

Lasting Consequences of Bilateral Medial Temporal Lobectomy: Clinical Course and Experimental Findings in H.M.

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The attention that has been devoted to the patient H.M. in terms of number of hours of evaluation and amount of journal and book space probably exceeds that devoted to any other single case. This circumstance is due to the unusual purity and severity of his amnesic syndrome, to its well-documented anatomical substrate, to the relatively static nature of his condition, and to his being a willing and cooperative subject. This article provides an overview of the history, 31-year postoperative clinical course, and neuropsychologic findings in this 58-year-old man.

HISTORY

PREOPERATIVE CLINICAL COURSE

H.M. was born in 1926. He was the only child of working-class parents. The hospital birth was apparently normal, but no details of the procedure are available. His development was said to have been unremarkable until age 7 years when he was knocked down by a bicycle. (Note that H.M.'s age at the time of this injury was given as 9 in an earlier report;¹ the correction was made following a subsequent conversation with his mother.) He sustained a laceration in the left supraorbital region, and was unconscious for 5 minutes. It should be noted, too, that three first cousins on his father's side of the family had epilepsy. H.M. experienced his first minor seizure at age 10 years, and his first major seizure on his 16th birthday. He still remembers that he was riding in the car with his parents at the time of the latter event, but states that it was his 15th birthday. He dropped out of high school

because the other boys teased him about his seizures. After a two-year interval, however, he entered a different high school and graduated in 1947, at age 21. In high school, he took the "practical" course, in preference to the "commercial" or "college" course, and states that he took as little mathematics as possible because he did not care for it. He was a member of the Science Club and was fond of guns, hunting and roller skating.

After high school, he worked on an assembly line and also held a job as a motor-winder until his seizures incapacitated him to the extent that he could no longer perform his duties. At that time, he was having on the average 10 petit mal seizures per day and 1 major seizure per week. Unsuccessful attempts had been made over a 10-year period to control these seizures with large doses of anticonvulsant medications, including Dilantin, phenobarbital, Tridione, and Mesantoin. The frequency and severity of the attacks ultimately led H.M. and his family to consider a brain operation. The proposal to do a radical experimental operation was discussed with them on several occasions before the decision to proceed was reached.

BRAIN OPERATION

In 1953, when H.M. was 27 years old, Dr. William Beecher Scoville performed a bilateral, medial temporal-lobe resection.² He approached the brain through two 1.5-inch supraorbital trephine holes. By inserting a flat brain spatula through each hole, he was able to elevate both frontal lobes, thereby exposing the tips of the temporal lobes. They in turn were retracted laterally in order to permit access to the medial surfaces, where electrocorticography was carried out in order to assess the activity of the uncus, amygdala, and hippocampus—structures that are often implicated in epilepsy. There was no clear-cut evidence of an epi-

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leptic focus in this region. An incision was then made that bisected the tips of the temporal lobes, and he resected the medial half of the tip of each temporal lobe. Next, Dr. Scoville removed by suction all of the gray and white matter medial to the temporal horns of the lateral ventricles, sparing the temporal neocortex almost entirely. The removal was bilateral, and it is said to have extended 8 cm back from the tips of the temporal lobes. It included the prepyriform gyrus, uncus, amygdala, hippocampus, and parahippocampal gyrus, and must have produced an interruption of some of the white matter leading to and from the temporal lobes (Fig. 1). H.M. was awake and talking during the operation.

Five pieces of excised brain tissue underwent gross neuropathologic study. Microscopic examination of three of them, taken from one uncus and both amygdalae, found them to be without inflammation or scarring.

POSTOPERATIVE CLINICAL COURSE

The operation reduced the frequency of H.M.'s major seizures to the point where now his attacks are infrequent, and he may be free of generalized convulsions for as long as a year. The minor seizures persist; they are atypical petit mal attacks that

do not noticeably disturb him. His current seizure medications are Dilantin, 100 mg three times daily, and Mysoline, 250 mg three times daily. The reduction in seizure frequency is juxtaposed against the unexpected handicap produced by the resection: Since the time of his operation, H.M. has had a profound anterograde amnesia that is especially salient because his overall intelligence and neurologic status are relatively well-preserved. H.M.'s global amnesia has put marked limitations on his daily activities and accomplishments. Once the harmful effects of bilateral medial temporal lobectomy were recognized, Dr. Scoville campaigned widely against its use.³

Living Situation and Daily Activities

After his operation, H.M. returned home to live with his mother and father. His daily activities included accompanying his mother on errands, helping with household chores, mowing the grass, watching television, and doing crossword puzzles. His father, whom H.M. resembles both physically and in his gentle, passive nature, died in 1967. Beginning in that year, H.M. attended a rehabilitation workshop on a daily basis for about 10 years. There, he performed simple, repetitive tasks, went

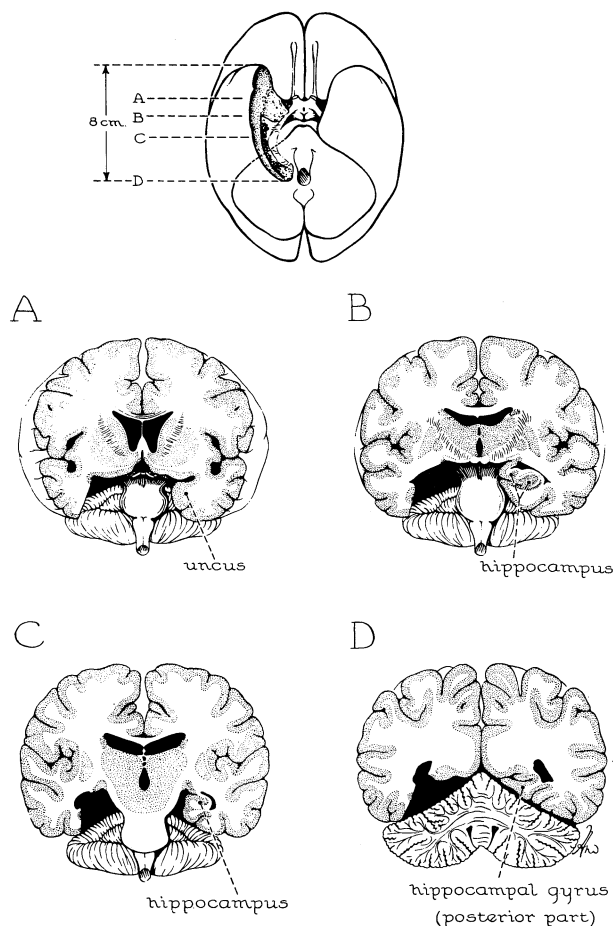


Figure 1. These cross-sections of human brain were prepared by Dr. Lamar Roberts to show the extent of H.M.'s resection. For didactic purposes, the resection is shown on the right side of the brain, and the intact structures on the left side of the brain, but note that the lesion is bilateral. At the top is a drawing of the base of the brain that shows where the cross-sections are taken from. Level A=uncus; level B=anterior hippocampus; the amygdala would be in a section between A and B, but is not shown; level C=more posterior hippocampus; level D=parahippocampal gyrus at the posterior limits of the resection (from Scoville and Milner, 1957).

on field trips, and also worked in this protective setting as a handyman. H.M. and his mother lived by themselves until 1974, when owing to his mother's advanced age, they went to live with a relative. Three years later, H.M.'s mother was admitted to a nursing home. Then, in 1980, because the relative who cared for him was terminally ill, H.M. moved to the nursing home where he currently resides (though not the one where his mother was living). His mother died in 1981 at age 94.

Currently, H.M. is assisted with his bath or shower, but dresses himself with the clothes that are laid out for him. He is reminded to shave, brush his teeth, and comb his hair. He spends much of his time doing difficult crossword puzzles and watching television. He also participates in the daily activities of the nursing home, such as poetry reading, crafts projects, games, and entertainment. His appetite is good, and he is reported to sleep well, but all-night electroencephalogram (EEG) recordings reveal that he wakes up often because of sleep apnea.

Motivation and Affect

One of H.M.'s most striking characteristics is that he rarely complains about anything. In 1968, his mother stated that "the trouble with H. is that he doesn't complain—ever. There could be something quite seriously wrong with him, but you would have to guess." At the nursing home, when H.M. is observed to be acting differently, the nurses question him by running through a list of possible complaints, such as toothache, headache, stomachache, until they hit upon the correct one. He will not spontaneously say, for example, "I have a headache," causing one to wonder whether he knows what is wrong. Similarly, he does not ask for food or beverages, and unless questioned, does not say that he is hungry, full, or tired. He sometimes asks to go to the bathroom, however. H.M. appears to be content at all times, and is always agreeable and cooperative to the point that if, for example, he is asked to sit in a particular place, he will do so indefinitely. The rare exceptions to this placid demeanor occur when H.M. is stressed. For example, during the time that H.M. and his mother lived with their relative, his mother's constant nagging would cause H.M. to become very angry. Occasionally, he would kick her in the shin or hit her with his glasses. More recently, another patient in the nursing home apparently liked to annoy H.M. by calling him names, criticizing him, and disturbing his Bingo card. Her behavior angered H.M. to the point that he would shake the sides of his bed and walk around in circles. As soon as he was distracted, his anger would dissipate immediately. Since this woman's discharge from the nursing home, H.M. has not had any such outbursts. He is described as even-tempered and well-behaved; he does not throw objects, swear, or hit. Moreover, his sense of humor

is often evident, as it was the day that Dr. Harvey Sagar and H.M. walked out of a testing room into the hall, allowing the door to close behind them. Dr. Sagar commented to H.M., "I'm wondering whether I left my keys inside the room." H.M. replied, "At least you'll know where to find them!"

After H.M.'s father died, his mother believed that H.M. was depressed, and her concern for him motivated her to enroll him in the rehabilitation workshop mentioned above. When she died four years later, the staff at the nursing home where H.M. lives observed that his grief was mild. He told them what a nice woman she had been and that she had taken care of him all his life. He sometimes remembers that his parents are dead and mentions that he is all alone. His adjustment to all of the changes in his personal relationships and living situation has been smooth.

H.M. appears to have no interest in sexual relationships, as indicated by the absence of conversation on sexual topics and by his failure to seek sexual satisfaction. He does not flirt, he has never had a girlfriend, and he does not masturbate, as far as his caretakers have been able to determine. Hyposexuality is sometimes associated with temporal-lobe lesions, and thus it is tempting to speculate that H.M.'s sexual indifference is attributable to the brain operation; it may be due to other factors, however. Preoperative testing by a clinical psychologist, Dr. Liselotte K. Fisher, led her to conclude that H.M. had difficulty in his sexual adjustment. Moreover, anticonvulsant therapy produces elevated sex hormone binding globulin levels, which are associated with reduced plasma total testosterone, raised luteinizing hormone levels, and sexual dysfunction.⁴ Thus, the sexual disorder may have been present before the operation, and it may be due at least in part to drug-induced hormonal abnormalities. Further study of sex hormone patterns is warranted in H.M.

PHYSICAL EXAMINATION

We have documentation of H.M.'s medical history since 1966; he has been free of major illnesses. Information relevant to his neurologic status is described below.

NEUROLOGIC EXAMINATION

During the postoperative years that we have followed H.M. his neurologic status has remained stable. Neurologic examination in 1984 revealed an ataxia of gait, polyneuropathy, and a left ulnar neuropathy. These signs are identical to those found in 1966, except for progression of the polyneuropathy since 1970 and the appearance of the ulnar neuropathy in 1977. The relative absence of neurologic deficit is surprising when one considers the nature and extent of the abnormal conditions that coexist in H.M.'s brain. In this man, six factors con-

tribute to the total cerebral disorder: the longstanding neural abnormality that produced his frequent major and minor seizures; the lasting deleterious effects of repeated seizure activity; the effects of long-term use of anticonvulsant medications; the substantial loss of brain tissue due to bilateral medial temporal-lobe resection; the cortical and subcortical neuronal loss that normally occurs throughout life; and the chemical counterparts of the presumed morphologic changes.

LABORATORY TESTS

Urinalysis and routine blood tests show no consistent abnormality apart from a mild red cell macrocytosis, which is probably due to Dilantin therapy. The 1984 EKG tracing is within normal limits. In addition, urine testosterone, blood testosterone, free cortisol, and adrenocorticotropin levels measured in 1980 were all normal. These findings are of interest because there are numerous corticosterone receptors in the hippocampus, and

this structure is involved in the control of glucocorticoid secretion,⁵ and because the hippocampus sends extensive projections to the hypothalamus.⁶

A contrast-enhanced computed tomography (CT) scan was performed in 1984 on a GE 9800 scanner at the Massachusetts General Hospital. The use of this current generation scanner made it possible for the first time to visualize H.M.'s medial temporal-lobe lesions. Other evidence of the resection was dilation of the temporal horns of both lateral ventricles. Additional findings included cerebellar atrophy, possibly associated with long-term Dilantin treatment, and mild cortical atrophy, as is sometimes seen in a 58-year-old person (Fig. 2). These findings are in agreement with those obtained in 1978.

An EEG performed in 1978 showed a large amount of bilateral and diffuse seizure activity. The most prominent finding was that of wave and spike activity that was symmetrical and maximal in the frontal regions, and polyspike and wave activity in sleep. There was some slow activity in the temporal regions, which was greater on the left, but in that

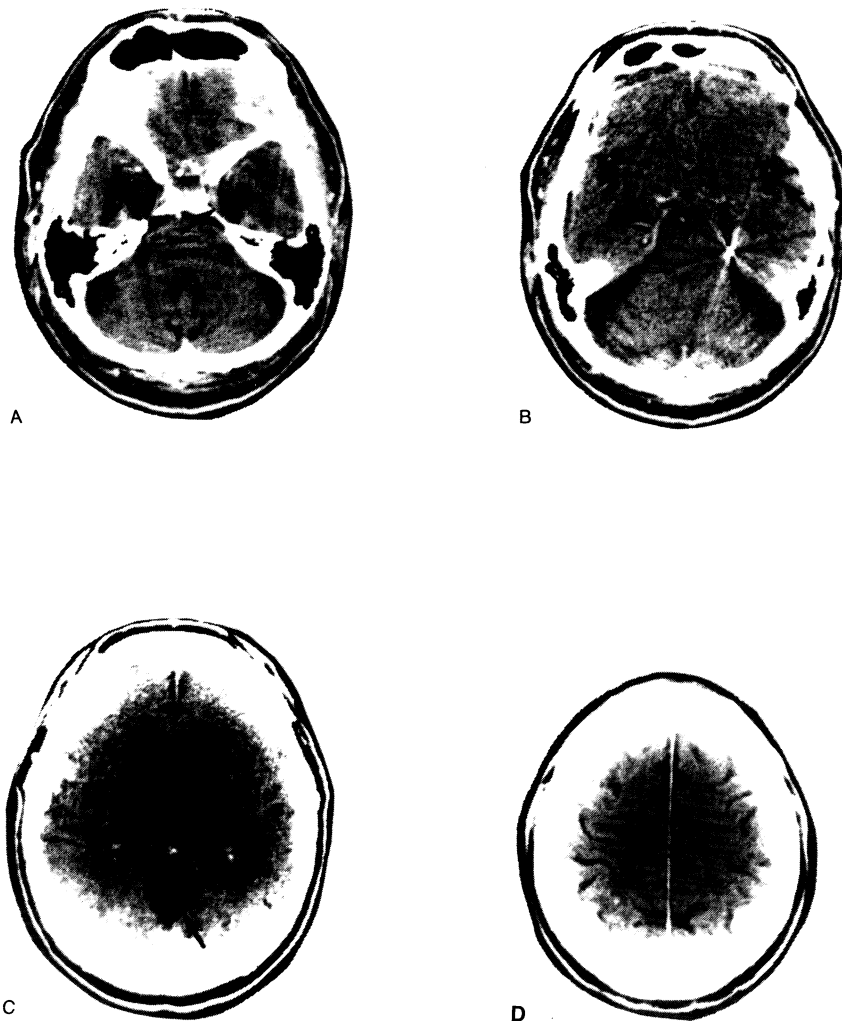


Figure 2. A, Areas of lower absorption value are observed bilaterally in the region of the medial aspects of the temporal lobes anteriorly. The changes are more prominent on the left side (arrow). These areas of low absorption value are consistent with partial volume averaging of tissue loss due to the surgical resection. B, Mild to moderate tissue loss is seen in the Sylvian cisterns anteriorly. An arrow denotes the enlarged Sylvian cistern on the left. These changes could be secondary to the surgical removal of tissue in the medial temporal lobes. The linear streaking more posteriorly is due to artifact from a surgical clip. C, The Sylvian cistern (arrow) is not well filled out by the superior cerebellar vermis, indicating atrophy of this structure. The cerebellum shows marked, diffuse atrophy. The ventricles are enlarged, consistent with the patient's age. D, The changes laterally, over the convexity, are consistent with the patient's age. The cortical sulci are prominent bilaterally, especially medially, in the interhemispheric fissure. Whether these changes reflect some secondary alteration in the region of the cingulate gyrus cannot be determined.

area only fragments of low amplitude spike activity were seen.

NEUROPSYCHOLOGIC EVALUATION

The information about H.M. described up to this point provides a background against which to consider the objective neuropsychologic test results. These findings serve two purposes: They illustrate the purity of H.M.'s amnesic syndrome, and they provide answers to a variety of questions about the organization of human memory systems. Now that H.M. is 58 years old, a new question has arisen: Will the aging process proceed normally in his brain, or will the symptoms of aging be accelerated in an already damaged structure? The experimental findings summarized here in brief have either been described in detail previously in separate research reports or will be the basis for future articles.

SENSORY AND SENSORIMOTOR FUNCTION

Visual field testing was carried out in 1966, 1970, and 1984 using the Tübingen perimeter.⁷ H.M.'s visual fields are normal, as are most other visual functions tested, including prism adaptation (Held, unpublished data), masking and metacontrast (Schiller, unpublished data), and perception of spiral after-effects. The single exception is his contrast sensitivity function, which is slightly reduced for his age (Nissen and Corkin, unpublished data). Because he viewed the stimuli through the upper lens of his bifocals, and because the correction may not have been optimal, testing will be repeated with H.M. wearing full frame glasses with the proper correction.

H.M.'s performance on a series of olfactory tasks indicated a dissociation of function: He is able to detect weak odors compared with distilled-deionized water, to appreciate odor intensity, and to adapt normally to strong odors.⁸ Discrimination, matching, and identification tasks, however, reveal that he is severely impaired in the perception of odor quality. This disorder is not surprising because the resection invaded primary olfactory cor-

tex in the uncus, and because retraction of the frontal lobes during the operation might have damaged the orbitofrontal cortex, olfactory bulb, or olfactory tracts. Nevertheless, these structures must have been at least partially spared in order to support the residual olfactory capacities demonstrated in H.M.

Since 1962, we have documented H.M.'s peripheral neuropathy on his hands and forearms with quantitative measures of somatosensory function, including pressure sensitivity, two-point discrimination, point localization, position sense, thermal discrimination, and pain sensitivity.^{9,10} On these tests, H.M. has mild to moderate deficits bilaterally, although his performance is variable and sometimes even falls within the normal range. His grip strength shows little fluctuation; in 1983, it was 70.3 pounds on the left, and 72.3 pounds on the right. H.M. appears to be right-handed, but he states that in second grade he was forced to switch his writing hand from left to right. On tests of repetitive finger tapping and visuomotor coordination,¹¹ H.M.'s scores for the two hands are comparable, and at the bottom of the normal range for his age. The exception is the Thurstone tapping test, in which his scores for the bimanual condition are markedly impaired; this abnormality is probably attributable at least in part to his cerebellar atrophy. His performance on a test of repetitive fine-finger movement¹² is asymmetric, with the left hand markedly inferior to the right, even on unimanual conditions. This finding suggests some interference with the primary motor cortex or other part of the pyramidal system, presumably in the right hemisphere.^{13,14} The sensorimotor deficit revealed in the laboratory is also apparent in his daily activities. For example, the staff at the rehabilitation workshop noted some clumsiness in working with his hands, although the quality of his work was said to have been excellent.

OVERALL INTELLIGENCE

The Wechsler-Bellevue scale was administered to H.M. on seven occasions, including an examination the day before his operation by Dr. Liselotte K. Fisher (Table 1). Postoperative testing

Table 1. The Amnesic Patient H.M.: Wechsler Intelligence-Scale and Memory-Scale Results (1953–1983)

Date	Age	Test	Verbal IQ	Performance IQ	Full Scale IQ	Memory Quotient	Delayed Recall	
							Verbal (Deficit ≤ 11)	Nonverbal (Deficit ≤ 7)
Preop								
1953	27	W-B I	101	106	104	*	*	*
Postop								
1955	29	W-B I	107	114	112	67	*	*
1962	36	W-B II	109	125	118	64	1	0
1977	51	W-B I	107	126	118	74	5	0
1978	52	W-B II	91	104	98	63	1	0
1980	54	W-B II	97	108	104	64	1	0
1983	57	W-B II	97	115	108	64	0	0

*Not assessed

also included the Wechsler memory scale (WMS); the discrepancy between the memory quotient (MQ) and the full scale IQ rating provides a crude index of the severity of global amnesia, although marked IQ-MQ differences can occur for other reasons, such as severe verbal memory impairment. Overall IQ ratings have been consistently in the average range, whereas performance IQ ratings fall in the average to superior ranges. Individual subtest scores vary considerably: Preoperatively H.M.'s equivalent weighted score on the arithmetic subtest was 1, reflecting his dislike of mathematics; the postoperative arithmetic scores ranged from 4 to 7. Object assembly and digit symbol were both 7 preoperatively, but all other scores were above 10. On postoperative testing, the object assembly score has risen to 12 and 13, but the digit symbol scores remain low, perhaps reflecting the effects of medication. The full scale IQ ratings cover the average and bright normal ranges, and all are at least 35 points above the memory quotient, indicating an inferiority of memory function to overall intelligence. A more sensitive index of memory impairment, however, is performance on delayed recall of verbal (WMS logical memory and associate learning) and nonverbal (WMS visual reproduction) material.¹⁵ On both tasks, H.M. is severely impaired on all occasions (see Table 1). More detailed studies of specific memory capacities are cited below.

A comparison of the 1977 and 1983 test results indicates that H.M.'s verbal IQ rating has dropped 10 points, his performance IQ rating 11 points, and his full scale IQ rating 10 points (see Table 1). In normal aging, IQ test performance is maintained until after age 70,¹⁶ so that H.M.'s losses, though not dramatic, may reflect premature aging produced by his multiple neural abnormalities. The manifestation of this process could be a decrease in the number of neurons, in the number of receptor sites, or in the efficiency of the remaining neurons. Alternatively, transneuronal degeneration in the limbic system, a rare cause of progressive intellectual loss, could underlie H.M.'s slight deterioration.¹⁷

LANGUAGE CAPACITIES

H.M. is able to appreciate puns and linguistic ambiguities,¹⁸ and although he does not usually initiate conversations himself, when someone begins a conversation with him, he talks readily and in general communicates effectively. Nevertheless, his language functions are now minimally impaired. Clinically, he has a slight anomia, but on the Boston naming test,¹⁹ he scores in the normal range (Huff, unpublished data). Although he also achieves perfect scores on six subtests of the Minnesota test for differential diagnosis of aphasia—three reflecting receptive language capacities and three expressive language capacities—this test is relatively easy, and on more challenging language tests, he is less accurate. Thus, on the token test of lan-

guage comprehension,²⁰ he achieves 34 of 36 and 32 of 36 correct on separate occasions (deficit ≤ 33), and on the reporter's test of language production,²¹ he succeeds on 19 of 26 and 23 of 26 items (deficit ≤ 24). His spelling is poor, although this disorder may have antedated the brain operation. In addition, he is clearly impaired on tests of semantic and symbolic verbal fluency^{11,22} (Nissen, unpublished data). Because other cognitive functions of the frontal lobes are preserved in H.M. (see later), it is believed that the fluency deficit is not related to frontal-lobe dysfunction, but rather reflects an alteration in more general cognitive capacities. Studies of language in aging and Alzheimer's disease reveal that performance on tests of verbal fluency is compromised early in the succession of cognitive changes.²³ H.M.'s mild language disorder, therefore, may be age-related. One of the issues of interest is the extent to which this deficit influences his performance on memory tests.²⁴

SPATIAL AND PERCEPTUAL CAPACITIES

O'Keefe and Nadel²⁵ proposed a model of hippocampal function in which the hippocampus is concerned with context-dependent memory. They provided evidence that the hippocampal system develops objective spatial representations, and for the human hippocampus they postulated that an analogous mapping of linguistic information also occurs. We were initially resistant to this notion because of certain preserved spatial capacities in H.M., but a review of his performance on a wide range of spatial tests that do not rely heavily on memory function indicates that some spatial capacities are compromised, whereas others are not: Deficits are revealed on the hidden figures test,^{11,26,27} visual locomotor mazes,²⁸ copy of the Rey-Osterrieth figure,²⁹ and the body scheme test.²⁸ He is similarly thwarted when given a floor plan of the MIT Clinical Research Center to use as a map and asked to walk the route from one room to another. In contrast, H.M.'s performance is exceptionally good on two other spatial tasks and two complex perceptual tasks, the block design subtest of the Wechsler-Bellevue scale, a modified version of Hebb's triangular blocks test,²⁹ the Mooney faces test,³⁰ and the McGill picture anomalies.¹⁵ Moreover, his recognition of fragmented line drawings from the Gollin incomplete-pictures test is normal,^{24,30} and he shows savings from one test session to the next: In 1962, 1980, 1982, and 1983, his respective error scores were 21, 16, 8, and 7. He is also able to draw an accurate floor plan of the house where he lived during the postoperative years from 1960 to 1974, showing all the rooms in their proper location. He believes that he still lives there and can recognize the floor plan, drawn by someone else, when it is presented with four foils. In the nursing home where he lives, he can find his way from the ground floor to his room, which is one flight up. These latter two instances of preserved spatial capacities oc-

cur in environments where H.M. has had thousands of learning trials, however. Because patients with right temporal-lobe lesions are often impaired on the complex spatial tasks that H.M. performs efficiently,^{15,31,32} the distinction between the tests on which he succeeds and those on which he fails may reflect a contrasting specialization of the temporal neocortex and medial temporal-lobe structures, respectively.

FRONTAL-LOBE CAPACITIES

The constellation of symptoms observed in H.M. may be contrasted with that seen in patients with less pure amnesias due to ruptured anterior communicating artery aneurysm or to Korsakoff's syndrome; they show frontal-lobe dysfunctions that are believed to contribute to the memory impairment.³³⁻³⁵ Specifically, they fail to show release from proactive interference, and are poor at judging the temporal order of events and at problem solving. Unlike these patients, H.M. shows preservation of the cognitive functions of the frontal lobes, aside from verbal fluency discussed above. Thus, on six of seven administrations of the Wisconsin card sorting test,³⁶ he has achieved more than three categories; on the seventh occasion, his Dilantin level was in the toxic range, and understandably he did not achieve any sorting categories. H.M. makes few perseverative errors, and he shows normal release from proactive interference (Cohen, unpublished data). Moreover, his test quotient on the Porteus maze test³⁷ has gone up from 110 in 1977 to 126 in 1983. The number of qualitative errors is abnormally high, but they are attributable to awkwardness in reorienting his hand, and not to a predilection for rule breaking.

SELECTIVE ATTENTION

Because of the importance of attention for the conscious remembering that takes place in conventional memory tests, it was important to determine whether H.M.'s memory impairment is accompanied by an attentional disorder. One way in which we probe for such a deficit is to ask whether detection of a stimulus is faster when it is in the expected position than when it is in the unexpected position. On a visual simple reaction time task,³⁸ H.M. responds more slowly than control subjects, but demonstrates normal effects of spatial and temporal expectancy, indicating that his selective attention is unaffected (Nissen and Corkin, unpublished data).

CLASSICAL CONDITIONING

Classical conditioning has been attempted only once with H.M., but without success because the unconditioned stimulus, a shock delivered to the right ankle, did not elicit the expected increase in galvanic skin response (Kimura, unpublished data). This kind of experiment should be pursued with

H.M., however, using discrete striated muscle responses because of the reports that cerebellar lesions in animals permanently abolish classical conditioning of such responses with aversive unconditioned stimuli,³⁹ and because of the finding that the hippocampus plays a role in such conditioning.⁴⁰ H.M. does show an electrodermal response to white noise, which habituates during a testing session. In this paradigm, he shows savings several hours and one day later (Merker and Pastel, unpublished data).

RECENT-MEMORY CAPACITIES

Immediate Memory

A consistent finding with H.M. since 1955 has been the preservation of his immediate memory capacities. His digit span increased postoperatively, and since then his immediate memory span for both digits and block patterns has been borderline normal.^{24,41} Nevertheless, his forward digit span was 6 through 1977, and dropped to 5 in each of four subsequent years, indicating a small deterioration of immediate memory function. Decay in short-term memory is normal, as measured by both recognition⁴² and recall tasks²⁴ (see also Corsi). H.M.'s initial acquisition of complex visual stimuli, color photographs of scenes and objects from magazines, is also unimpaired (Grove, unpublished data). Thus, H.M. is able to register new information; his striking disability becomes apparent when his immediate memory span is exceeded, if only by a single item,^{41,43} when distraction is introduced during retention intervals,³¹ and with the mere lapse of time if the material cannot be rehearsed verbally.^{44,45}

Long-Term Memory

A striking feature of H.M. is the stability of his symptoms during the 31 postoperative years. He still exhibits a profound anterograde amnesia, and does not know where he lives, who cares for him, or what he ate at his last meal. His guesses as to the current year may be off by as much as 43 years, and, when he does not stop to calculate it, he estimates his age to be 10 to 26 years less than it is. In 1982, he did not recognize a picture of himself that had been taken on his 40th birthday in 1966. Nevertheless, he has islands of remembering, such as knowing that an astronaut is someone who travels in outer space, that a public figure named Kennedy was assassinated, and that rock music is "that new kind of music we have." The following pieces of anecdotal evidence illustrate the severity of his anterograde amnesia and provide some examples of the information that he has been able to recall.

In July 1973, H.M. could not identify Watergate, John Dean, or San Clemente, in spite of the fact that he watched the news on television every night. He did not know who the President was, but

when told that his name began with an "N," H.M. said "Nixon." When H.M. was asked whether he could tell the examiner anything about Skylab, he replied, "I think, uh, of a docking place in space." When asked how many people were in Skylab, he correctly said "three," but was not confident of his answer because he immediately added, "But then I had an argument with myself, then, was it three or five?" In response to the question, "What's it like to move around up there?" he said, "Well, they have weightlessness . . . I think of magnets to hold them on metal parts so they . . . won't float off away, and to hold them there so they can move around themselves and stay in one area, and they won't move away unvoluntarily (sic)." In 1980, he erroneously stated that a hippie is a dancer, that Howard Cosell does the news on television, and that Barbara Walters is a singer. However, he correctly said that "grass" could refer to drugs or marijuana, that Raymond Burr plays the part of a detective on television, and that Archie Bunker calls his son-in-law "Meathead." He is comfortable dealing with the products of new technology, such as computerized tests and portable radios with headphones. These anecdotes indicate that although H.M.'s fund of general knowledge is meager, it is not void.

The severity and pervasiveness of H.M.'s memory disorder have been documented repeatedly by his performance on a wide variety of neuropsychologic tests. For example, delayed recall is impaired whether the stimuli are stories, verbal paired associates, digit strings, new vocabulary words, drawings, nonverbal paired associates, block patterns, songs, common objects, or object locations^{24,41,46} (Corkin and Sullivan, unpublished data; Cohen, Gabrieli, and Corkin, unpublished data). Further, H.M. does not benefit from the use of visual imagery in paired-associate learning,⁴⁷ and he is unable to learn the correct path from start to finish in both visual and tactual stylus mazes^{48,49} unless the number of turns is within his immediate memory span.³⁰ H.M. is also impaired on continuous recognition of words, nonsense syllables, numbers, geometric drawings, and nonsense shapes,⁵⁰ and on forced-choice recognition of faces, houses, words, and tonal sequences (Corkin, unpublished data). Although the pattern of memory deficits in H.M. resembles that seen after unilateral temporal lobectomy coupled with hippocampectomy, the magnitude of H.M.'s losses are more marked than those typically seen after unilateral excisions.⁵¹

In the face of H.M.'s profound anterograde amnesia, it is impressive that certain classes of memory function are preserved. The first hint of a residual learning capacity was Milner's 1962 report that H.M.'s error and time scores on a mirror-drawing task decreased over three days of training, despite his being unaware that he had done the task before.⁵² Later experiments provided further evidence of his ability to acquire new motor skills.^{49,53} More recent studies make it clear, however, that the domain of preserved learning was formulated

too narrowly as motor learning. Thus, H.M. can also acquire certain perceptual skills, such as reading of briefly presented words and mirror reading⁵⁴ (Cohen and Corkin, unpublished data), and the cognitive skills required to solve the Tower of Hanoi puzzle.^{55,56} Other evidence of preserved learning is that H.M. shows the biasing effects of experience with words, while at the same time being unable to recall that experience. For example, H.M. is shown a word, such as "DEFINE," and asked to indicate how much he likes or dislikes it on a 1 to 5 scale. Next, he is given the stem "DEF" and asked to say the first word that comes to mind. Here he typically responds with the previously experienced word, even though it is not the most frequent completion of the stem "DEF" when biasing is absent. In contrast, he fails dramatically on subsequent recall and recognition testing with the same words (Gabrieli, Cohen, and Corkin, unpublished data).

In summary, H.M.'s impaired performance on traditional tests of delayed recall and recognition memory is in marked contrast to his normal performance on tests of motor, perceptual, and cognitive skill learning and on measures of biasing effects of experience with words. Among the various dichotomies that have been proposed to account for such findings, the distinction between procedural learning (knowing how) and declarative learning (knowing that) is perhaps the most appropriate to conceptualize the kind of knowledge that is spared in H.M. and the kind that is preserved.⁵⁷ Declarative knowledge appears to require medial temporal-lobe structures bilaterally for its expression; procedural knowledge is independent of that system.

REMOTE-MEMORY CAPACITIES

In an effort to explore some of H.M.'s pre-morbid memories in a natural environment, Dr. Neal Cohen and I accompanied H.M. to his 35th high school reunion in 1982. A number of his classmates remembered him and greeted him warmly; one woman even gave him a kiss. As far as we could determine, however, H.M. did not recognize anyone's face or name. But he was not alone in this respect. We met a woman who claimed that she too did not know anyone in the room. Clearly, she and H.M. were the exceptions in this regard, but her comment reminds us that as people age, they also forget. Thus, in evaluating H.M.'s remote memory function with objective tests, it has been important to compare his performance with that of age-matched control subjects.

In 1968, Milner, Corkin, and Teuber³⁰ reported that H.M.'s retrograde amnesia was restricted to about 2 years preceding the operation. This conclusion was based upon information from the neurosurgeon's office notes and on postoperative interviews with H.M. and his mother. Recently, objective tests have been used to probe the

limits of H.M.'s remote memory for public and personal events.^{58,59} The new data confirm the finding that H.M.'s remote memory impairment is temporally limited, but they extend the limits of the deficit back to 1942, 11 years before the medial temporal-lobe resection. The public events tests measure recall of famous tunes, verbal recognition of public events, and recall and recognition of famous scenes. In the famous tunes test (Marslen-Wilson, unpublished data), subjects hear samples of 48 tunes from the 1920s to the 1960s, and are asked to provide the titles. H.M.'s ability to name famous tunes is below the normal range for the 1930s, 1940s, and 1960s. A comparison of H.M.'s performance with that of two other amnesic patients suggests that the severity of the remote memory loss may be related to the severity of their anterograde amnesia. Errors in dating famous tunes were defined as the difference between the subject's dating and the actual date. Normal control subjects have an equal number of overshoots and undershoots, as does a patient with global amnesia secondary to encephalitis, although he is less accurate. H.M., in contrast, has a tendency to attribute most tunes to the 1940s so that he systematically overshoots in the 1920s and 1930s, and systematically undershoots in the 1950s and 1960s. On the verbal recognition test of public events,⁶⁰ there are 88 questions about events from the 1940s through the 1970s. On this test, H.M.'s performance is normal for the 1940s, borderline for the 1950s, and clearly impaired for the 1960s and 1970s. A comparison of these results with those for other amnesic patients suggests that the extent in time of the retrograde loss is related to the duration of the amnesic syndrome. The postencephalitic patient who had been amnesic for 26 years is impaired, whereas two other patients who had been amnesic for 10 years and 1 year, respectively, both performed normally. Items for the famous scenes test were selected because they depict an event that cannot be deduced from the picture itself. There are four pictures at each of five decades from the 1940s through the 1980s. In the recall test, subjects are first asked whether they have seen the picture before. They are then given one minute to describe the content and action in the picture, and what event it depicts. If the subject omits important details, they are probed for by specific questions. Finally, subjects are asked, "When was the picture taken?" A content score and a dating score are given for each picture. On the recall test, H.M.'s content scores are impaired for all decades except the 1940s, and his dating scores are impaired at all decades tested. The number of datings per decade is also noted, the actual number for each decade being four. Reminiscent of the famous tunes test, H.M. preferentially chooses the 1940s and 1950s at the expense of the 1960s through 1980s: His dating is shifted into his nonamnesic time period. It is striking that with this preference for the 1940s and 1950s, H.M. is still impaired in dating 1940s

and 1950s items. Similar findings are obtained with the famous scenes recognition test.

The personal events test is a modified version of the Crovitz personal remote memory test.^{58,59,61} Here, subjects are given eight concrete nouns, one at a time, and are asked to relate some personally experienced event cued by each noun, from any period of their life, and to state when the event took place. In order to establish the consistency of the memory, an attempt is made to invoke the same memory a day later, and to assess its content and dating. Day one and day two memories are scored from 0 to 3, according to their specificity. On this task, a perfect score is 30, and all subjects perform efficiently. A drop from day one to day two means either that the subject could not produce the day one memory on day two at all, or that the day two memory was less specific. H.M. and one other amnesic patient show a slight drop from day one to day two. Every time that a subject gives a memory that is specific enough to be scored 3, he is asked to date that memory. Normal control subjects and three amnesic patients who have been amnesic from 1 to 26 years produce memories across their life span up to their current age. In contrast, H.M.'s memories are all from age 16 years or younger, even though his operation took place at age 27. It is important to note that his major seizures began at age 16, however. This absence of memories over age 16 replicates our previous results (Cohen and Corkin, unpublished data). Consistent with this finding are the observations that H.M. does not remember the end of World War II, nor his high school graduation, both of which occurred after his 16th birthday and before his operation. The fact that H.M. produces no memories after age 16 is not evidence that he is unable to do so. He was therefore given the same words again and asked to relate memories only after the age of 16. Because the task becomes more difficult for everyone when responses are restricted to a particular time period, H.M.'s performance was compared with the performance of another amnesic patient whose responses were similarly constrained. The results indicate that H.M.'s total score is about half of what it was in the unconstrained condition, and poorer than the scores of the other amnesic patients in the constrained condition; that the memories that he does give are for ages 17 and 18 only, and when he is asked to redate these memories the same day and the next day, he dates three of the four below age 16; and that the consistency of memories from day one to day two is practically 0, again in contrast to his unconstrained performance and to the constrained performance of the other patient. These experiments, taken together, provide clear evidence that H.M.'s remote memory impairment extends from the present time back to age 16, 11 years before the operation that resulted in the severe anterograde amnesia. There are at least three factors that may account for this finding. First, there is likely to be a retrograde amnesia covering a period of

years before the operation. This impairment would be a true loss of previously established memories. Second, there may also be an anterograde component due to the occurrence of seizures and the toxic doses of anticonvulsant medications prescribed to prevent them. This condition could have interfered with the acquisition of new information. Third, another factor may be a progressive deterioration of remote memories over the years due to impoverished rehearsal secondary to retrograde amnesia, anterograde amnesia, or both.

COMMENT

H.M.'s legacy to cognitive science and brain science has been to provide evidence relevant to distinctions between memory systems and among amnesias of different etiologies based upon the selective preservation or disturbance of specific capacities. H.M. shows a sparing of immediate but not lasting memory function, of skill learning and priming effects but not learning of facts and events, and of remote memories up to 11 years before operation but not after that. These findings suggest that processes in the storage of immediate memories are biologically independent of those underlying memories that endure, and that the acquisition of skills and priming effects is not supported by medial temporal-lobe structures, whereas the remembrance of people and episodes is. Further, H.M.'s preservation of immediate memory capacity and span, and his temporally limited remote memory loss distinguish him from patients with Korsakoff's syndrome and patients with Alzheimer's disease, who do show deficits in immediate memory, as well as in remote memory across all time periods examined.^{24,62,63} The additional deficits seen in Korsakoff's syndrome and Alzheimer's disease are in part related to the more extensive pathologic changes in the brain. Results from patients with a variety of brain pathologies are needed to understand the neurology of memory.

In 1984, 31 years after H.M. underwent bilateral medial temporal lobectomy, research with this patient continues to provide new insights into the cognitive and biologic processes that constitute normal human learning and memory. Neuroscientists of present and future generations are indebted to H.M. for his ongoing contributions to our knowledge. We should also recognize the neurosurgeon Dr. Scoville for encouraging research with H.M., and for publicizing it himself in an effort to ensure that, in the patient group to which H.M. belongs, $N = 1$.

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