex as a primary mechanism in the control of affective responses. The relationship of affect and memory has been discussed in the Introduction.

When the corpus callosum, anterior and hippocampal commissures are divided, the memory of an event entirely confined to one hemisphere cannot be recalled by the other hemisphere. This would support the contention that under normal circumstances there is probably moderately rapid delocalization of the engram.

Bilateral lesions in the cingulate gyrus may cause a temporary inability to organize events in a correct time sequence. Memory is not altered by other frontal lobe lesions.

Lesions in the lateral temporal, parietal, and occipital lobes have not been associated with permanent alterations in memory function as a whole. Complete loss of all past memory and inability to record new information for special functions such as meaning of a word or identification of an object are found with certain neocortical lesions.

ACKNOWLEDGMENTS

The author is grateful to NRP Associate Dr. Heinrich Klüver for reviewing and discussing a draft of the first edition of this survey during one of his visits to the NRP Center in 1964. He also thanks the members of the NRP Communications Staff and of his research staff at Massachusetts General Hospital for their valuable assistance.

In 1964 a Fellowship with the Neurosciences Research Program was made possible by a grant from the Medical Foundation of Boston, Inc., and the guidance of NRP Associate Dr. William H. Sweet, Chief of the Neurosurgical Service at Massachusetts General Hospital.

APPENDIX

TESTS OF MEMORY FUNCTION

Wechsler Memory Scale (98)Subtests

1. Six simple questions of personal and current information. Example: Who is the president of the U.S.?
2. Five simple questions to test immediate orientation. Example: What year is it?
3. Mental Control
 - a. Counting backwards from 20 to 1.
 - b. Repeating the alphabet
 - c. Counting by three's
4. Logical memory (immediate recall).

The patient is given two passages to memorize. The score is based on the average number of ideas which are correctly recalled from the two passages.
5. Memory span for digits forwards and backwards.
6. Visual reproduction.

The patient is asked to draw from memory single geometric figures exposed for a period of 10 seconds.
7. Associate learning.

The patient is presented with 10 paired associates, some easy and some hard, which he is required to learn in three trials.

The details of the complete test are outlined by Wechsler. (98)

The memory quotient (MQ) is determined as follows:

1. Scores for each of the seven subtests are added.
2. To this total a value is added which depends on the age of the individual.
3. This corrected score is then found in a table which gives the corresponding memory quotient.

(98) Wechsler, D. (1945): A standardized memory scale for clinical use. J. Psychol. 19:87-95.

The method is essentially empirical and was arrived at by plotting the mean memory scores for different ages against the weighted scores of the Bellevue Scale (age group 20-24 years) and then trying out various constants which would keep the mean MQ for any age group equivalent to the mean IQ of the age group.

Konorski Compound Auditory and Visual Test for Recent Memory

Examination of recent memory using the methods described by Konorski, (99) as outlined by Stepien and Siepinski⁽⁴¹⁾:

"We applied the compound auditory and visual stimuli, the duration of the presentation period for each signal being 2 seconds and the interval between two signals of the compound from 10 to 120 seconds. The pairs of identical and different pitch of tones or the red light of identical and different intensity of brightness were used in our examinations. The stimulus tones and lights were produced by a generator apparatus with an automatic timer which controlled the duration of the stimulus and registered the strength and the latent period of reaction. As the aim of our investigations was the examination of recent memory and not of the ability to perform difficult or delicate differentiations of the auditory and visual stimuli, we always applied very large differences in tones as well as in brightness of the red light.

"At the beginning of the examination we explained the apparatus to the patient and he was instructed to press the spring connected with the recording instrument when the two signals of the compound auditory or visual stimulus would be identical. On the other hand, when the second signal would differ from the first, he should leave the spring alone. These instructions were repeated and trials given until we were quite sure that the patient understood the task.

"When the patient showed no difficulty in differentiation with an interval of 120 seconds between two signals, the task was made more difficult by introducing in the middle of the interval an additional, distracting stimulus, which turned the patient's attention from the proper task, i.e., from keeping in mind the recent memory traces of the first signal. The distracting stimulus was always from another analyser than the one by which recent memory was examined. For example,

(99) Konorski, J. (1948): Conditioned Reflexes and Neuron Organization. (Transl. S. Garry.) London: Cambridge University Press.

during examination of auditory recent memory the distracting stimulus, given in the interval between two tones, was the red or green light. When the red light was applied the patient should press the spring of the recording apparatus but after lighting the green lamp he should leave the spring alone.

In a control group of 12 patients with peripheral nerve injuries or epilepsy, no difficulty was observed in differentiation with a 120-second interval between two signals and with a distracting stimulus in the middle of the interval."

Benton Visual Retention Test

This test is described in detail in the monograph by Benton⁽¹⁰⁰⁾ The subject is presented with a series of 10 cards on which designs, consisting of one or more figures, have been drawn. The individual is asked to study the design for 10 seconds; the card is removed and he is asked to draw the design. Several modifications of this basic test are described. For normal individuals, Benton found that the results of this test correlate fairly well with scores on standard intelligence tests and with chronologic age.

Nelson New Word Learning and Retention Test

Meyer and Yates⁽³⁸⁾ have described this test, originated by Nelson: "In this test the subject is first given a vocabulary test in the usual way (Binet is used preoperatively, Wechsler postoperatively) until five consecutive words are failed. The subject is then required to learn the meaning of these five unfamiliar words until he has given three successful definitions -- not necessarily three consecutive successful definitions. The definitions given to the subject are taken from Binet's and Wechsler's forms, and are changed at each presentation to avoid rote learning. It was known (Nelson, 1953) that normal subjects learned in five trials, i.e., required only one definition for each word in order to learn the meaning of it."

Ghent-Mishkin-Teuber Tests for Short-Term Memory

Ghent, Mishkin and Teuber⁽⁷⁶⁾ described four tasks,

(100) Benton, A.L. (1955): The Revised Visual Retention Test: Clinical and Experimental Applications. New York: The Psychological Corporation.

devised to test short-term memory, involving a stimulus"... that cannot be categorized easily at the moment of exposure either verbally or with reference to an external framework."

"Line test. A rod 1 yd. in length and 10 ft. away will be tilted to a certain angle and then it will be lit for 2 sec. You will see it as a very dim red slanting line. Right after the rod light is switched off (or, sometimes, 15 sec. after), it will be switched on again, but this time the line will be vertical. It will then be moved slowly in the direction of its original tilt, and you are to tell me when it has reached its original position."

"Tactual point-localization. The S with his eyes closed, palm upturned on knee, with his fingers extended and held flat by E. A 60-mm. line, with 24 divisions 2.5 mm. apart, was stamped lengthwise on the middle of S's palm. A point on the line was touched lightly with a blunt stylus for 2 sec., and S was told to remember the position of this point (the standard). Either immediately, or after 15 sec., 12 points, including the original one, were touched briefly in a prearranged random order, with an interval of 1 sec. between successive contacts. At each contact S was asked whether it fell at the original position or not. The error was defined as that point furthest from the correct point which S accepted as matching it."

"Visual point-localization. The S was seated before a standard perimeter in the completely darkened room and was instructed to fixate a dim red light in the center of the perimeter....The rider on the perimeter, carrying a 1° target made luminous with white fluorescent paint, was moved to one of the four standard positions along the horizontal meridian in either the left or the right field. The four positions were 24° , 48° , 12° and 36° (in that order) from the fixation point. The target was exposed for 2 sec., and S was instructed to attend to its position without shifting fixation. For each standard position there were 12 choice points, including the standard position itself, 1.5° apart, thus covering an angular distance of 18° along the horizontal meridian."

"Body tilt. The S was seated in a tilting chair and then blindfolded. The chair was tilted 20° for 5 sec., and S was told to remember the degree of tilt. The chair was then quickly brought to the upright position and tilted again slowly (about 1° per sec.) until S indicated that he was in the same position of tilt as before; a delay condition was not included."

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HYSTERESIS AND MACROMOLECULAR MEMORY*

A Discussion Paper Dated September 24, 1965

N 67-225.83

by

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*This paper completes the set of presentations by individual contributors which were discussed at the two NRP Work Sessions on "Information Storage and Processing in Biomolecular Systems," chaired by Manfred Eigen and Leo C.M. De Maeyer in May and August, 1964, and reported in the Neurosciences Res. Prog. Bull. Vol. 2, No. 3, and Vol. 3, No. 3. The senior author presented the basic idea of this paper at the Seventh Stated Meeting of NRP Associates. (Staff Editor: Catherine M. LeBlanc)

I. INTRODUCTION

The modern recognition that human and animal memory can be treated by the methods of exact science has opened up a wealth of stimulating studies of biochemical and biophysical nature. Without going into any details of the current research in this intriguing field, we would like to introduce our consideration by summing up the requirements imposed on memory devices as an integral part of cybernetic self-organizing systems. By "memory devices" we mean in the following paper the means for recording, storage and readout of individual experience, to be distinguished from the hereditary memory which underlies the master plan of an organism. The restricted "phenotypic memory" discussed here requires therefore a priori communication with the external world which permits the transmission of suitable stimuli to the site of recording and storage. In a general sense, the external stimulus is to act as an input which causes an internal transition from one state to another and by relatively small energy expenditure. Moreover, we expect the new state of the memory device to persist for sufficiently long periods of time -- or to put it in another form -- the memory record should be retained and stored. A dead storage of information is evidently of little use, so that a suitable readout mechanism is needed capable of "bringing memory to mind," recalling or remembering past experience. Finally, the retrieved information should be reorganizable, or there should exist a possibility of matching the memory recalled from storage with new information flowing in from the surroundings.

It is clear that these requirements limit severely the choice of possible memory mechanisms, both from the energetic and structural points of view. The consensus of opinion tends to regard the classical point of view, which believed that memorizing is based only on suitable neuronal circuits, to be untenable on energetic, physiological and statistical grounds. While the first step in the process of memorizing seems to be indeed a short-lived nervous current, established in response to an external stimulus, it is followed by a long-lived imprint, probably on a subcellular level. The record in the first step can be wiped out by physical and chemical agents, while the more permanent second step can withstand sleep or coma, concussion or electrical shock, epileptic fit and the intracranial action of several metabolic poisons. A subcellular record may be stored in macromolecules

or in intracellular structures whose nature is still open to wild speculation. In the following we shall discuss a physical recording mechanism which may play some role in biological storage of acquired information.

During the past five years several working hypotheses have been advanced for the interpretation of subcellular memory storage and readout. L. Szilard⁽¹⁾ and afterwards Anker⁽²⁾ and Smith⁽³⁾ suggested that an induced enzyme is involved in the process. It was assumed that a transmitter substance of acetylcholine type causes the formation of an induced enzyme, which then develops an inhibitor to stop the process. Silverstein pointed out that there is a close analogy between memory and immunity mechanisms.⁽⁴⁾ There is no need to recite the interesting experiments of Hyden and his co-workers⁽⁵⁾ on the quantitative and structural relation between nuclear RNA and learning processes in several lower mammals. These experiments were followed by the well-known experiments of McConnell⁽⁶⁾ and of Corning and John⁽⁷⁾ on the relation between planarian learning and RNA accumulation and transmission. Whatever be the significance of RNA in learning and memorizing processes, it seems that a relation between protein synthesis and memory is established by the experiments of Flexner and his co-workers⁽⁸⁾ on intracranial injection of puromycin into mice before and after learning and by the experiments of Agranoff with goldfish.⁽⁹⁾ As pointed out by Appel⁽¹⁰⁾ whatever be the molecular mechanism of acquired memory imprinting, it is highly improbable that single and definite macromolecules may act as durable carriers of long-term memory. The lifetime of RNA or protein molecules in the living cell is so short that in order to perpetuate an information-rich molecule, a synthetic process has to be involved, or the imprint has to be transmitted to a structure of higher permanence such as a cellular or intracellular membrane.

All the mechanisms suggested above assume that memory imprints involve changes in the primary structures of suitable macromolecules. The aim of the present paper is to indicate that there exists also the possibility of a physical record in biopolymers based on conformational changes in single macromolecules or in cellular macromolecular structures such as membranes. Well-known examples of physical memory devices are the magnetic tape of tape recorders and the ferromagnetic and ferritic memory devices of electronic computers. All these systems utilize hysteresis cycles and are characterized by their ability to retain an irreversible imprint of previous

experience -- which is not wiped out either by the readout process or by the impact of ordinary environmental factors. On the other hand, by applying a suitable field it is possible to overcome the energy barriers which had maintained the permanence of the imprint, bring the system to its initial state and enable a new record to be accommodated. This group of physical recording devices are "time-independent irreversible" systems, in which the long time that the records are retained suggests an equilibrium state of stability; but the fact that the records may be transformed irreversibly, and at low expenditures of energy, to the memoryless initial state shows instead that the record is in the non-equilibrium state of metastability.

The present consideration is based partially on an unpublished paper of Cox and Katchalsky on hysteresis phenomena in RNA solutions. Since hysteresis is a suitable indicator for the existence of metastable forms of high permanence, the following discussion of hysteresis will serve us as an introduction to a more general consideration of metastable macromolecular conformations endowed with a capacity to memorize the imprint of surrounding events.

II. GENERAL CONSIDERATION OF HYSTERESIS PHENOMENA

A. Macroscopic Systems

Since the discovery of ferromagnetic hysteresis a hundred years ago, it has been realized that hysteresis cycles are endowed with a physical memory -- a point stressed in particular by Ludwig Boltzmann. Since by definition equilibrium states are reversible, only states of equilibrium are memoryless and independent of the path of their formation, while all non-equilibrium states comprise a memory of previous events by virtue of their dependence on the irreversible path of their formation. The peculiar property of hysteresis cycles is that despite their irreversible nature, the states formed are time-independent under ordinary conditions. Indeed, it is this intriguing time independence of a process dependent on the history of the system which underlies the very definition of hysteresis, according to Everett⁽¹¹⁾: "If upon going from A to B and from B to A, the independent parameter (responsible for the change) causes the dependent parameter to retrace the same values, we have an equilibrium or reversible process. There are however processes in which even though the changes are carried out exceedingly slowly the

path from A to B is different from that during the change from B to A. If the points on both paths correspond to stable, reproducible values of the dependent variable, then the change $A \rightarrow B$ is said to exhibit hysteresis." Everett further adds that hysteresis phenomena are also characterized by scanning curves, which are also stable and reproducible (see below).

A wealth of hysteresis phenomena have been described in the physical and chemical literature. In ferromagnetics, the intensity of magnetization as a function of magnetic field strength exhibits a pronounced hysteresis cycle; similarly, for ferroelectrics, the dependent variable is the electric polarization while the independent parameter is the external field strength. These two cases are well known in electrical technology, and during the last years came to prominence as memory devices in electronic computers, either as bulk materials or as ultrathin films. The physical chemists are familiar with the hysteresis of an adsorption-desorption cycle, where the partial pressure of the vapors plays the role of an independent variable, while the amount adsorbed is the dependent variable. During the last twenty years a wealth of data has accumulated on hysteresis in melting-crystallization cycles of simple crystals such as NH_4Cl , NH_4Br and solid hydrogen halides. Finally, it is well known that the application of stress to many solids produces strain which follows a closed hysteresis loop and plays a special role in the definition of the performance of technical rubbers.

B. Elementary Processes

Despite the requirement that the macroscopic run of a hysteresis cycle is required to correspond to stable values of the dependent parameter, there is little doubt that the elementary processes underlying the phenomenon imply metastable states and abrupt irreversible transitions, smeared out in a larger assembly of elements. Thus, following the discussion of T.L. Hill⁽¹²⁾ on adsorption phenomena, we may state that the basic transition of a single element is characterized by a curve of a van der Waals type with well-developed metastable states, schematically diagrammed in Fig. 1. When sufficiently high energy barriers prevent the equilibrium transition at E, it might be expected that metastability will develop, followed by the abrupt non-equilibrium transition characteristic of metastability. The transition from A to B will take place at a different value of the external parameter from that from B to A. Thus, in contradistinction to a state of equilibrium the internal parameter is not a single-valued function of the external parameter; and

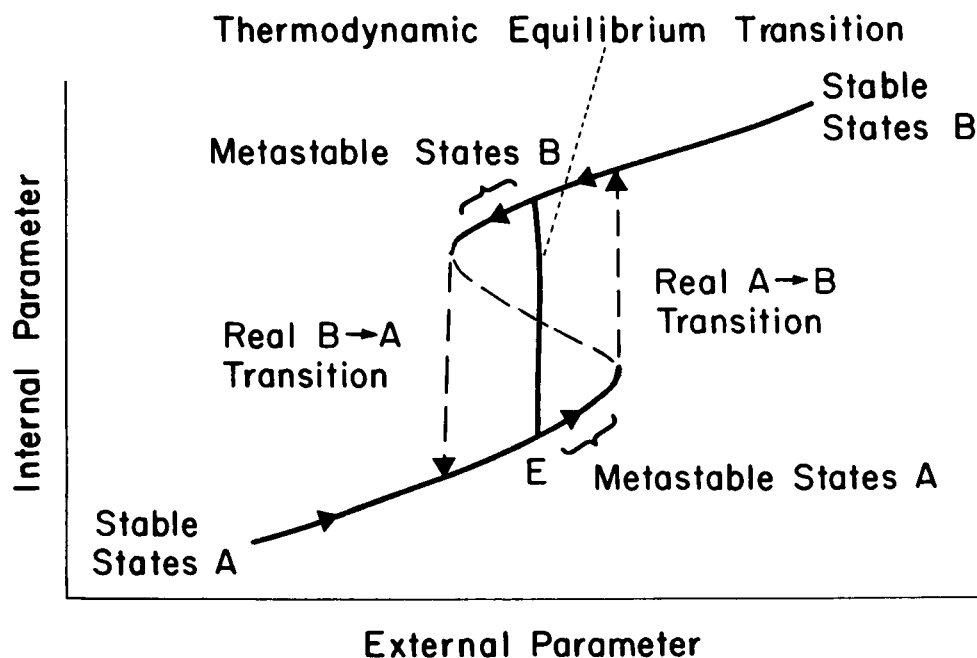


Figure 1. Hysteretic behavior resulting from the existence of metastable states (schematic). [Katchalsky]

in both metastability ranges of A and B, the value of the internal parameter will depend on the history, i.e., on whether the curve is traced from A towards B or from B towards A.

A visual model proposed by Everett may serve for a better grasp of the behavior (Fig. 2). Consider an electric circuit operated by a source of electromotive force E and provided with an ammeter G . The circuit may be closed by establishing contact between two contact points C , rigidly fixed on two magnets M which attract each other. One of the points and magnets is fixed in position, while the other point with its magnet is attached to a bimetallic element. The bimetal changes its shape according to thermally produced strain which varies with the temperature of the surrounding heat bath of variable temperature T . Upon increasing the temperature, the bimetal is bent towards the closed position; and at a certain temperature T_1 , when the magnets are sufficiently close, the magnetic attraction will become stronger than the thermomechanical forces and effect a meeting of the contact points, and the circuit will close. Any further increase in temperature will have no effect on the flow of electricity (i) since i is determined by E and by the resistance R , both of which stay outside the thermostat. Thus, upon increasing the temperature from its initial value T_0 to T , the path ABCD of Fig. 3 will be traced.

Upon reducing the temperature from T to T_1' the contact will not be opened and the value of i will not fall to zero as expected in a reversible process because the attraction of the magnets will prevent the contacts from opening. It is only when T will be reduced to T_2 that the mechanical stress in the bimetal will suffice to overcome the magnetic attraction and revert the circuit to its initial open state. Thus, the path traced upon cooling will be DCEFA, and an area of metastability BCEF will remain as a kind of "hysteresis loop." The cycle depicted in Fig. 3 is time-independent and may be repeated any number of times without following the equilibrium transition (dashed line) between the open and closed circuit states. Here the macroscopic energy barriers are clearly provided by the attraction of the magnets and by the rigidity of the bimetal, and it is these energy barriers which compel the system transitions to go around equilibrium, at higher and lower temperatures, respectively, than the equilibrium temperature.

It will be noted however that the cycle of the model is not a true, closed, hysteresis loop since the temperatures T_1 and T_2 correspond to points of discontinuity. It is only by the joint operation of numerous elements of the type depicted

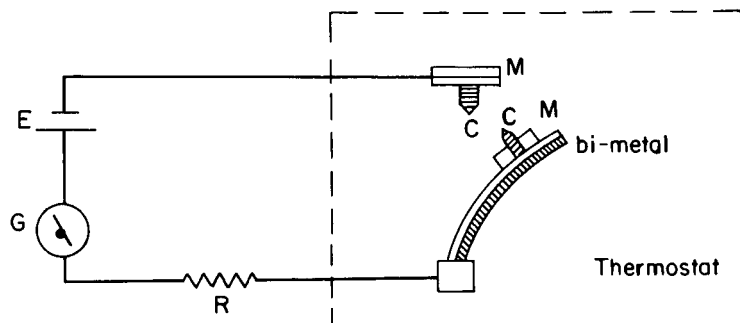


Figure 2. Everett's model. [Katchalsky]

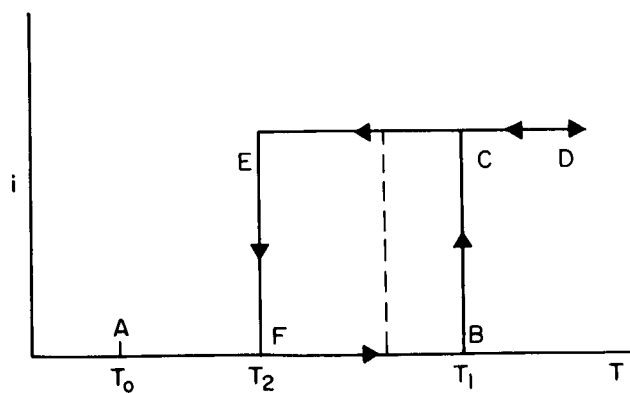


Figure 3. Electric current i as function of temperature T . [Katchalsky]

in Figs. 2 and 3, with a given distribution of transition points for both the forward and backward change from A to B and from B to A, that we may expect a smooth and continuous hysteresis cycle. In real systems the elementary processes have been demonstrated to take place in microscopic domains, each characterized by a single set of transition parameters. In a slow magnetization of a hard polycrystalline ferromagnetic material, Barkhausen could demonstrate that the smooth macroscopic curve consists of numerous jumps which could be amplified to audible clicks. Later, Francis Bitter could make domains visible as dark and light paths on single crystals of Fe_3O_4 . An indirect but readily demonstrable phenomenon underlying hysteresis is the existence of scanning curves: If a process is stopped at certain points on the hysteresis cycle and reversed in direction, it is possible to trace curves backward within the loop, which do not coincide with the boundary curves of a loop such as Fig. 1. The scanning curves are clearly due to the fact that upon reaching the starting point of such curves only part of the domains had been brought to transition, so that the scanning curve reflects an intermediate system which is partially in state A and partially in state B. A careful analysis of the scanning curves permits the evaluation of the distribution of domains and their characteristic transition points (Everett, (11) Enderby⁽¹³⁾).

C. Macromolecular Systems

On a priori grounds, it is imaginable that conformational transitions in macromolecules might also exhibit hysteresis phenomena, since such transitions are often based on crossing high-energy barriers intrinsic to the size and complexity of macromolecular structure, where equilibrium transitions would not be expected. Moreover, the existence of various distributions of functional side groups along the macromolecules makes possible the existence of different domains with a wide range of transition points. It is therefore of interest to investigate whether true hysteresis loops can be discerned in single macromolecules in solution or in macromolecular aggregates, whose domain structure may then serve as record of biological change.

III. AN ANALYSIS OF THE HYSTERESIS BEHAVIOR OF RNA

A. Experimental Results

Several years ago Cox et al. (14) found that upon titrating RNA from different sources potentiometrically, a

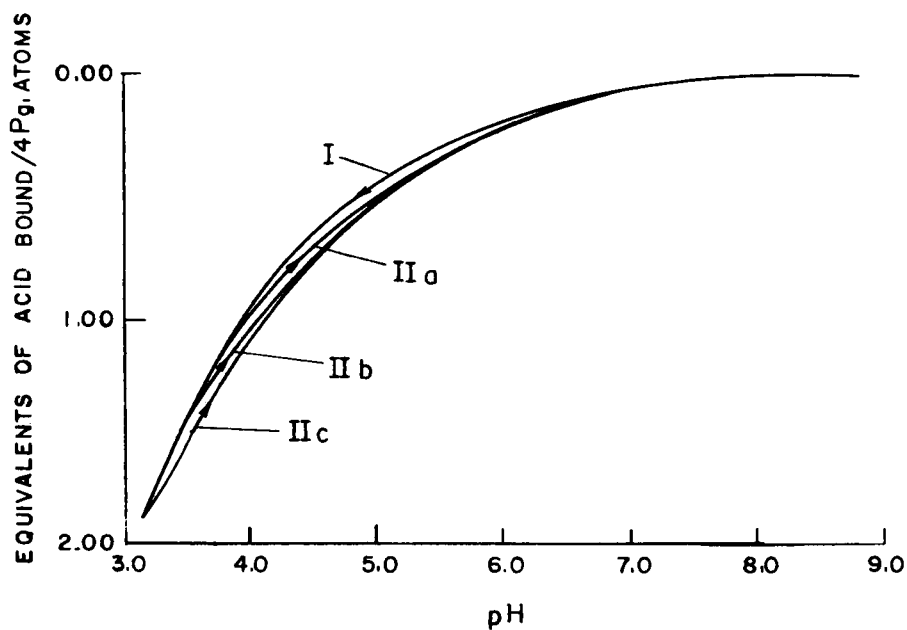


Figure 4. Hysteresis loop (curves I and IIc) with scanning curves (IIa and IIb) of ribosomal RNA from *E. coli* (in 0.1 M NaCl at 0.4°C; "4 P g. atoms" = four gram-atoms of phosphorus). [Cox⁽¹⁶⁾]

reproducible and time-independent hysteresis loop is obtained. A subsequent study by Cox and Littauer⁽¹⁵⁾ confirmed and extended the earlier observation and showed the generality of the phenomenon in a wide range of RNA's. Subsequent measurements by Cox in this laboratory⁽¹⁶⁾ showed that the area of the hysteresis loop is temperature-dependent, increasing upon decreasing the temperature of the solution. If the titration is stopped within the hysteresis loop and the process reversed the loop is not retraced, but typical scanning curves are obtained, similar in principle to the scanning curves of magnetization and demagnetization of hard ferromagnetic materials. Fig. 4 represents an RNA titration hysteresis loop obtained by Cox.

Close inspection of Fig. 4 revealed that the hysteresis loop lies in the pH range of the titration of adenine groups; thus, it was of interest to find whether the hysteresis behavior could be reproduced by the simpler polyadenylic acids or their complexes. Complexes of polyadenylic acid (poly A) with polyuridylic acid (poly U) were discovered some ten years ago by Warner⁽¹⁷⁾; he has shown that if the pH is sufficiently high (>6), complexes will form even at extremely high dilution of the polynucleotides. This complex formation was further studied by Felsenfeld et al.,⁽¹⁸⁾ and by Steiner and Beers.⁽¹⁹⁾ Rich et al.⁽²⁰⁾ showed that poly A at acid pH forms double-helical molecules. While solutions of pure polyuridylic acid do not exhibit any tendency to helix formation at temperatures higher than 8°C, polyadenylic acid "crystallizes" to a double helix in the acid range and undergoes a "chemical melting" to random coils at more alkaline pH's. Several months ago a more detailed study of the phase transitions in polyadenylic acid solutions was carried out by Luzzati.⁽²¹⁾ On the basis of low-angle scattering of X-rays, Luzzati could show that in the pH range of 5.0 to 5.9 the poly A molecules are rod-like, in correspondence with the findings of fiber diagrams; at pH 5.9 a phase transition takes place -- the molecular radius of gyration diminishes and the electron partial specific volume decreases, indicating an increase in molecular flexibility and the beginning of random movement. Above pH 5.9 the essential helical structure is, however, retained, and only at pH 7 does a second phase transition takes place which leads to a total separation of the molecular strands and the appearance of amorphous randomly kinked poly A coils.

The first indication that these macromolecular phase transitions are accompanied by metastable forms and high activation barriers which may lead to hysteresis phenomena was obtained by Warner and Breslow⁽²²⁾ and by Steiner and Beers.⁽¹⁹⁾

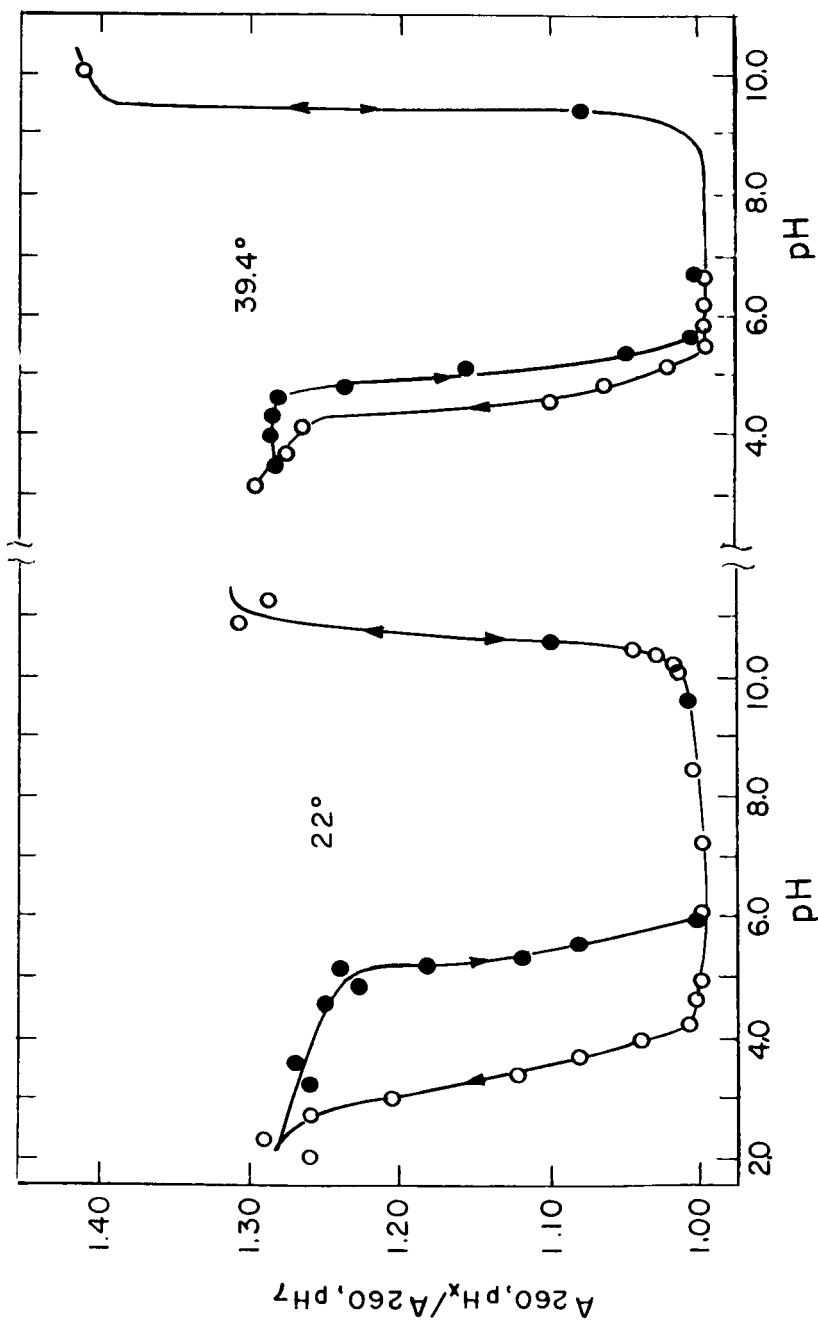


Figure 5. Spectrophotometric titration of poly (A+U) at 22°C and 39.4°C. Titration at 22°C: o-o, titration with acid (←) or alkali (→) from pH 7; ●-●, titration with alkali or acid from low or high pH values, respectively. Titration at 39.4°C: o-o and ●-●, as for 22°C. [Cox (23)]

It was found that upon mixing poly A with poly U at pH 6 a stable double helical complex is formed, which retains its crystalline structure upon reducing the pH until a pH of 4.6 is reached. On the other hand, if the components are mixed at some intermediate pH -- say, at pH 5.5 -- no complex formation takes place. It is thus evident that between pH's 5.5 and 4.6 the complex is metastable and may exhibit hysteretic behavior. That this is really the case was shown by Cox,⁽²³⁾ who obtained a full hysteresis cycle in potentiometric titrations of poly A - poly U mixtures, in which the acid binding was followed by the optical density of the solutions in UV at 260 mμ. A typical result is given in Fig. 5.

It will be observed that this cycle does not resemble the gradual smeared-out run of the RNA titration, but is closer to the elementary process depicted in Fig. 3. The behavior of the complex of poly A and poly U is therefore closer to that expected for a single domain of a ferromagnetic material and may be treated as such. On the other hand, the behavior of the complex RNA molecules is that of a multi-domain structure; this will be discussed in a subsequent publication (Cox and Katchalsky). Since the single domain properties are fairly well understood, we shall devote the following paragraphs to a thermodynamic analysis of the cycles exhibited by the simpler structures.

B. Thermodynamic Analysis

1. Phase Changes

Summarizing the data on the "melting points" of polyadenylic acid and its complexes with polyuridylic acid it is possible, in accordance with the work of Cox, to construct a phase diagram in which the melting point T_m is represented as a function of pH (Fig. 6). The melting points are the transition temperatures determined from, say, abrupt changes in UV absorption, and presumably correspond to the thermodynamic change from one molecular phase to another.

The curve POQ represents the melting points of polyadenylic acid. It divides the surface of the figure in such a manner that the area to the left of POQ is the assembly of temperatures and pH's at which poly A is crystalline and corresponds to a double helix poly (A+A), while the area to the right comprises the states in which polyadenylic acid is single-stranded, randomly coiled poly A. The curve AOB corresponds to the melting points of the complex of poly A and poly U, poly (A+U). At temperatures above the curve AOB the

complex is dissociated into its components, while the area beneath the curve is the assembly of states in which a double-helical complex exists. It will be observed that the intersection of POQ and AOB defines an area AOQ in which both pure crystalline poly (A+A) and the crystalline complex poly (A+U) can coexist. In the case of a true thermodynamic equilibrium, there should be found an equilibrium curve, say OC, into which both branches AO and OQ converge. Such a curve was not observed experimentally, but instead two regions of pronounced metastability -- the region AOC in which the metastable complex poly (A+U) survives for long periods, and the region COQ in which the crystalline poly (A+A) has a rather permanent metastable form. These long-lived metastable forms determine the hysteresis behavior of the mixture. This is demonstrated by the following considerations.

Let us follow the titration of the solution at, say, 25°C, represented in Fig. 6 by the straight line KLMN. Starting at pH 7 (point K), we are titrating a well-formed double helical complex, poly (A+U). Upon reducing the pH, the complex will not dissociate at the thermodynamic equilibrium point M, but will continue to exist until the melting point N is reached. At this point the complex is broken down and will be transformed instantaneously into the crystalline form of poly A and single-stranded poly U according to the scheme



Upon reaching pH 3, we reverse the process by successive additions of alkali. Here again complex formation will not take place at the thermodynamic equilibrium point M, but poly (A+A) will survive in a metastable form until the melting point L is reached. Only at L will single-stranded poly A molecules appear, which will combine avidly with the poly U molecules to give the double-stranded complex poly (A+U). Thus, in the range LN, titrating from right to left we titrate essentially adenylic groups in the form of a complex with uridyl groups while the titration NL from left to right acts on the crystalline poly (A+A). If complex formation changes the value of the acidic dissociation constant of the adenylic groups, the titration paths will be different, and an elementary hysteresis cycle will be obtained. This is depicted schematically in Fig. 7.

It may be noted that for the existence of the cycle there is no need for the existence of metastable forms of both poly (A+U) and poly (A+A). If only one of the double helices exists as a metastable form, the curve OC of Fig. 6 will

coincide with either AO or OQ, and the titration cycle of Fig. 7 will assume the form of a triangle instead of a parallelogram.

Upon increasing the temperature, the range LN decreases, and when point O of Fig. 6 is reached the hysteresis cycle shrinks to zero.

2. Free Energy Changes

For further analysis, it is advantageous to cast the data into another form which is clearer from a thermodynamic point of view. We shall now represent the behavior of the solution as the average free energy, G , per mole of nucleotide, and consider three extreme cases: where all the polymeric chains are in the amorphous molten state, where all the adenine residues are in the form of crystalline poly (A+A), and where all the adenine residues are combined with uracyl residues as complex poly (A+U). The isothermal dependence of G on pH is given in Fig. 8.

Titration from pH 7 on point K of Fig. 6, the system is found in Fig. 8 on point K of curve III, since in this pH range, curve III is the lowest in free energy. Upon lowering the pH, the free energy increases along curve III, but at point M should pass to curve II of lower energy content. As is evident from the previous discussion, the transition from one crystalline form (poly (A+U)) to another crystalline form (poly (A+A)) is, however, prevented by an energy barrier, which can be circumvented only by melting prior to transition.

During the lowering of pH from M to N, the system will therefore continue along the metastable part of III until it meets the amorphous curve I and the complex undergoes a dissociation into single, random molecules. Here no additional barriers prevent the transition to lower-energy, more stable form, so that the system will pass in a jump to curve II, with the irreversible liberation of free energy ΔG_1 . Further decrease in pH beyond N will cause the system to follow the stable low branch of curve II. Upon reversing the process, again no reversible phase transition will take place at M but the free energy will climb up metastably along curve II until the melting point at L is reached. An irreversible jump ΔG_2 will again take place and the system will revert to its initial stable path along curve III.

During the irreversible transitions at L and N, the binding capacity of the polynucleotides changes. At constant

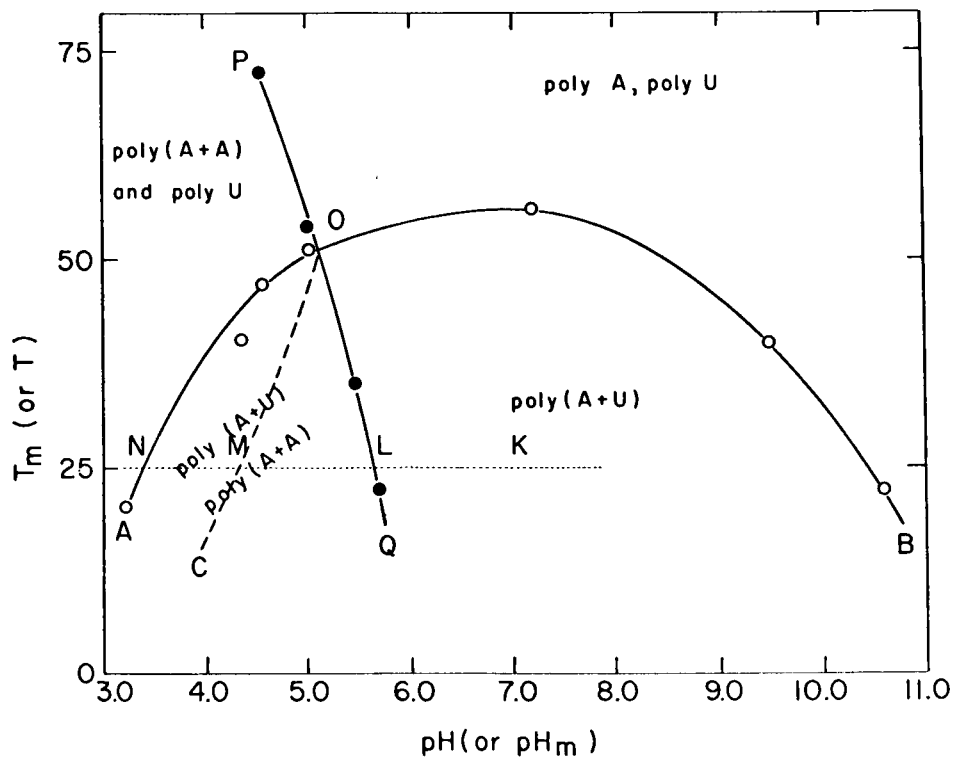


Figure 6. Phase diagram for poly (A+U) and poly A. $\circ-\circ$, poly (A+U); $\bullet-\bullet$, poly A (acid form). [Adapted from Cox⁽²³⁾]

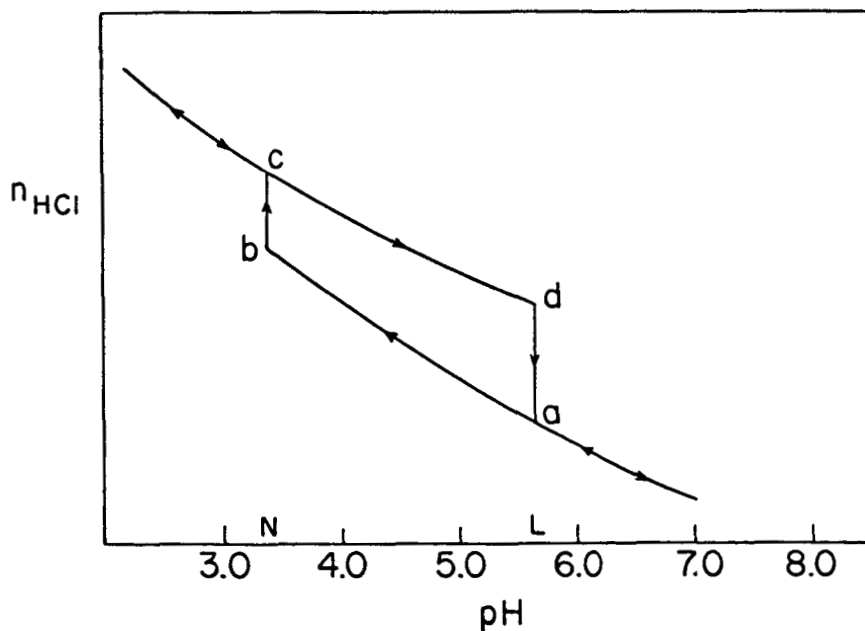


Figure 7. Schematic titration curve of a solution containing poly A and poly U in a 1:1 nucleotide ratio. The ordinate gives the number of moles HCl bound by a mole of adenylic residues. [Katchalsky]

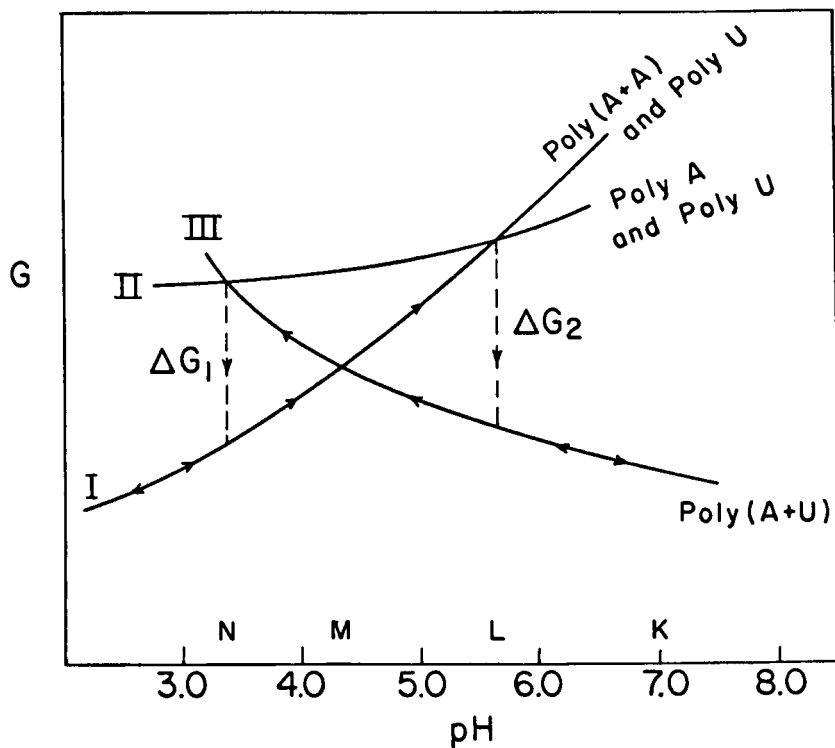


Figure 8. The free energy G , as function of pH, of a solution containing poly A and poly U in a 1:1 nucleotide ratio (schematic). [Katchalsky]

chemical potential of the added acid, denoting the change in number of moles acid bound at N by Δn_1 and the chemical potential of the acid by μ_1 , we can write

$$\Delta G_1 = \mu_1 \Delta n_1 + \Delta G_{irr,1}$$

where $\Delta G_{irr,1}$ is the irreversible change in free energy. Similarly for the second jump we get

$$\Delta G_2 = \mu_2 \Delta n_2 + \Delta G_{irr,2}$$

For the closed cycle as a whole, the change in free energy, $\oint dG$, equals zero since free energy is a function of state only. Applying these considerations to the cycle depicted in Fig. 7, we may write

$$\begin{aligned} 0 &= \oint dG = \int_a^b \mu_{HCl} dn_{HCl} + \Delta G_1 + \int_c^d \mu_{HCl} dn_{HCl} + \Delta G_2 \\ &= \int_a^b \mu_{HCl} dn_{HCl} + \mu_1 \Delta n_1 + \int_c^d \mu_{HCl} dn_{HCl} + \mu_2 \Delta n_2 + \Delta G_{irr,1} + \Delta G_{irr,2} \\ &= \oint \mu_{HCl} dn_{HCl} + \Sigma \Delta G_{irr} \text{ or } \oint \mu_{HCl} dn_{HCl} = - \Sigma \Delta G_{irr} \end{aligned}$$

But in any irreversible process $\Delta G_{irr} < 0$, so that for our cycle $\oint \mu_{HCl} dn_{HCl} > 0$ which determines the direction of cyclic process. Now

$$\oint \mu_{HCl} dn_{HCl} = - \oint n_{HCl} d\mu_{HCl}$$

Further, if it is assumed that the titration is carried out in excess chloride ions so that $d\mu_{Cl^-} = 0$ we may write

$$d\mu_{HCl} = d\mu_{H^+} + d\mu_{Cl^-} \simeq d\mu_{H^+} = 2.3 \log a_{H^+} = - 2.3 RT d \text{ pH}$$

and hence

$$\oint n_{HCl} d \text{ pH} = - (2.3 RT)^{-1} \Sigma \Delta G_{irr} > 0.$$

Since the nature of the jumps is not specified, and we did not consider explicitly the number of domains undergoing irreversible transitions, the last equation should hold also for a real cycle of the type exhibited by RNA and would determine its direction of change, as well as the total change in free energy accompanying all the transitions.

C. Conclusion

For more detailed analysis of the irreversible energy changes accompanying the transitions in the interaction of poly A and poly U, the reader is referred to the paper of

Katchalsky, Oplatka and Litan. (24) In the present work it suffices to consider the overall change in free energy during a hysteresis cycle of RNA. On the basis of the data of Cox, (16) we find that $2.303 RT \ln_{HCl} pH$ for RNA from *E. coli* is about 0.18 RT, while the corresponding value for rat-liver RNA is 0.2-0.25 RT per nucleotide. Since not all the nucleotides are involved in the process, this may be regarded as the lower bound of energy change per participating nucleotide. Assuming that the smallest number of nucleotides in a domain is about 8-10, we find that the energy involved in a phase transition of a nucleotide is higher than 2 RT, which is a plausible figure if memory recording in domain structures be considered. The figure is sufficiently high to make a signal changing the domain structure distinguishable from the thermal noise, but small enough to be of use in the low-energy transformations of living organisms.

Though this discussion does not prove that biological memory is recorded through the mechanism presented above, nor does it strengthen the theory that RNA is involved in the record, the possibility that metastable macromolecular states of high permanence participate in memorizing should not be excluded. It is of particular interest to consider also larger crystalline domains in macromolecular structures, such as extra- or intracellular membranes which would permit a wider range of information storage. Analysis of two-dimensional hysteresis phenomena, based on domains in biological films, is relegated to another publication.

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