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Human Amnesia and the Medial Temporal Region: Enduring Memory Impairment Following a Bilateral Lesion Limited to Field CA1 of the Hippocampus

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During the past 100 years clinical studies of amnesia have linked memory impairment to damage of the hippocampus. Yet the damage in these cases has not usually been confined to the hippocampus, and the status of memory functions has often been based on incomplete neuropsychological information. Thus, the human cases have until now left some uncertainty as to whether lesions limited to the hippocampus are sufficient to cause amnesia. Here we report a case of amnesia in a patient (R.B.) who developed memory impairment following an ischemic episode. During the 5 years until his death, R.B. exhibited marked anterograde amnesia, little if any retrograde amnesia, and showed no signs of cognitive impairment other than memory. Thorough histological examination revealed a circumscribed bilateral lesion involving the entire CA1 field of the hippocampus. Minor pathology was found elsewhere in the brain (e.g., left globus pallidus, right postcentral gyrus, left internal capsule), but the only damage that could be reasonably associated with the memory defect was the lesion in the hippocampus. To our knowledge, this is the first reported case of amnesia following a lesion limited to the hippocampus in which extensive neuropsychological and neuropathological analyses have been carried out.

Nearly a century ago, von Bechterew (1900) first suggested that memory impairment could occur following damage to the medial temporal lobe of the brain. He presented neuropathological findings from the brain of a 60-year-old man who had memory problems during the last 20 years of his life. The patient's brain showed bilateral softening of the gyrus uncinatus (the piriform and periamygdaloid cortices and the underlying amygdaloid complex) and the gyrus cornu ammonis (the hippocampal formation).

A half century later, Grunthal (1947) and Glees and Griffith (1952) published separate case studies linking defects in memory to medial temporal damage. Both cases resulted from a vascular accident that bilaterally damaged the hippocampus and surrounding cortex. Other brain regions, including the amygdala and the mamillary bodies, were reported to be normal. The evidence for impaired memory in these 2 cases was anecdotal and based on clinical impressions. Nevertheless, both patients seemed to have had considerable anterograde memory problems, and one seemed to have had retrograde amnesia covering several years (Glees and Griffith, 1952).

In 1954, Scoville described a case of severe anterograde amnesia that followed bilateral medial temporal lobe resection in a patient with intractable seizures. The removal extended posteriorly along the medial surface of the temporal lobes for a distance of approximately 8 cm from the anterior poles, probably destroying the anterior two-thirds of the hippocampus and hippocampal gyrus bilaterally, as well as the amygdala and periamygdaloid cortex (Scoville, 1954; Scoville and Milner, 1957). This case (H.M.) has been studied extensively during the past 30 years (Corkin, 1984).

Formal memory testing of H.M. and 9 other patients with less extensive bilateral medial temporal lobe removal led to the view that damage to the hippocampus was responsible for the amnesia (Scoville and Milner, 1957). Memory impairment was observed whenever the hippocampus and hippocampal gyrus were damaged bilaterally. A patient whose resection included only the amygdala and uncus (presumably the periamygdaloid cortex), while sparing the hippocampus, was not amnesic. The importance of hippocampal damage in memory impairment was further supported by the finding that patients with left or right unilateral medial temporal lobe resections exhibited verbal or nonverbal memory deficits, respectively. The severity of the deficits correlated with the extent of hippocampal damage (Milner, 1972).

The hippocampus has also been linked to memory impairment in cases of viral encephalitis (Damasio et al., 1985a; Rose and Symonds, 1960), posterior cerebral artery occlusion (Benson et al., 1974), and hypoxic ischemia (Volpe and Hirst, 1983). In addition, impaired memory has been attributed to hippocampal lesions in several single case studies (Cummings et al., 1984; DeJong et al., 1968; Duyckaerts et al., 1975; Gol and Faibish, 1967; Muramoto et al., 1979; Van Buren and Borke, 1972; Woods et al., 1982). However, the assessment of memory functions in these cases was often based on anecdotal reports (but see Damasio et al., 1985a). In addition, damage in many cases was not confined to the hippocampus but extended into the amygdala and parahippocampal gyrus. In other cases, only cursory neuropathological analysis was carried out. Thus the human cases have, until now, left some uncertainty as to whether lesions limited to the hippocampus are sufficient to cause amnesia.

Alternatives to the view that hippocampal damage is sufficient to cause memory dysfunction have also been proposed. For example, Horel (1978) pointed out that none of the human cases available through the 1970s had well-documented lesions lim-

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ited to the hippocampus. He proposed that the "temporal stem," a fiber system that lies superficial to the hippocampus and that links the temporal neocortex with subcortical regions, was the critical structure damaged in medial temporal lobe amnesia. He suggested that this fiber system would necessarily be damaged by the surgical procedures carried out during anterior temporal lobectomy. An alternative view was advanced in the same year by Mishkin (1978), who pointed out that all human surgical cases exhibiting amnesia had damage to both the hippocampus and amygdala. Accordingly, the evidence from the surgical cases is as consistent with the view that conjoint hippocampal–amygdaloid damage is needed to produce amnesia as with the view that hippocampal damage alone is sufficient.

Recent successes at developing an animal model of human amnesia in the monkey (Mahut and Moss, 1984; Mishkin et al., 1982; Squire and Zola-Morgan, 1983) have provided a way to address these issues experimentally. Monkeys with lesions limited to the temporal stem were not amnesic (Zola-Morgan and Squire, 1984; Zola-Morgan et al., 1982), and monkeys with conjoint hippocampal–amygdaloid lesions were amnesic even when the lesions caused no damage to the temporal stem (Mahut et al., 1982; Moss et al., 1981; Zola-Morgan et al., 1982). Therefore, damage to the temporal stem does not seem to be a factor in memory impairment. The same conclusion about the temporal stem was reached in a recent clinicopathologic case study of a patient who had become amnesic following an ischemic episode (Cummings et al., 1984).

Studies in monkeys have also compared the amnesic effects of separate hippocampal lesions with the effects of combined hippocampal–amygdaloid lesions (Mahut et al., 1982; Mishkin, 1978; Squire and Zola-Morgan, 1985; Zola-Morgan and Squire, 1985). While hippocampal lesions produced a statistically significant impairment, the combined lesion produced an even larger deficit. Thus, the results with experimental animals suggest that hippocampal lesions alone produce a measurable impairment in memory, though the severity of the deficit is increased when the amygdala and surrounding cortical areas are included in the ablation.

These results from monkeys leave some question as to whether a patient with damage limited to the hippocampus would demonstrate a memory impairment. Would the deficit be substantial or only minor? Recently, we obtained extensive clinicopathological information from a patient who developed a clinically significant memory impairment as the result of an ischemic episode. This patient survived for 5 years following the episode, during which time he participated in our neuropsychological studies of memory and amnesia. We report here a well-documented case of amnesia with neuropathological evidence of bilateral damage to the hippocampus.

Materials and Methods

Case history: patient R.B.

Pre-operative history. R.B. was a white male postal worker, retired in 1976 at 50 years of age because of medical disability. In 1960, he had experienced shortness of breath and chest pain, which was diagnosed as angina. In 1970, an electrocardiogram done at rest and during physical exercise was normal. In August 1976, he again developed shortness of breath with right chest pain and was hospitalized in an Intensive Care Unit for 6 d. On the basis of angiographic findings, coronary artery bypass surgery was performed 1 month later, with 1 graft to his circumflex artery. Anginal episodes continued during the next 2 years. In July 1978, an angiogram showed that the graft was occluded, and a second bypass surgery was recommended. Up to this point there had been no history of neurologic problems except several transient episodes of hypoesthesia of the anterior right thigh.

Surgery and perioperative event. In September 1978, R.B., now 52 years of age, was hospitalized, and on September 18 a second coronary artery bypass operation was performed, this time on the left anterior descending circumflex artery and the posterior descending artery. The surgery was uneventful, and the patient was transferred to the surgical Intensive Care Unit, where his condition remained stable throughout the early evening. He was noted to be awake and able to move all 4 limbs in response to commands. At about 1:00 AM on September 19, a sudden atrial tear resulted in the loss of 800–1000 cc of blood in less than 2 min. A systolic pressure of 40 mm was recorded at this time. His chest was opened and internal cardiac massage initiated. Manual massage was continued while the patient was transferred to the operating room. His electrocardiogram was flat at this time, and his pupils were 2 mm in diameter and fixed. The atrial tear was repaired, and cardiac rhythm and blood pressure were eventually brought to within normal limits with the help of a pacemaker and an intraaortic balloon pump. It was estimated that a total of 5000 cc of blood was lost. At about 9:00 AM, the patient was returned to the Intensive Care Unit. He was ventilated artificially and given a neuromuscular blocking agent (pancuronium bromide) intermittently for several days to control chest muscle fasciculation and shivering. During that period he was generally unresponsive, presumably because of the neuromuscular blockade, but there were times between drug administrations when he appeared to understand verbal stimuli and opened his eyes on request.

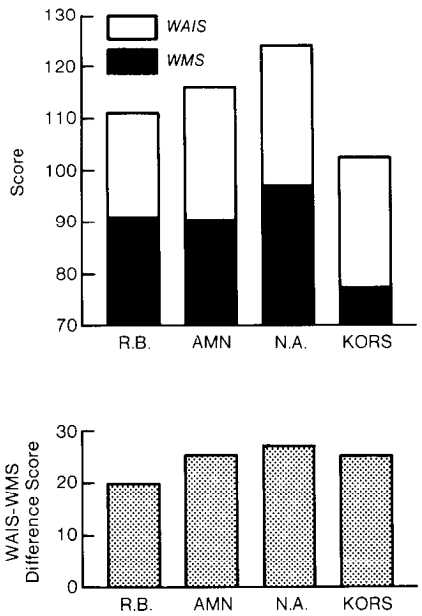

Figure 1. *Top panel* shows full-scale Wechsler Adult Intelligence Scale scores (*WAIS*) and Wechsler Memory Scale scores (*WMS*) for patient R.B., 3 patients with amnesia due to anoxia or ischemia (*AMN*), case N.A., and 8 patients with Korsakoff syndrome (*KORS*). In normal subjects, the WMS is equivalent to the WAIS. *Bottom panel* shows the average WAIS-WMS difference score for the same patients.

Postoperative course. On September 20, R.B. was returned to the operating room after a routine chest x-ray suggested further bleeding. In the operating room he had 2 arrhythmias, and a systolic pressure of 90 mm was recorded. For the next 4 hr pressor drugs were adjusted, cardiac output eventually normalized, and the patient was returned to the Intensive Care Unit, where his blood pressure ranged between 80–110/45–60 mm. At about 6:00 PM on the same evening, the patient had an episode of supraventricular tachycardia. His blood pressure dropped to 60/40 mm. He was cardioverted 9×, and a heart rate of 110 beats/min was established. During this period, the patient was noted to have fixed pupils, 5–6 mm in diameter. On September 21, an electroencephalogram (EEG) showed diminished amplitude and continuous slow delta activity. He was able to open and close his eyes to command, but there was no correlated change in the EEG. Over the next 2 d, the patient's need for pressor agents decreased.

On September 23, lidocaine and pancuronium bromide were discontinued and the patient was able to breath without mechanical assistance. Later that day, he opened his eyes when his name was called and appeared to understand what was being said to him. That evening he attempted to talk and was able to move all extremeties. He could move

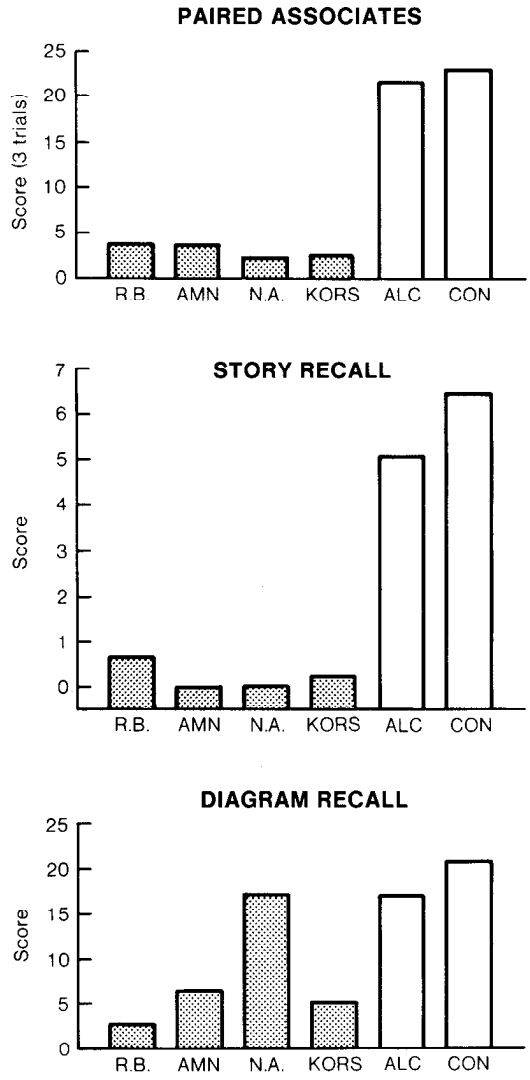

Figure 2. Performance on 3 tests of new learning ability by patient R.B., 3 other amnesic groups (see Fig. 1), alcoholic control subjects (*ALC*; $N = 6$), and healthy control subjects (*CON*; $N = 6$). For the patients, the score is the average for 3 separate test administrations. R.B. was tested 6 months, 9 months, and 23 months after the onset of amnesia.

his fingers but could not grasp. On the following day he recognized his son. At this time, reduced grip strength was noted in the left hand, and paresthesia was noted in the left hand and forearm. On September 24, the balloon pump, the right atrial and intracardiac lines, and the chest tubes were removed. He could respond readily to verbal stimuli and could nod appropriately. On September 25, he asked for a drink of water and asked where he was. On the next day, it was noted that he appeared to forget things easily.

On September 29, the patient suffered an apparent respiratory arrest and was intubated and respirated artificially. During this episode, blood pressure ranged between 60/40 mm and 110/60 mm. He required mechanical ventilation over the course of the next month, although he was reported to be alert and responsive during this time. On October 30, he was successfully weaned from the respirator. At this point 2 chart entries indicated that he was disoriented as to time and place. On November 11, he was moved from Intensive Care to a medical ward for 2 weeks of convalescence. A neurological exam on November 12 noted impaired memory: he could not recall or recognize any of 3 words presented a few minutes previously. He had poor recall of current events as well as of the surgical events of the previous weeks. He was less impaired on questions about the distant past. Spontaneous speech, naming, reading aloud, and comprehension were judged to be normal. He was discharged on November 21, 1978.

Patient R.B. was hospitalized 5× during the following 5 years. He suffered shortness of breath, edema, decreased exercise tolerance, as well as atrial flutter. In each case, myocardial infarction was ruled out. His blood pressure was never lower than 90/70 mm during any of these short hospital stays. On September 22, 1983, R.B. suffered a fatal cardiac arrest. Cause of death was reported as end-stage congestive heart failure secondary to severe and widespread atherosclerosis.

Neuropsychological evaluations. In March 1979, about 6 months after his surgery, R.B. was given a battery of standard neuropsychological tests as part of his follow-up evaluation. He obtained a full-scale WAIS IQ of 111 (verbal: 108; performance: 114), and he was considered to have severe impairment on tests of verbal and nonverbal memory functions (prose passage: immediate recall, 5 segments; delayed [20 min] recall, 0 segments; Rey-Osterreith figure: copy, 30/36 segments; delayed [20 min] recall, 1/36 segments). During the testing session, he stated that he had severe memory problems. He explained that he needed to ask his wife repeatedly to tell him what had gone on and, if he talked to his children on the phone, he did not remember anything about it the following day. He said that he did notice some improvement in his memory and was able to recall a few things from television or the newspaper.

At this time, through discussions with staff of the Neurology and Psychology Services, we became aware of the patient and his memory problem. During the next 4 years, we evaluated R.B.'s performance on a variety of tests of anterograde and retrograde amnesia, and compared his performance to that of other amnesic study patients and control subjects.

To facilitate interpretation, quantitative data for patient R.B. are presented here, together with comparable data for 3 other kinds of amnesic patients: (1) Patients with Korsakoff syndrome: These 3 women and 5 men with amnesia have been tested as a group for several years. They have 12.4 years of formal education (range = 12–14 years) and averaged 50.5–52.3 years of age at the time of the testing summarized here. (For additional information about this group, see Shimamura and Squire, 1984.) (2) Case N.A.: This man has been amnesic for verbal material since 1960 when, at the age of 22, he sustained a stab wound to the brain from a miniature fencing foil (Kaushall et al., 1981; Teuber et al., 1968). Radiographic evidence identified a lesion in the left dorsal thalamus (Squire and Moore, 1979). He has had 13 years of formal education. The testing summarized here was done when he was 40–47 years of age. (3) Ischemia and anoxia: These 3 males have amnesia as the result of ischemia or anoxia. Case 1: Cardiac arrest and anoxia in 1976. Testing occurred 5–8 years after the episode. His age at completion of testing was 46 years, and he had received 20 years of education (Ph.D. in clinical psychology). Case 2: Hypotensive episode during surgery in 1983. Testing occurred 1–2.5 years after the episode. His age at completion of testing was 44 years, and he had received 13 years of education. Case 3: Respiratory arrest and anoxia during epileptic seizure in 1984. Testing occurred 7–13 months after the episode. His age at completion of testing was 55 years, and he had received 15 years of education.

Figure 1 shows the full-scale Wechsler Adult Intelligence Scale (WAIS) IQ and the Wechsler Memory Scale (WMS) score for each kind of amnesic patient. The difference between the WAIS and the WMS provides 1 index of the severity of memory impairment. In normal subjects, the WMS score is equivalent to the WAIS IQ. In March 1979, 6 months after his episode, R.B.'s WAIS was 111, and his WMS was 91.

Figure 2 shows the scores for 3 tests of new learning ability that assess the severity of anterograde amnesia. The data for the amnesic patients are average scores for 3 separate administrations of each test (except for N.A.'s diagram recall score, which is based on a single test). R.B. was tested at 6 months, 9 months, and 23 months after the onset of his amnesia. For paired associate learning, subjects were given 3 consecutive trials to learn 10 unrelated word pairs (Jones, 1974). R.B. recalled 3.7 pairs during the 3 trials (maximum = 30). For story recall, subjects were read a short prose passage (Gilbert et al., 1968) and asked to recall it immediately after hearing it and again, without forewarning, 10–12 min later. R.B. recalled an average of 5 segments of the passage immediately but only 0.7 segments after the delay. For diagram recall, subjects copied a complex figure and then, without forewarning, were asked to reproduce it from memory 10–20 min later. We used the Rey-Osterreith figure (Osterreith, 1944), the Taylor figure (Milner and Teuber, 1968), and a similar complex figure developed in our laboratory. The maximum score for each figure was 36. R.B. averaged 29 points for his copy and 3 for his reproduction. Note that patient N.A., who has a left diencephalic lesion, performed much better on diagram recall than on the other two

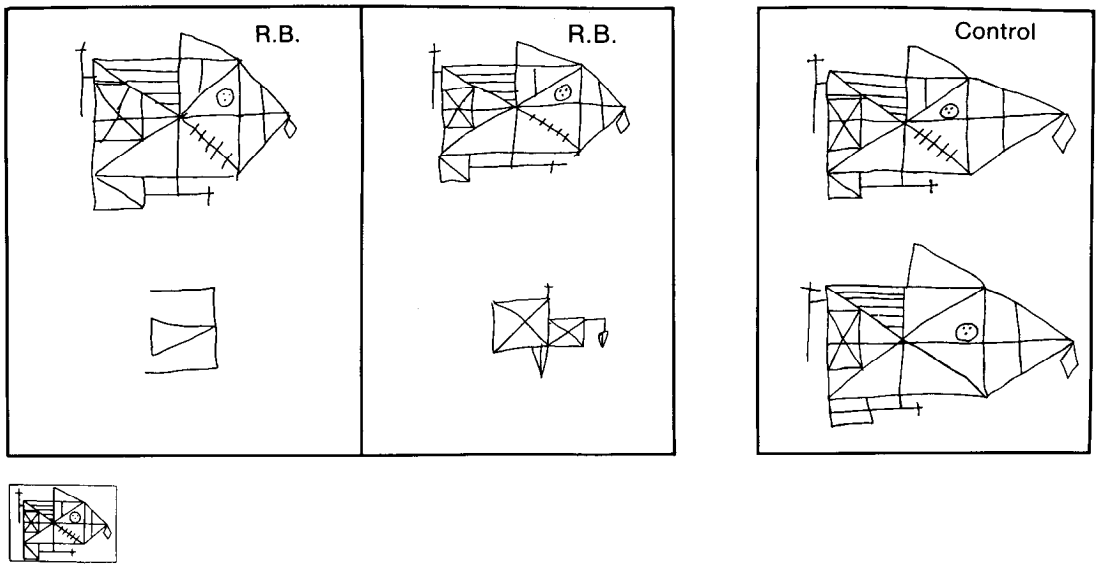

Figure 3. Performance by patient R.B. on 2 separate administrations of the Rey-Osterreith complex figure test. R.B. was first asked to copy the figure illustrated in the small box to the *left*. Then, without forewarning, he was asked to reproduce the figure from memory 10–20 min later. *Left panel,* R.B.'s copy (*top*) and reproduction (*bottom*) 6 months after the onset of his amnesia. *Middle,* R.B.'s copy and reproduction 23 months after the onset of amnesia. *Right,* Copy and reproduction from 1 of the 6 healthy control subjects matched to R.B. for age and education.

verbal memory tests. Figure 3 shows R.B.'s copy and delayed reproduction of the Rey-Osterreith figure, done at 6 and 23 months after the onset of his amnesia.

Figure 2 also presents scores for 2 control groups, who were given 1 administration of each test. Alcoholic subjects (2 females and 4 males) were current or former enrollees in an alcoholic treatment program. They averaged 52 years of age (range = 40–58) and had 12.6 years of education (range = 11–15). They report having had a drinking problem for an average of 9.5 years and having abstained from alcohol for an average of 2 years prior to testing. Healthy control subjects (5 females and 1 male) averaged 50.2 years of age (range = 44–55) and had 15 years of education (range = 13–18). They had WAIS-R subtest scores of 22.5 for information (R.B.'s WAIS-R score = 18) and 52.8 for vocabulary (R.B.'s WAIS-R score = 52).

Figure 4 shows that R.B.'s memory impairment was still present 4 years after his injury. Subjects were read a list of 10 words twice in succession, each time in a different order, and were then asked to write down as many of the words as they could remember. Five filler words (3 at the beginning of each list and 2 at the end) were included to prevent primacy and recency effects. Descriptions of each group have been published previously (shaded bar in Graf et al., 1984, Experiment 1—liking condition; open bar in Graf et al., 1985, Experiment 1—visual presentation). For patient R.B. and the control group (CONT), the shaded bar shows average free-recall performance for 4 separate lists of 10 words. All the other data show free-recall performance for 2 lists of 10 words.

R.B.'s anterograde amnesia was apparent on tests of recognition memory, not only on tests of free recall. In 1 test (Squire et al., 1978), subjects were presented 36 words and, after a 20 min delay, were tested for 2-choice recognition (12 target words and 12 novel words), yes–no recognition (12 target words and 12 novel words), and cued recall using the initial 3 letters of 12 target words. R.B. was given this test on 8 different occasions with 8 different forms of the test. He averaged 9.5 correct out of 36 (corrected for guessing). Six control subjects (mean age = 49.7 years, range = 43–60) averaged 19.3 correct (range = 14.9–23.5) on 3 different forms of the same test.

Figure 5 presents scores for R.B. and a control group on 6 tests that assess retrograde amnesia, i.e., memory for events that occurred before the onset of amnesia. Data for other amnesic patients on these tests, and descriptions of all the tests, have been published previously (Cohen and Squire, 1981; Zola-Morgan et al., 1983). R.B. was first given a test that asked about 88 news events that had occurred in 1 of the 4 decades from 1940–1979. The test was first given in a form (recall) that asked for a short answer to each question, e.g.,"What was the S.L.A.?" The same test was then given as a 4-choice, multiple-choice test (recognition). Finally, R.B. was asked to recall as much as he could remember about the same events, and his answers were scored according to how many facts he could recall (detailed recall). For these 3 tests, R.B. was compared to 8 male medical inpatients matched to him with respect to age (mean = 54.6 years, education = 12.1 years; information subtest of WAIS: mean = 18.6 [R.B.'s WAIS score = 16]; vocabulary subtest: mean = 52.1 [R.B.'s WAIS score = 51]). R.B. performed better than his control group on all 3 tests, and only 1 of his scores was noticeably lower: detailed recall of facts about the 1970s. For the 1970s, R.B. scored lower than 6 of 8 control subjects.

R.B. was next given the Boston Famous Faces test (Albert et al.,

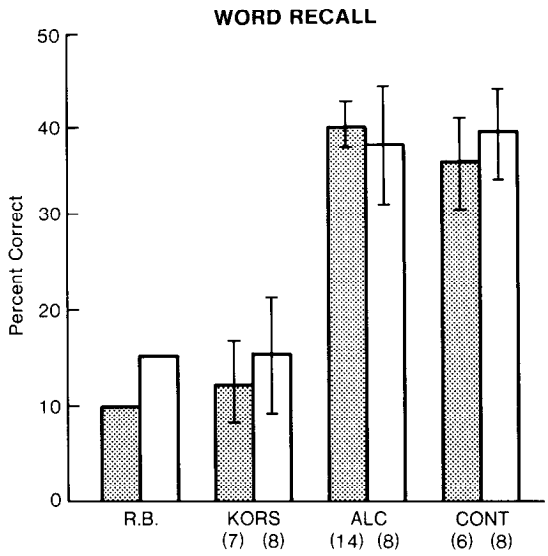

Figure 4. Recall of 10-word lists in 2 separate studies by patient R.B., patients with Korsakoff syndrome (*KORS*), an alcoholic control group (*ALC*), and a control group of medical inpatients (*CONT*). The numbers under the *bars* show the number of subjects in each group. R.B. was tested 43 months (*shaded bars*; data from Graf et al., 1984) and 51 months (*open bars*; data from Graf et al., 1985) after the onset of his amnesia.

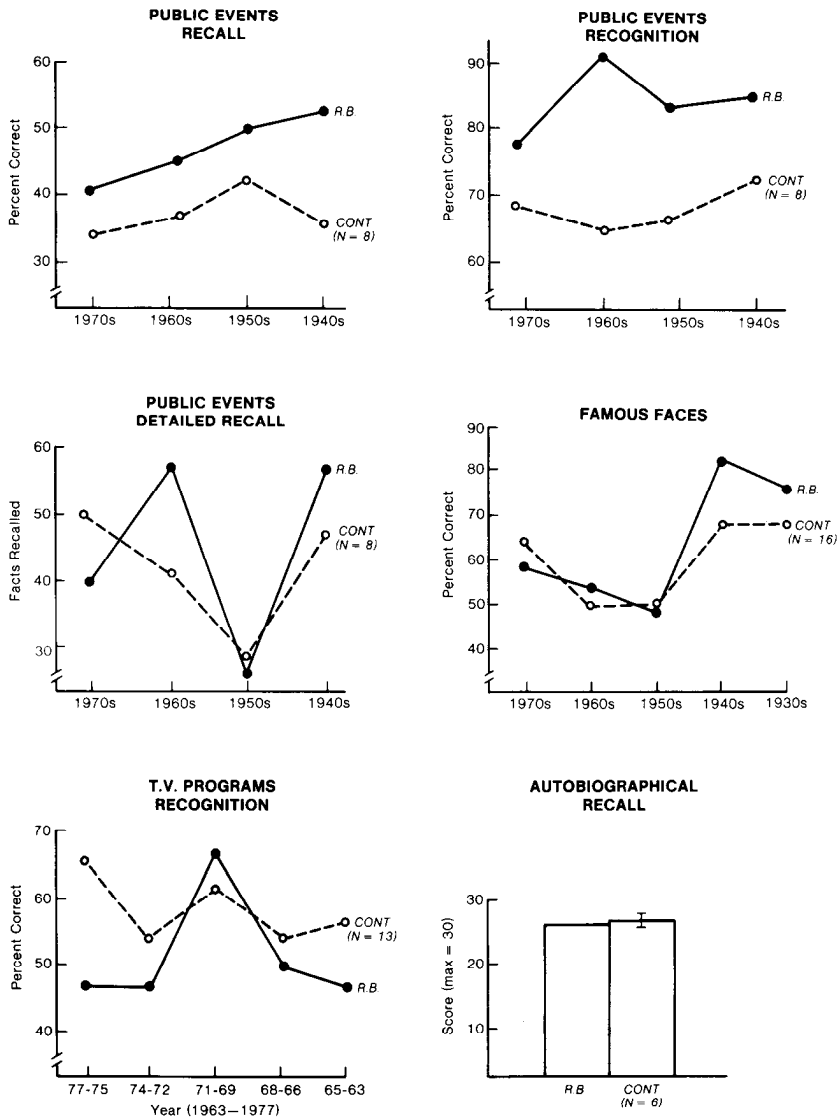

Figure 5. Performance by R.B. and matched control groups on 6 tests of retrograde amnesia. The first 5 tests were given in 1979, 7–10 months after the onset of his amnesia. Autobiographical recall was tested 2 years after the onset of amnesia. R.B. had little, if any, retrograde amnesia, except perhaps for a few years in the late 1970s.

1979), which asked for identification of 130 photographs of people who had come into prominence at various times between 1930 and 1979. The test had been updated to include faces from the latter part of the 1970s (Cohen and Squire, 1981). He was also given a 4-choice multiple-choice test, which asks subjects to recognize 74 television programs that were broadcast for a single season between 1963 and 1977 (approximately 5 for each year; Squire and Fox, 1980). For these 2 tests, R.B. was compared to a group of 29 nonalcoholic medical inpatients or hospital volunteers (23 males, 6 females; mean age = 55.3 years, mean education = 12.9 years). Sixteen were given the Famous Faces test, and 13 were given the television test (Cohen and Squire, 1981). R.B. performed normally on the Famous Faces test. On the television test, he performed close to the normal level, but achieved a noticeably lower score than the control subjects for the period 1975–1977.

Finally, R.B. and 6 male control subjects (mean age = 52.8 years, mean education = 11.7 years; information subtest of WAIS: mean = 16.7 [R.B.'s WAIS score = 16]; vocabulary subtest: mean = 46.0 [R.B.'s WAIS score = 51]) were given a test of autobiographical recall (Crovitz and Schiffman, 1974). Ten concrete nouns were read one at a time (e.g., flag, bird, window) together with the instruction to recall a specific event from any time in the past that involved the target word. Transcripts were scored from 0 (a generic response) to 3 (for an episodic memory that occurred at a particular time and place). R.B. was as good as the control subjects at producing past episodic memories. In addition, the time periods from which the memories were drawn were similar for R.B. and his control subjects.

Together, these retrograde amnesia tests indicate that R.B. had little if any loss of information about premorbid events. The possibility remains that he could have suffered some retrograde amnesia for a period of a few years prior to his coronary surgery in 1978. Although some of his test performance is consistent with this possibility (detailed recall of public events; television test), the tests are too coarsely grained and performance is too variable to reliably detect such a deficit in a single subject.

In addition to formal memory tests, anecdotal evidence derived from R.B. himself and from people who knew him also attest to his anterograde memory impairment. As described earlier, R.B. often depended on his wife to recount details of recent events or conversations. During his contacts with our research group, he frequently told the same stories and asked the same questions within a short period. The physician who treated R.B. on an outpatient basis recognized the memory impairment in the context of the physical exam. Thus he noted that, even 4 years after R.B.'s injury, he was often unable to recount how he was feeling the day before his visit.

R.B. showed no signs of significant cognitive impairment other than loss of memory. His WAIS IQ of 111 (verbal, 108; performance, 114), was above the normal level, and with 1 exception his subtest scaled scores were average or above average (Information: 10; Comprehension: 13; Arithmetic: 11; Similarities: 10; Digit Span: 11; Vocabulary: 11; Digit Symbol: 8; Picture Completion: 12; Block Design: 10; Picture Arrangement: 12; Object Assembly: 10). The digit–symbol substitution subtest presumably depends on memory to some extent and has been reported previously to be difficult for patients with memory impairment (Kapur and Butters, 1977).

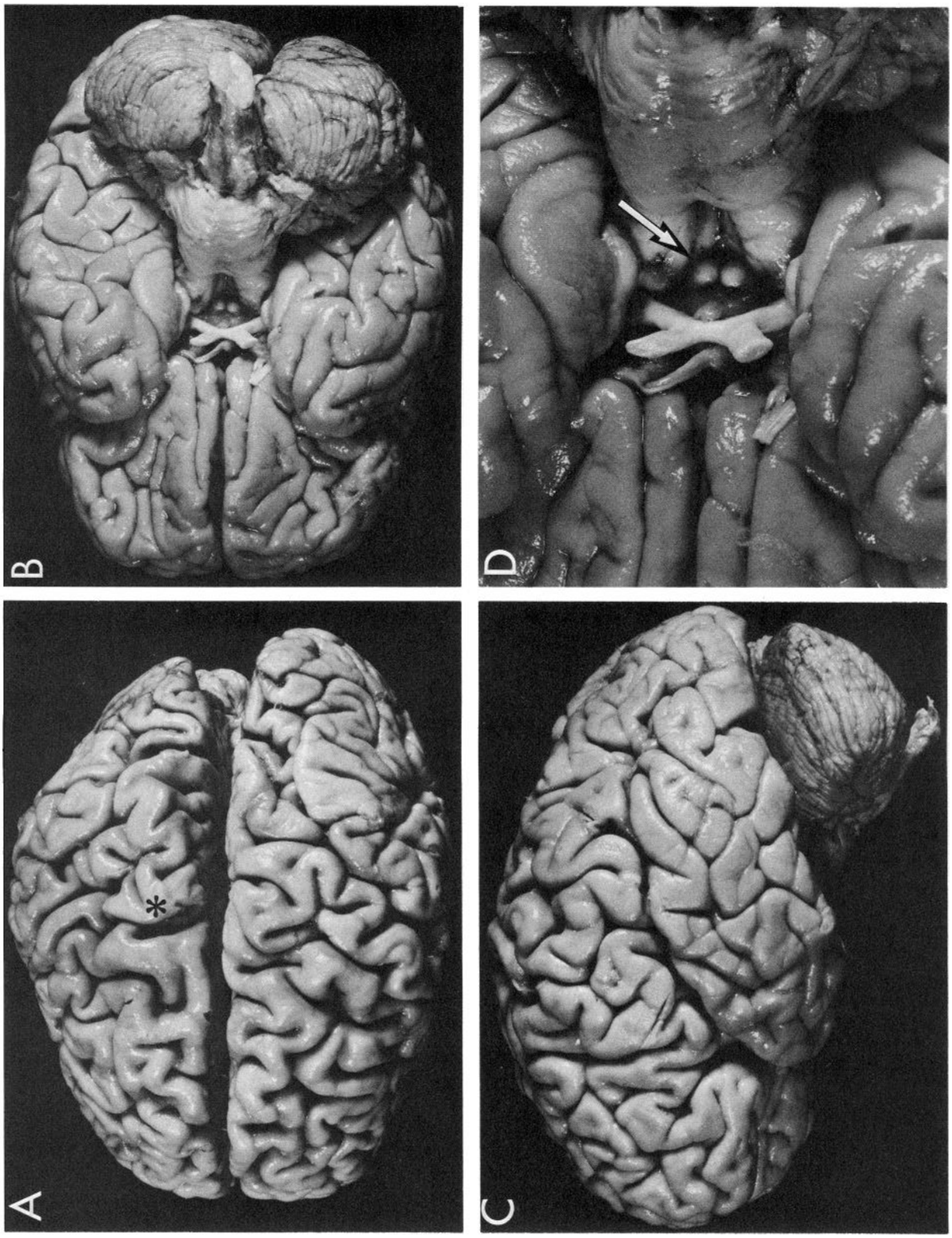

Figure 6. Photographs of the dorsal (*A*), ventral (*B*), and lateral (*C*) surfaces of R.B.'s brain. There is no generalized cortical atrophy. The widened central sulcus (*asterisk in A*) indicates the position of an infarct in the posterior bank of the central sulcus. Mamillary nuclei were of normal size and shape (*arrow in D*).

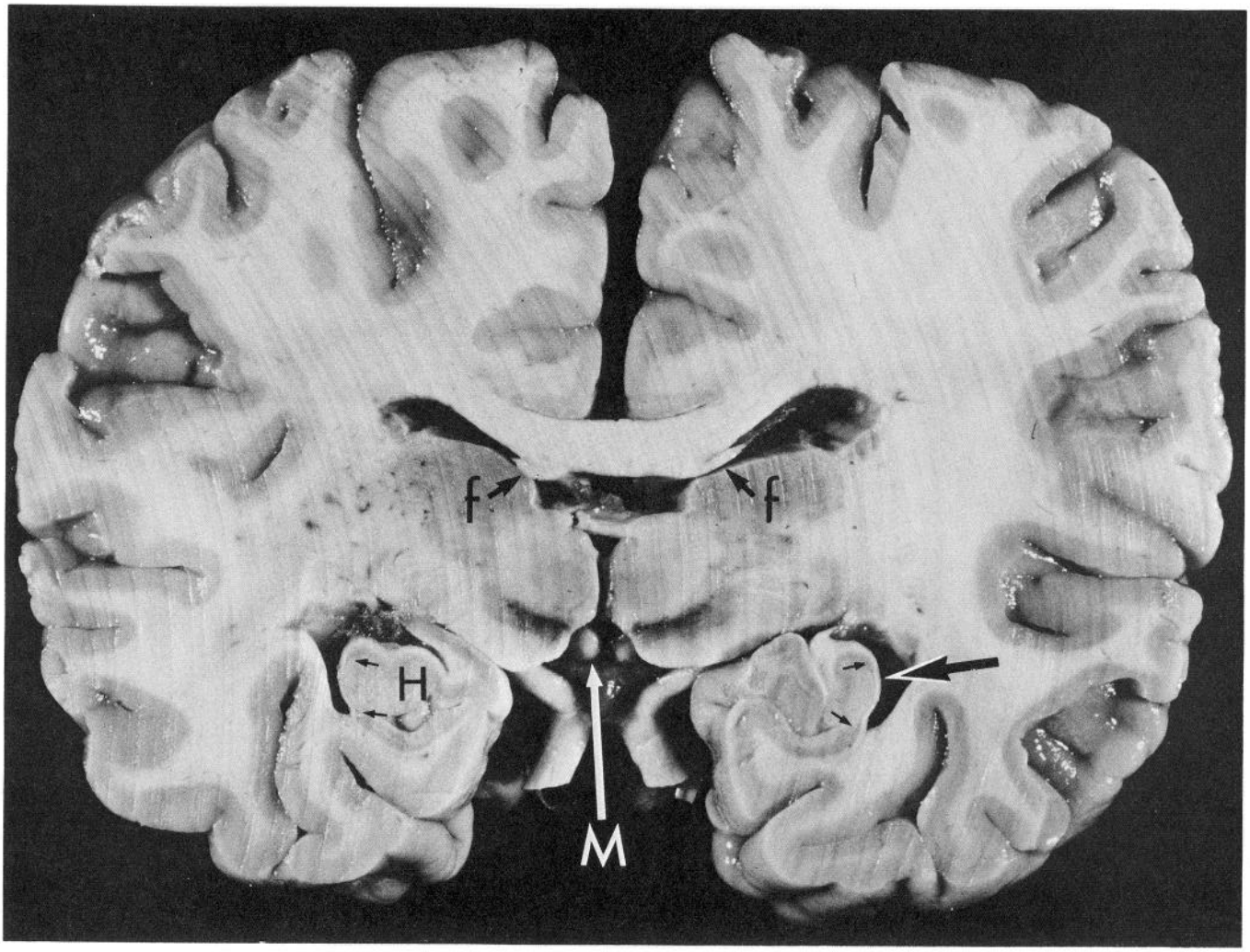

Figure 7. Photograph of a 1½-cm-thick unstained coronal section of R.B.'s brain at a level through the anterior hippocampal formation. The hippocampus (*H on left, arrow on right*) has a relatively normal appearance except for a region of thinning (between the *smaller arrows*) in the CA1 region. The mamillary nuclei (*M*) and the two fornices (*f*) are also indicated.

Six months after his episode of cardiac dysfunction, R.B. was given the Boston Naming Test, Aphasia Screening Test, the Parietal Lobe Battery, and the Apraxia Test (Goodglass and Kaplan, 1972). On the Boston Naming Test, R.B. obtained a score of 88% correct (mean of 8 control subjects = 92%). On the Aphasia Screening Test, R.B. demonstrated 1 spelling error ("traingle" for "triangle"), but otherwise performed perfectly. On the Parietal Lobe Battery, R.B. obtained a score of 208 out of 249 possible points (the Diagram-Copy subtest was not given). Eight control subjects obtained a mean of 242 points. R.B. lost 26 points on this test because of his poor performance on the tactile–visual finger subtest. Here, the examiner lightly touches a finger on the subject's hand while it is hidden from view; the subject then points to the touched finger on a drawing of a hand. R.B. had no experience of being touched on any fingers of his left hand (score: 0 out of 16), and he correctly matched only touches of the thumb and little finger of his right hand (score: 6 out of 16). On the Apraxia Test, R.B. was able to carry out correctly all movements to oral commands and obtained a perfect score. Reports from R.B.'s family were in agreement with these neuropsychological findings. The memory impairment was readily apparent to them, but there was never any mention of personality change or of any other cognitive deficit.

Results: Neuropathological Findings

Acquisition and preparation of tissue

The brain was removed at autopsy approximately 4 hr after death and placed in 30 liters of 10% formalin in 0.1 M phosphate buffer (pH 7.2). Approximately 2 weeks later, the brain was suspended upside down in the same solution with strings attached to the basal vasculature. The brain was fixed for 7 months prior to any histological processing, and during this period the formalin solution was changed every 2 weeks.

Before the brain was sectioned, photographs were taken of the dorsal, ventral, and lateral surfaces. Thereafter, the brain was cut transversely into 6 blocks approximately 1½ cm thick (much of the visual cortex was not further sectioned), and the surfaces of these blocks were photographed. The blocks were then subdivided to a size appropriate for sectioning on a freezing sledge microtome. Initially, the tissue blocks were cut to approximately 36 cm^2, and the sections through the diencephalon and medial temporal lobe were of this size. However, with the introduction of a modified freezing stage, much larger blocks (up to 120 cm^2) could be sectioned, and much of the cortical tissue was processed in this way. The blocks were placed in a cryoprotectant solution of 20% glycerol in 0.1 M phosphate buffer at least 1 week prior to sectioning.

Continuous 50 μm sections were cut through each block, and every fifth section (through the diencephalon, the medial temporal lobe, and much of the neocortex) or every tenth section (through portions of the neocortex and cerebellum) was mounted on gelatin-coated slides and stained with 0.25% thionin. In addition, selected sections through the medial temporal lobe

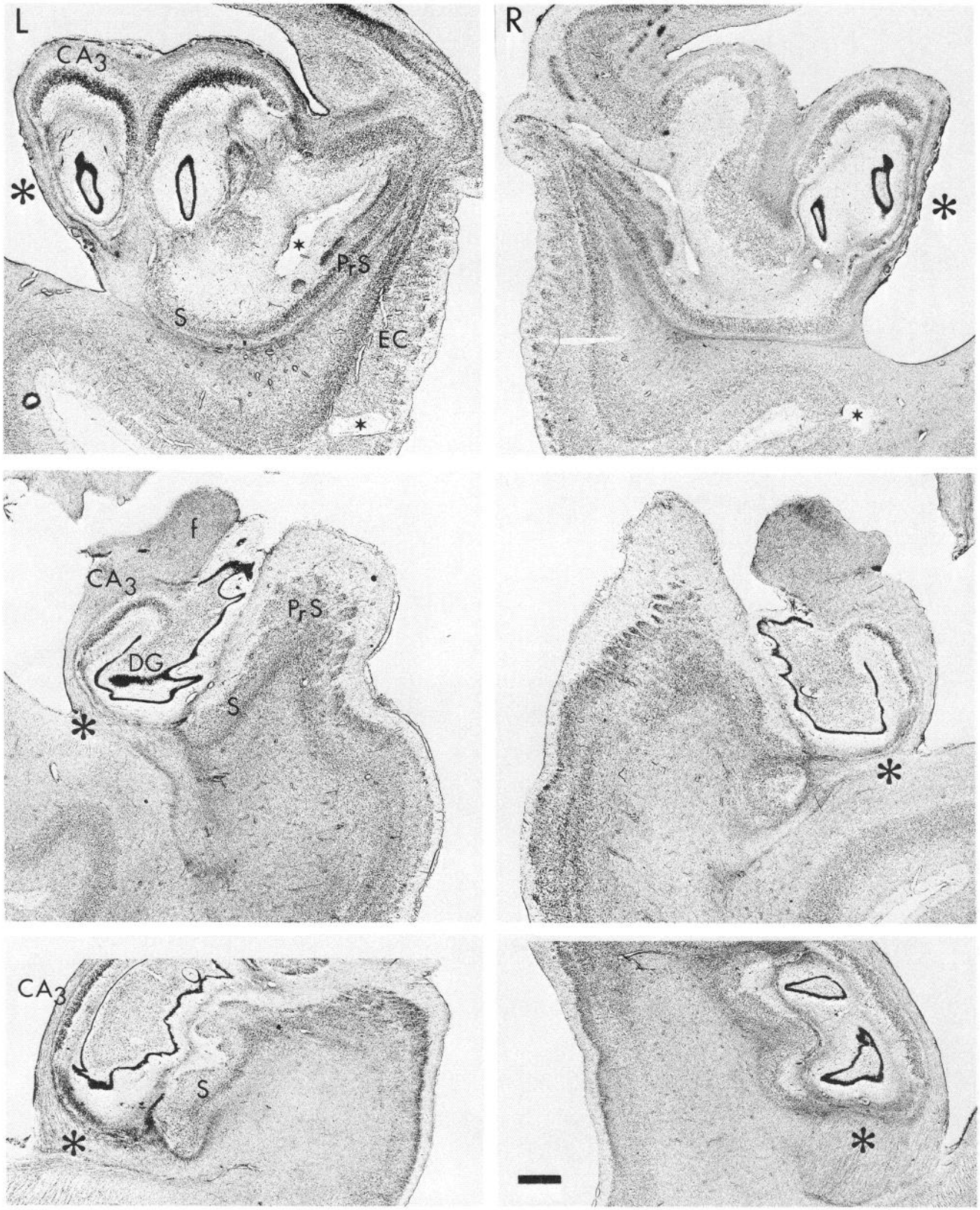

Figure 8. Photomicrographs of thionin-stained coronal sections through the hippocampal formation of R.B.'s brain. Sections are from the left (*L*) and right (*R*) sides of the rostral extreme (*top*), the midportion (*middle*), and the caudal extreme (*bottom*) of the hippocampal formation. The only pathology evident in these sections is the complete loss of pyramidal cells confined to the CA1 field of the hippocampus (*asterisks*). *CA3,* Field CA3 of the hippocampus; *DG,* dentate gyrus; *EC,* entorhinal cortex; *PrS,* presubiculum; *S,* subiculum. Holes in tissue in top panels (*small stars*) are artifactual. Calibration bar, 2 mm.

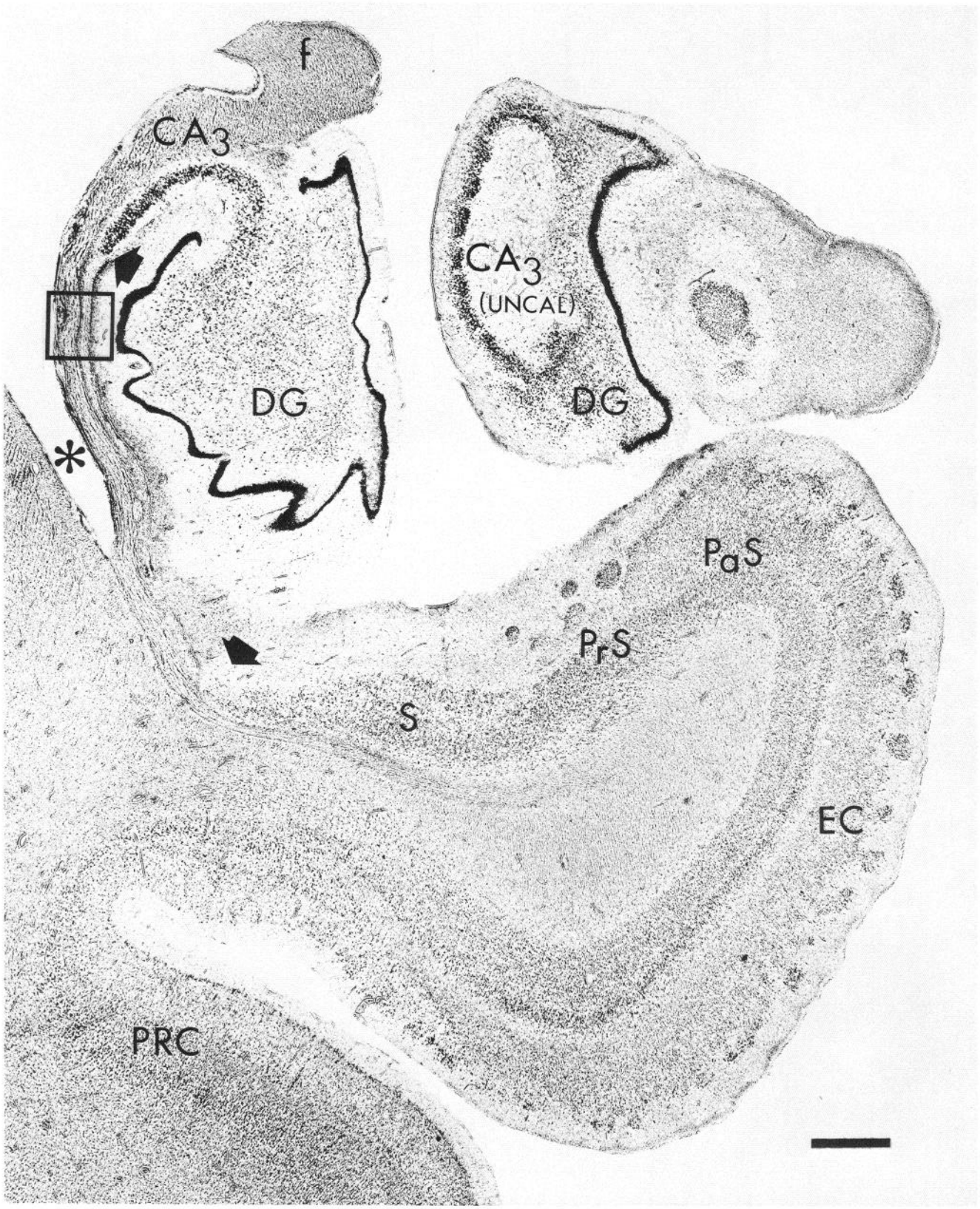

Figure 9. Higher-magnification photomicrograph of a coronal section through the left hippocampal formation. The region of cell loss in field CA1 (*asterisk*) is delimited by 2 *bold arrows*. The sharp boundary with field CA3 is apparent in this section. All other fields of the hippocampal formation have normal cell densities and appropriate laminar organization. The *rectangle* outlines the region shown at higher magnification in Figure 10. Additional abbreviations: *PaS,* parasubiculum; *PRC,* perirhinal cortex. Calibration bar, 2 mm.

and diencephalon were stained by a recent modification of the Heidenhain procedure for the demonstration of myelinated fibers (Hutchins and Weber, 1983). The unmounted sections were stored in 10% formalin solution.

Sections were analyzed with a Wild stereomicroscope or a Leitz Dialux 20 microscope equipped for 35 mm photomicrography. Low-magnification photographs were made with a point-source photographic enlarger through which sections were projected onto 4 × 5 negatives.

Gross appearance of the brain

The gross appearance of the brain was essentially normal (Fig. 6). There was no indication of general atrophy of the cortex, and only one infarct was visible in the depths of the posterior bank of the central sulcus of the right hemisphere (asterisk, Fig. 6*A*). This infarct had a yellow/brown appearance, and extended laterally from a point 2 cm lateral to the midline to a point 3.5 cm lateral to the midline; the rostrocaudal extent of the lesion was not visible from the surface. No other pathology was apparent on the surface of the brain. In particular, the mamillary nuclei were of normal size and shape (Figs. 6*D*, 7).

Microscopic appearance of the brain

Medial temporal lobe. The primary lesion in this brain occurred in field CA1 of the hippocampus (Figs. 8–10). There was a complete and bilateral loss of cells through the full mediolateral and rostrocaudal extent of this field (Figs. 8, 9). The radial dimension of field CA1 was markedly shrunken, and there was an apparent increase in the density of stained glial cells above and below the empty pyramidal cell layer (Fig. 10, *A, B*). This increased glial density did not extend into the pyramidal cell layer and was presumably a consequence of the abnormally close apposition of cells related to the fibers of the alveus and perforant path, rather than an indication of a reactive process. The lesion had an old appearance, as judged by the absence of reactive gliosis, and presumably originated at the time of the initial ischemic event.

Throughout most of the hippocampus, the lesion was confined to the CA1 field and did not invade field CA3 or the subiculum. Figure 9 demonstrates the strikingly abrupt transition from normal cells in field CA3 to a complete loss of cells in field CA1. In the caudal one-third of the hippocampus, however, the area of cell loss extended slightly into the subiculum and CA3. This was observed only in 2 sections (representing a rostrocaudal distance of 0.5 mm), and caudal to these sections the lesion was again restricted to field CA1. Fiber preparations through the hippocampus demonstrated that neither the alveus (which runs subjacent to the pyramidal cell layer of CA1) nor the perforant path (which originates in the entorhinal cortex and runs in the superficial layers of CA1) were affected by the pathology (Fig. 10, *A, B*). Fibers of the perforant path were seen to travel through CA1 to reach their normal termination in the dentate gyrus and field CA3 of the hippocampus. The fimbria had a normal appearance, though there was a small patch of gliosis located ventromedially in the region that was presumably occupied by the degenerated fibers originating in CA1.

No cell loss was detectable in any field of the hippocampal formation other than CA1. The granule cell layer of the dentate gyrus appeared normal bilaterally along its rostrocaudal extent, and the molecular layer appeared to be of normal thickness. While damage to cells in the hilar region of the dentate gyrus is a common finding in experimental ischemia (Plum, 1983), a normal density of cells was seen there in this case. Other than the focal cell loss in CA3 described above, this field had a normal appearance at all other levels of the hippocampus. The subiculum, presubiculum, and parasubiculum all had a normal appearance. The entorhinal cortex demonstrated its distinctive laminated appearance (Figs. 9, 11), and there were no obvious patches of cell loss like those observed in the neocortex (see below).

Sections were also examined through the rostrocaudal extent of the amygdaloid complex. All subdivisions of the amygdala were present and all appeared to be populated by an appropriate density of neurons (Fig. 11). There was a small area containing patchy cell loss bilaterally at the junction of the amygdaloid complex, with the substantia innominata in what appeared to be the anterior amygdaloid area. The cell loss, which occurred in foci of about 1 × 0.5 × 0.5 mm, involved only a small portion of this latter area.

Diencephalon. Damage to the mamillary nuclei (Barbizet, 1973; Brierley, 1977) and the midline and mediodorsal thalamic nuclei (Talland, 1965; Victor et al., 1971) have long been associated with memory impairment. We therefore paid particular attention to the analysis of these structures. In accordance with the apparently normal gross appearance of the medial mamillary nuclei, there was no indication of cell loss in any component of the mamillary complex (Fig. 12, *A, B*). Nor was there any increase in glial staining within the fornix or the principal mamillothalamic tract. Both of these fiber bundles also appeared normal in the myelin preparations. The mediodorsal nucleus had a generally normal appearance, except for a small perivascular patch of gliosis (<1 mm in width) just within the internal medullary lamina of the left thalamus. There was no evidence, however, of cell loss in this nucleus (Fig. 12, *C, D*). There were also no pathological changes in any other subdivision of the thalamus.

Cortex. Tissue sections were examined from all regions of the cortical mantle except for primary visual cortex. The only significant focus of cortical damage was an infarct in the right postcentral gyrus (primary somatosensory cortex). At its caudal border, the infarct also involved a portion of area 5 but did not appear to extend into area 7 of the posterior parietal lobe. The infarct extended for approximately 1.5 cm mediolaterally and 1 cm rostrocaudally and was located in the region of the hand and forelimb somatic representation. Damage in this region was heaviest in the white matter and involved the cortex itself only at the center of the infarct where there was a cavity that was partially filled with fibrous processes. Adjacent regions of somatosensory cortex had an entirely normal appearance.

There were no other infarcts of this size or type in any other cortical region. There were, however, small foci of cell loss distributed throughout the cortex. These foci (Fig. 10, *C, D*) tended to be small; they generally involved a volume of 0.125 mm^3 or less, though the largest occupied a volume of 1 mm^3. They were confined mainly to only 2 or 3 cellular layers of the cortex and were seen as often in a supragranular as in an infragranular position. They rarely occupied all cell layers (Fig. 10*D*), and in these cases formed a column of cell loss. There was no indication that the white matter subjacent to the foci was involved in the pathology. The foci were characterized by an irregular region of complete cell loss with a slightly increased density of glial cells and occasional patches of apparent neuronal debris. There was often an increased vascularity in the focus, and at its periphery there appeared to be an increase in the density of stained neurons. We have not found descriptions of this type of damage in the neuropathological literature. These foci of cell loss are clearly smaller than the lacunae described by Fisher (1965), which are generally found in subcortical structures.

To estimate the number and distribution of these foci, we counted them from sections through the temporal lobe at levels adjacent to the amygdaloid complex and hippocampal formation. In the sections stained in this region, we noted 64 such foci. While this would appear to represent a sizable amount of damage, it can be seen in Figure 10*C* (in which the largest of

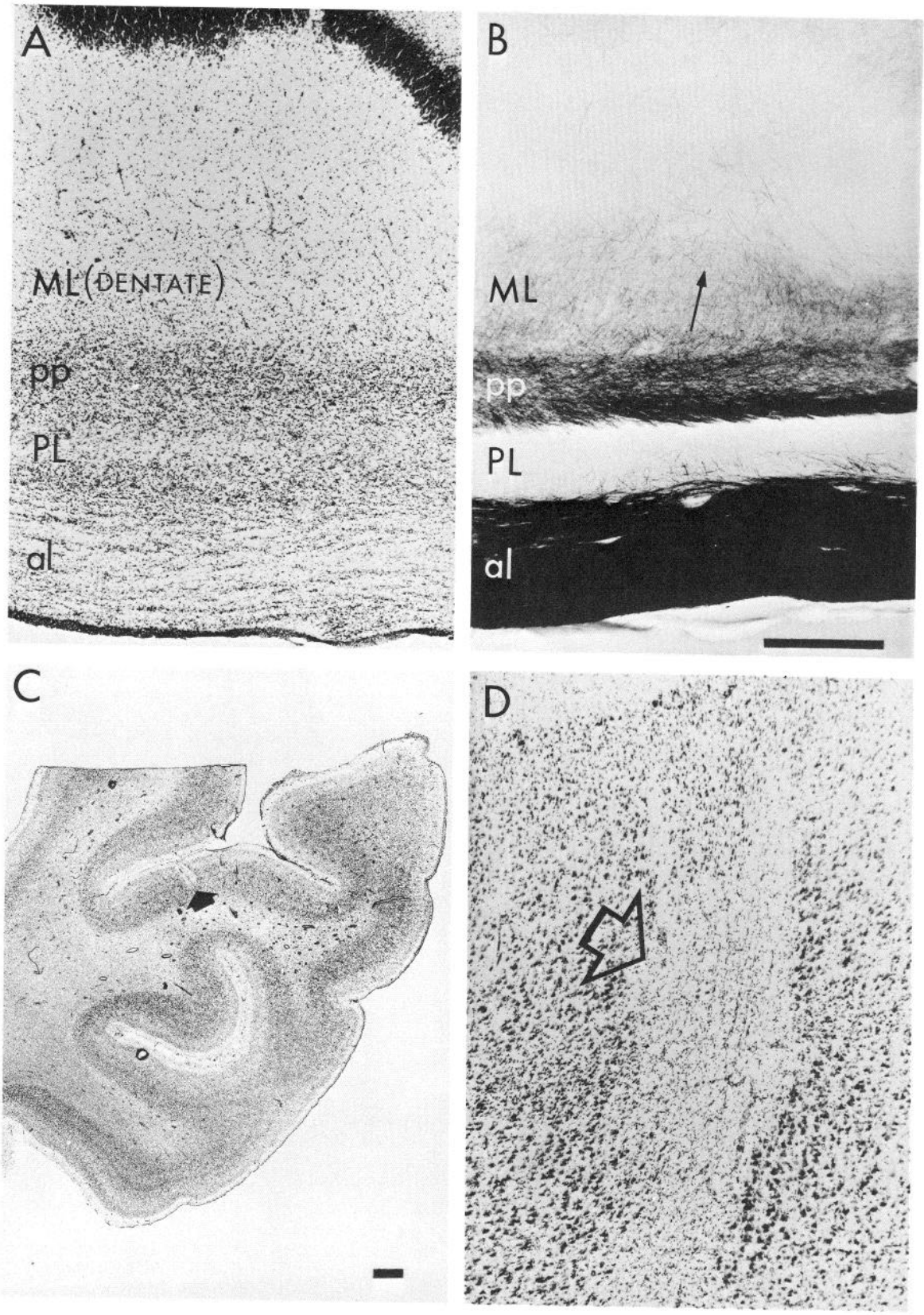

Figure 10. *A* and *B*, Photomicrographs of adjacent coronal sections from the CA1 field of the hippocampus (see rectangle, Fig. 9), stained for cell bodies (*A*) or for myelinated fibers (*B*). No pyramidal cells were observed in the pyramidal cell layer (*PL*). The granular staining above and below the pyramidal cell layer is associated with the fibers of the perforant path (*pp*) and alveus (*al*), respectively; neither pathway was affected by the damage. Fibers leave the perforant path (arrow in *B*) to enter the molecular layer of the dentate gyrus (*ML*). *C*, Low-power photomicrograph of the right temporal lobe. An acellular focus located along the superior temporal sulcus is indicated with a *bold arrow*. *D*, Higher-magnification photomicrograph of a second acellular focus (*open arrow*) located in the perirhinal cortex. These foci were characterized by lack of neuronal staining,

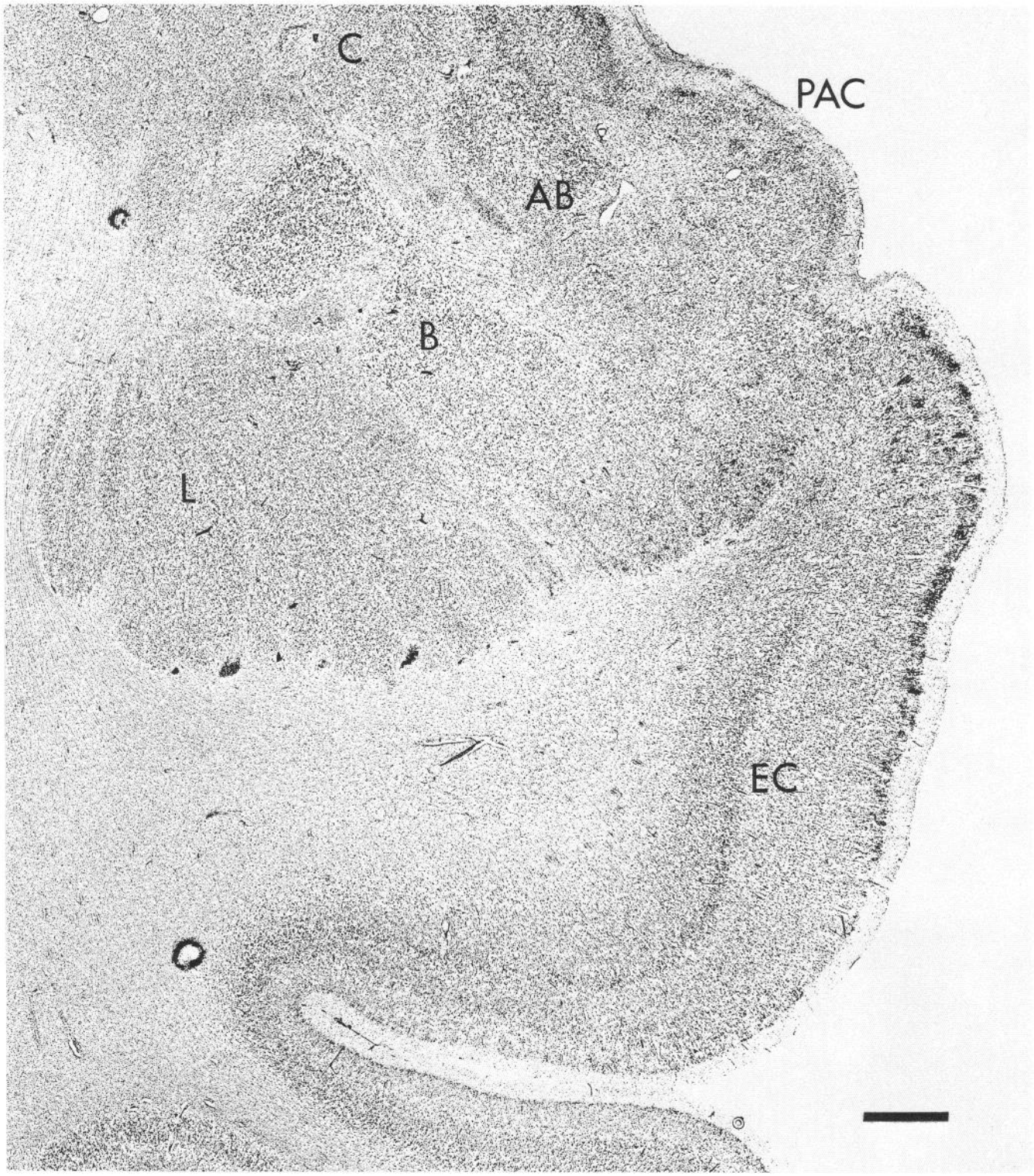

Figure 11. Photomicrograph of a coronal section through the left amygdaloid complex. All subdivisions of the amygdala have a normal appearance. *AB,* Accessory basal nucleus; *B,* basal nucleus; *C,* central nucleus; *EC,* entorhinal cortex; *L,* lateral nucleus; *PAC,* periamygdaloid cortex. Calibration bar, 2 mm.

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slightly increased glial staining, a prominent vascularization, and increased density of stained neurons around their periphery. While many foci were confined to 2 or 3 layers of the cortex, this focus extended throughout all 6 layers. Calibration bar in *B* (applies to *A* and *D* as well), 500 μm. Calibration bar in *C,* 2 mm.

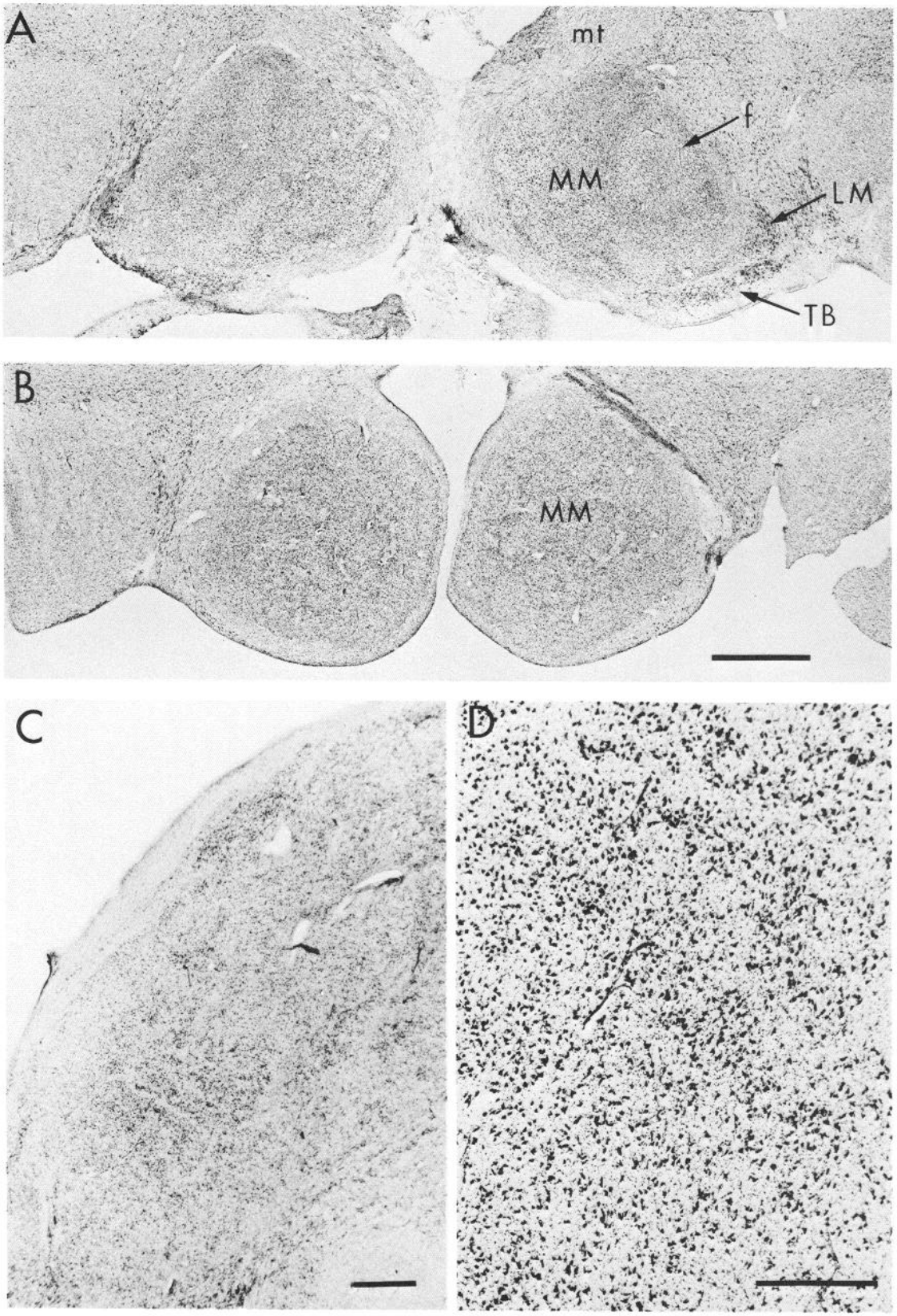

Figure 12. Photomicrographs of coronal sections through rostral (*A*) and caudal (*B*) levels of the mamillary complex. Both the medial (*MM*) and lateral (*LM*) nuclei had a normal density of neurons, with little indication of gliosis. Neither the fornix (*f*) nor the principal mamillothalamic tract (*mt*) demonstrated abnormal glial staining. *C*, Low-power photomicrograph of the medial, magnocellular division of the mediodorsal nucleus of the thalamus. The normally patchy appearance of the nucleus is apparent at this magnification. *D*, Higher-magnification photomicrograph of the same region that shows normal density of neurons. *TB*, Tuberomamillary nucleus. Calibration bar in *B*, 2 mm (also applies to *A*). Calibration bar in *C*, 1 mm; in *D*, 500 μm.

these foci has been illustrated) that these foci of cell loss represent a very small portion of the cortical surface. The foci were not bilaterally symmetrical and appeared to be randomly distributed throughout the cortex. Some regions, such as primary motor cortex, appeared to have a smaller number of such foci.

It should be noted that the neocortex generally appeared normal and had an appropriate laminar organization. There was no indication of laminar necrosis, as is seen in human cases of prolonged ischemia (Garcia and Conger, 1981; Plum, 1983) and in experimental models of ischemic damage (Pulsinelli and Brierley, 1979; Siesjo, 1981; White et al., 1984). Moreover, the density of neurons in the various cortical regions appeared normal. It is possible, however, that a small amount of cell loss (<10%) would not be detected by our qualitative analysis.

Other regions. There was a prominent lesion in the left globus pallidus. The lesion was focused in the lateral medullary lamina but involved both the medial and lateral segments of the globus pallidus. The lesion consisted of a dorsoventrally oriented strip of dense gliosis with bands of gliosis associated with fiber bundles extending laterally into the putamen. The right globus pallidus appeared normal. There was also a small (<250 μm-wide) focus of gliosis in the left internal capsule located dorsomedially between the caudate nucleus and nucleus ventralis anterior of the thalamus. The only other region in which any cell loss was detected was the cerebellar cortex. There appeared to be a patchy loss of Purkinje cells, with an apparent increase of glial staining within the Purkinje cell layer.

Finally, although damage in the basal forebrain has previously been linked to memory impairment (Damasio et al., 1985b), no cell loss was detected in this region in the present case. In particular, the large cells of the basal nucleus of Meynert appeared to be present in normal density, and they were not involved in the globus pallidus lesion.

In summary, the major finding was a bilateral lesion involving the entire CA1 field of the hippocampus. Minor pathology was observed in a few areas: the right postcentral gyrus, the left globus pallidus, the left internal medullary lamina of the thalamus, small foci (less than 1 mm^3) in the dorsomedial portion of the anterior amygdaloid area, a small (less than 250 μm in width) focus of gliosis in the left internal capsule, patchy loss of cerebellar Purkinje cells, and scattered small foci of cell loss (0.125 mm^3 or less) in the neocortex.

Discussion

This case shows that circumscribed damage to field CA1 of the hippocampal formation results in a clinically meaningful memory impairment. To our knowledge, this is the first reported case of amnesia following a lesion limited to the hippocampus in which extensive neuropsychological and neuropathological analyses have been carried out. R.B. exhibited normal performance on a variety of neuropsychological tests sensitive to cognitive impairments other than memory. These findings were consistent with the neuropathological findings that R.B.'s brain exhibited no gross cortical abnormalities. The one exception was an infarct involving the forearm representation of the right somatosensory cortex. This infarct was consistent with the finding that R.B. had hypoesthesia of the dorsal surface of his left arm and hand, and of his fingers. This lesion also explains, in part, his impaired performance on the tactual–visual finger subtest of the Parietal Lobe Battery.

The possibility should be considered that R.B.'s memory impairment resulted from the combination of the CA1 lesion and other damage. For example, it might be suggested that cortical damage, i.e., the small acellular foci, contributed to R.B.'s memory impairment. This seems unlikely. First, R.B.'s impairment was limited to the domain of memory; his performance was normal on several tests of other cognitive abilities. These findings suggest that the cortical damage was of little clinical relevance. Second, work with nonhuman primates has demonstrated that bilateral damage to the hippocampus is sufficient to produce amnesia (Mahut et al., 1981, 1982; Mishkin, 1978; Zola-Morgan and Squire, 1986a). Third, damage observed in other regions of R.B.'s brain, such as the globus pallidus or cerebellum, has never been associated with the syndrome of amnesia.

The severity of the memory impairment. The severity of amnesia can vary widely among patients. For example, H.M., the noted patient who became severely amnesic following bilateral medial temporal lobe resection (Scoville and Milner, 1957), is so impaired that he is capable of almost no new learning and forgets the events of daily life as quickly as they occur. His WAIS-WMS difference score of 43.7 (average of 6 tests from 1955 to 1983; Corkin, 1984) reflects the severe nature of his memory impairment. R.B.'s memory impairment was not as severe as that of H.M.; his WAIS-WMS difference score, for example, was only 20 points. Yet his deficit was readily detectable by formal memory tests and apparent to casual observation. His performance on tests of anterograde memory (e.g., paired associate learning, story recall, and diagram recall) was similar to that of other amnesic patients studied in our laboratory (Fig. 2).

The neuropsychological findings from this case are consistent with the results from recent studies in monkeys (Mahut et al., 1981; Mishkin, 1978; Squire and Zola-Morgan, 1983; Zola-Morgan and Squire, 1986a) and rats (Jarrard, 1978; Olton et al., 1979), in which lesions limited to the hippocampal formation impaired learning and memory. Particularly relevant to the present case is the recent finding that experimentally induced ischemia in rats damages the CA1 region of the hippocampus and results in a long-lasting deficit in new learning ability (Davis et al., 1986; Volpe et al., 1984). The behavioral deficits following hippocampal lesions in animals, though statistically significant, are not always quantitatively impressive. The information from the present case indicates that the deficit following hippocampal lesions is nonetheless clinically important; it reflects a degree of memory impairment that in humans would be expected to have a significant impact on daily learning ability and quality of life. Behavioral tests used in studies of experimental animals will need to be sensitive to the full range of impairment that is of clinical relevance.

The persistence of the memory impairment. The present case also shows that the memory impairment following limited damage to the hippocampal formation is stable and long lasting. Figure 4 shows that a marked deficit in verbal recall was still present more than 4 years after the injury. At the same time, it is possible that some degree of recovery did occur. R.B.'s wife noted that, while R.B. never fully regained his memory after the injury, his memory impairment seemed more severe during the first year than in subsequent years. In addition, Figure 3 shows that R.B.'s memory performance was slightly better, albeit still very impaired, after 23 months (middle), compared to after only 6 months (left).

Recent studies of monkeys that have been operated on support the finding that memory impairment following hippocampal damage can be long lasting. Monkeys with conjoint removal of hippocampus and amygdala were just as impaired 1.5 to 2 years after surgery as during the first 2 months after surgery (Zola-Morgan and Squire, 1985). A similar result has been observed after lesions limited to the hippocampal formation (Mahut et al., 1982; Zola-Morgan and Squire, 1986b).

The hippocampus and the neuropsychology of memory. The neuropsychological findings from this case are entirely compatible with recent descriptions of the human amnesic syndrome (see Baddeley, 1982; Hirst, 1982; Squire, 1987a; Squire and Cohen, 1984; Weiskrantz, 1982). Amnesia has long been recognized as the combination of intact general intellectual capacity,

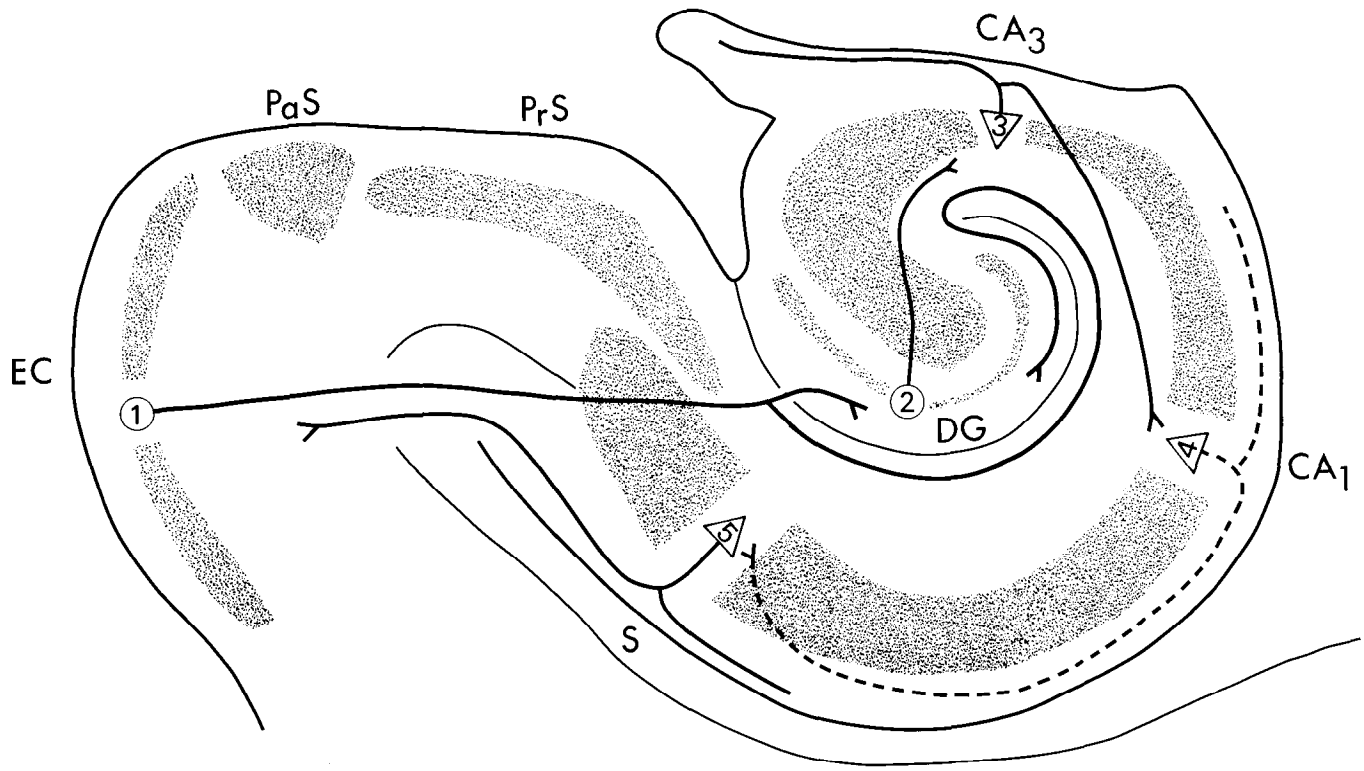

Figure 13. Schematic drawing of the primate hippocampal formation. The *numbers* and the *solid lines* connecting them show the unidirectional flow of information (from entorhinal cortex *1*, to dentate gyrus *2*, to CA3 *3*, to CA1 *4*, to the subiculum *5*). In case R.B., a lesion of the CA1 field (represented by cell *4* and the *dashed lines*) disrupted the sequence of information flow in the hippocampus. *EC*, Entorhinal cortex; *PaS*, parasubiculum; *PrS*, presubiculum; *S*, subiculum; *DG*, dentate gyrus; *CA1* and *CA3*, fields of the hippocampus.

intact digit span (immediate memory), intact personality, language, and social skills, together with impaired new learning capacity for verbal and nonverbal material and variable retrograde amnesia. More recently, it has also been appreciated that amnesia spares some memory functions, including motor and cognitive skill learning, and priming.

The amnesic syndrome has been useful in revealing information about the organization of memory and about the normal function of the damaged neural system. The finding that R.B. could recall events that occurred prior to his ischemic episode is consistent with the view that the hippocampus is not a repository for storage of remote memories (Damasio et al., 1985a; Milner, 1972). Nonetheless, R.B. may have had some difficulty recalling events from 1 to 2 years prior to his episode; temporally limited retrograde amnesias covering a few years have been observed in other amnesic patients. It has been suggested, in fact, that the medial temporal region, including the hippocampus, has an essential role in memory functions for a considerable time after learning (Squire, 1987b; Squire et al., 1984).

R.B., like other amnesic patients, exhibited intact word priming; that is, like normal subjects, his performance on word-completion tests (MOT-) could be biased for a time by prior exposure to test words (MOTEL) (Graf et al., 1984, 1985; Experiment 1, Case 1). Priming, like skill learning, occurs in amnesic patients without conscious awareness, and without recognition of the previously presented stimulus material. These and other findings have suggested a distinction between memory for facts and episodes (declarative memory), which is impaired in amnesia, and memory for skills and procedures (procedural memory), which is intact (Cohen, 1984; Cohen and Squire, 1980; Squire and Cohen, 1984). The findings from the present case support the idea that declarative memory is impaired in amnesia, and that the hippocampus is an essential component of the damaged neural system. Procedural memory is independent of this system.

Field CA1: neural circuitry. The hippocampal formation consists of several cytoarchitectonically distinct subdivisions, including the dentate gyrus, the hippocampus proper (which is subdivided into fields CA1, CA2, and CA3 after Lorente de No, 1934), the subicular complex (the subiculum, presubiculum, and parasubiculum), and the entorhinal cortex. One distinguishing characteristic of these fields is that they are linked by a largely unidirectional flow of information (Fig. 13). The entorhinal cortex provides the major input, via the fibers of the so-called perforant path, to the dentate gyrus. While the dentate gyrus does not reciprocate the projection of the entorhinal cortex, it does provide a major excitatory input to the pyramidal cells of CA3 of the hippocampus via the axons (the mossy fibers) of the dentate granule cells. Field CA3, in turn, gives rise to a powerful associational projection (the Schaffer collaterals) to field CA1, which then projects to the subicular complex. The subicular complex completes the circuit by projecting to the entorhinal cortex, among other regions.

Within this circuit, a lesion confined to field CA1 of the hippocampus essentially breaks the chain of information-processing that begins at the dentate gyrus and ends in the subicular complex and entorhinal cortex. This lesion, while spatially limited, would be expected to have a profound influence on the functioning of the hippocampal formation because the subicular complex and entorhinal cortex are the main sources of output from the hippocampus to subcortical structures such as the mamillary nuclei and the anterior thalamus, and to limbic and cortical structures such as the amygdaloid complex, the perirhinal and parahippocampal gyri, and the orbitofrontal cortex (Amaral, 1987; Van Hoesen, 1982). [In each hemisphere, the CA1 field of the human hippocampus contains approximately

4.63 million pyramidal cells. Fields CA2 and CA3 contain an additional 2.35 million pyramidal cells (Brown and Cassell, 1980; M. D. Cassell, personal communication, 1985). The CA1 region of the human hippocampus has undergone the greatest enlargement in area relative to the other fields of the hippocampal formation (Stephan, 1983; Stephan and Manolescu, 1980)].

Field CA1: mechanisms of damage. The question arises as to why the brain damage in this case was so circumscribed and involved only field CA1 of the hippocampus. Sommer (1880) noted the selective vulnerability of this region more than a century ago in patients who had suffered from epilepsy. In one case, in which sections through the hippocampus were studied microscopically, Sommer noted a discrete region of marked cell loss. Since there was no established nomenclature for the hippocampus or its subfields at that time, Sommer described the area of destruction as a sector of an ellipse superimposed over the coronal section of the hippocampus. This area of the hippocampus closely approximates field CA1 of Lorente de No (1934), and it has come to bear the name "Sommer's sector."

The pattern of brain damage (including CA1 cell loss) seen in the present case is consistent with the idea that the responsible event was an ischemic episode. Depletion of pyramidal cells in the CA1 field of hippocampus and in the Purkinje cell layer of cerebellum have been identified as neuropathological markers of ischemia in both humans (Brierley and Cooper, 1962; Plum, 1983; Siesjo, 1981) and animals (Levine, 1960; Pulsinelli and Brierley, 1979). Ischemia refers to a reduction in normal blood flow to a level that is insufficient to meet metabolic demands (Garcia and Conger, 1981). During an ischemic episode, oxygen delivery may fall below critical levels, producing an anoxic state. In some cases, oxygen pressure can be maintained artificially during hypotensive states, and tissue requirements for oxygen may be reduced in response to hypotension (Garcia and Conger, 1981). During R.B.'s acute episode, he lost approximately 5000 cc of blood and was presumably ischemic during this episode. He was provided with oxygen at the time of the ischemia, and thus it is difficult to know whether he was ever anoxic.

The mechanism of selective neuronal death following ischemia is not well understood (for reviews, see Plum, 1983; Siesjo, 1981; White et al., 1984). One possibility is that the CA1 region of the hippocampus is selectively vulnerable because of the architecture or mechanics of the blood supply to this region. However, such an explanation does not seem altogether satisfactory. First, the blood supply to field CA1 also supplies the subicular complex. It seems unlikely, therefore, that compression of this vasculature could lead to damage of the CA1 field while at the same time sparing the subiculum. In addition, the sharp boundary of the pathology at the CA3–CA1 border cannot easily be explained by the known vascular pattern of the hippocampus (Coyle, 1978; Lindenberg, 1963; Nilges, 1944). Second, in studies of barbiturate-induced systemic hypotension in experimental animals, the hippocampus did not exhibit a greater reduction in blood flow than other brain areas (Gamache and Dold, 1975; Gamache et al., 1976). Third, damage to the CA1 field of hippocampus is a common finding in the brains of epileptic patients (Dam, 1980; Margerison and Corsellis, 1966; Sommer, 1880). Yet blood flow in the hippocampus during experimentally induced seizures is increased rather than decreased (Sloviter, 1983).

It has recently been proposed that the selective damage of CA1 cells during ischemia is due to the neurotoxic properties of glutamate or a related excitatory amino acid (Fagg, 1985; Meldrum, 1985; Olney, 1978; Siesjo, 1981). A number of independent observations support this idea. First, there is a high density of glutamate receptors in the CA1 field of the hippocampus; these are primarily of the *N*-methyl-D-aspartate (NMDA) type (Greenamyre et al., 1984; Monaghan et al., 1983). Second, the major excitatory input to the CA1 pyramidal cells (the Schaffer collaterals from field CA3) appears to use glutamate as a transmitter (Storm-Mathisen, 1981, 1984; Wolf et al., 1984). Third, injection of an excitatory amino acid antagonist, 2-amino 7-phosphonoheptanic acid (AHP), into the hippocampus prior to ischemia can protect against pyramidal cell loss (Meldrum, 1985). Fourth, decreasing the synaptic activation of the CA1 field by eliminating the main excitatory input to the hippocampus (the perforant path) has also protected the CA1 cells from ischemic damage (Wieloch et al., 1985). In addition, the administration of antiepileptic drugs such as barbiturates has reduced the extent of ischemic cell loss (Siesjo, 1981). And fifth, sustained electrical stimulation of the perforant path produces a pattern of hippocampal damage that includes extensive cell loss in the CA1 subfield (Olney, 1983; Sloviter, 1983).

Overview. Over the last 100 years, amnesia has been associated in clinicopathological studies with damage to several regions of the brain. Among these are the amygdala and hippocampal formation in the medial temporal lobe, and the mamillary bodies and mediodorsal nucleus of the diencephalon. It has remained unclear, however, whether damage confined to any one of these structures would produce a clinically significant memory impairment. The present case shows that a circumscribed bilateral lesion limited to the CA1 field of the hippocampal formation is sufficient to produce amnesia.

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