wanted side effects as the deposition of immune complexes in the kidney. Whether or not toxic side effects prove to be a problem clinically with naked antibodies, they will almost certainly be significant with antibody-coupled drugs, toxins, or alpha-emitters. If necessary, local toxicity at the point of injection could be reduced by distributing the dose over a number of local sites.

Likely candidates for lymphatic immunodiagnosis and immunotherapy are mammary, lung, and colon carcinomas, lymphomas, and melanomas. With melanomas, for example, one would eliminate interference from antigenic determinants on normal melanocytes in the skin by using the lymphatic route to metastases in the regional nodes.

In the studies reported here, normal cells were used as targets in order to establish the principles for delivering antibodies to lymph nodes. More recently, we obtained specific localization of an antitumor antibody in guinea pig nodes containing metastases from a hepatocarcinoma (*18*).

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The Neuroanatomy of Amnesia: Amygdala-Hippocampus versus Temporal Stem

Abstract. *Using a task known to be sensitive to human amnesia, we have evaluated two current hypotheses about which brain regions must be damaged to produce the disorder. Monkeys with bilateral transections of the white matter of the temporal stem were unimpaired, but monkeys with conjoint amygdala-hippocampal lesions exhibited a severe memory deficit. The results indicate that the hippocampus, amygdala, or both, but not the temporal stem, are involved in memory in the monkey and suggest that a rapprochement between the findings for the human and the nonhuman primate may be close at hand.*

Damage to the medial temporal region of the human brain has been known for many years to cause a profound amnesic syndrome, and the critical structure in bitemporal amnesia has been presumed to be the hippocampal formation (*1*). Yet studies of nonhuman primates with surgical lesions of the hippocampus, which

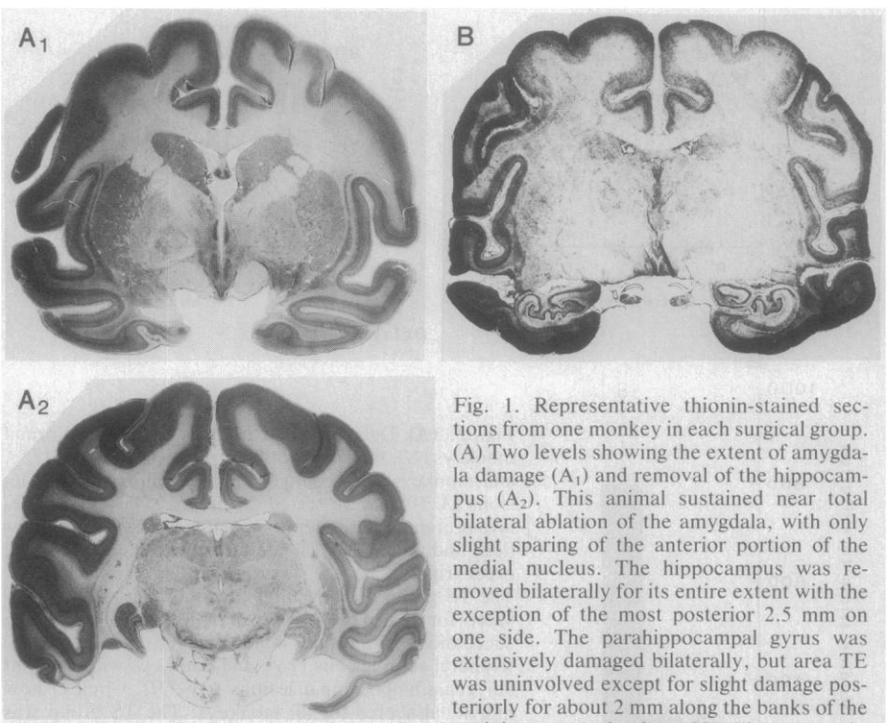

Fig. 1. Representative thionin-stained sections from one monkey in each surgical group. (A) Two levels showing the extent of amygdala damage (A_1) and removal of the hippocampus (A_2). This animal sustained near total bilateral ablation of the amygdala, with only slight sparing of the anterior portion of the medial nucleus. The hippocampus was removed bilaterally for its entire extent with the exception of the most posterior 2.5 mm on one side. The parahippocampal gyrus was extensively damaged bilaterally, but area TE was uninvolved except for slight damage posteriorly for about 2 mm along the banks of the occipito-temporal sulcus. No other gross abnormalities were seen except for gliosis of the fornix throughout its extent. (B) The temporal stem was transected for an anterior-posterior extent of approximately 15 mm from just behind the temporal pole to approximately the middle level of the lateral geniculate nucleus. The upper bank as well as the cortex at the fundus of the superior temporal sulcus was removed for most of the extent of the lesion. The hippocampus was undamaged throughout its extent.

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could confirm the role of this structure in memory, have so far had mixed success at establishing an animal model of the human amnesic syndrome (*2–4*).

One explanation for this discrepancy between the findings for monkeys and humans has been that the behavioral tests used with monkeys have not been comparable to those used in the analysis of human amnesia (*2–5*). An additional possibility is that the brain regions damaged in amnesic patients have been misidentified to some extent. Two hypotheses have been advanced recently: (i) The critical brain region is not the hippocampus at all, but the temporal stem, a band of white matter that lies adjacent to the hippocampus across the lateral ventricle (*6*); and (ii) hippocampal damage is critical in human amnesia, but additional damage to the amygdala is required for the amnesic syndrome to appear (*7*).

We have compared these two hypotheses by preparing two groups of monkeys (*Macaca fasicularis*), five with bilateral lesions of the temporal stem (TS) and four with bilateral conjoint removal of the amygdala and hippocampus (A + H). Three control subjects did not have surgery (N). A principal feature of this study was the use of a behavioral test known to be sensitive to human amnesia. We selected delayed nonmatching-to-sample with trial-unique stimuli (*8*) and tested the ability to remember, across delays ranging from seconds to many minutes, which of two objects had been seen previously.

The temporal stem lesion first required aspiration of the upper bank of the superior temporal sulcus to gain access to the white matter or temporal stem underlying the fundus of the sulcus. The temporal stem was then transected for 10 to 15 mm along its anterior-posterior extent with the temporal horn of the lateral ventricle serving as a visual guide. Since the ventricle was not crossed, the hippocampus was left entirely intact. The combined A + H lesions were performed in a single stage, with two surgical approaches to each hemisphere. First, the amygdala and periamygdaloid cortex medial to the rhinal sulcus were removed by an approach under the frontal-temporal junction. The hippocampus and parahippocampal gyrus were then removed by an approach medial to the occipito-temporal sulcus, which permitted excision of the pes hippocampus, the uncus, and the body of the hippocampus caudally to the region where it curves dorsally. This approach to the hippocampus spared the temporal stem because the lateral ventricle was not crossed during the operative procedure. Figure 1 illustrates the extent of surgical removal for one representative monkey from each surgical group.

Two months after surgery, training was begun on delayed nonmatching-to-sample with a delay of 8 seconds (*8*). All monkeys learned this task to criterion. [Mean scores, for group N: 140 trials, 32 errors; group TS: 192 trials, 53 errors; A + H: 790 trials, 204 errors. The A + H group was significantly impaired on both trial and error scores relative to each of the other two groups (Mann-Whitney $U = 0$, $P < .05$). There were no significant differences between the N and the TS groups ($U = 6.5$, $P > .10$).] After training was completed, the delay between sample and choice was lengthened to 15 seconds, then to 60 seconds, and finally to 10 minutes. Each stage was tested for 100 trials.

As longer delays were interposed between sample and choice, the performance of monkeys with A + H lesions gradually deteriorated until at the 10-minute delay they were performing at chance levels (A + H versus N and A + H versus TS: $U = 0, P < .05$) (Fig. 2A). The TS group, by contrast, scored 74 percent correct at the 10-minute delay, nearly equal to the 79 percent score of the normal animals ($U = 3$, $P > .10$). The same results were observed in the second phase of testing when the same delays (8, 15, and 60 seconds and 10 minutes) were presented in a randomly mixed order during each daily session until monkeys had accumulated 50 trials at each delay (Fig. 2A). The similarity of results under the two conditions strengthens the conclusion that the gradual deterioration in the scores of the A + H group with increasing delays reflects a genuine memory loss.

To understand the difference between the two groups with lesions, it is essential to know both (i) whether the observed impairment in monkeys with A + H lesions is at all specific and (ii) whether the normal performance of TS monkeys is due simply to the relatively small size of their lesions. One way to address both questions is to demonstrate a double dissociation of symptoms (*9*), that is, to show that one lesion impairs task A but not task B, whereas a second lesion causes the reverse effect. We chose visual pattern discrimination learning as task B and trained the monkeys on two separate, two-dimensional pattern discrimination problems: □ versus + and N versus W (*10*). Monkeys with temporal stem lesions were severely impaired on learning these problems

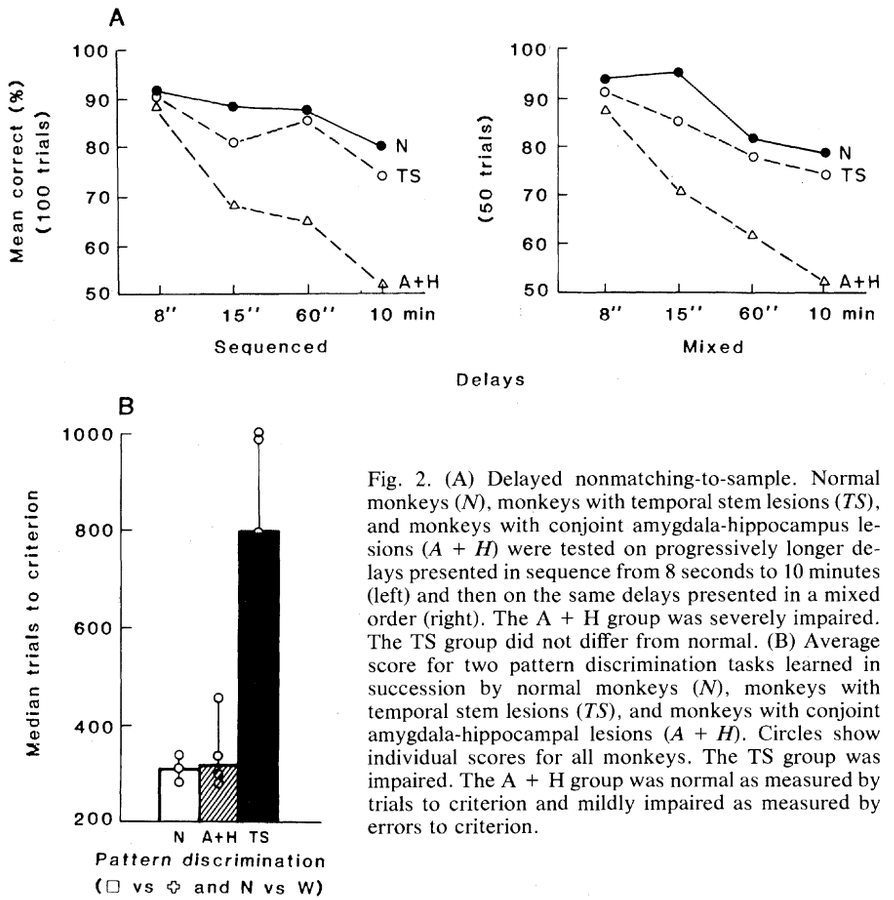

Fig. 2. (A) Delayed nonmatching-to-sample. Normal monkeys (*N*), monkeys with temporal stem lesions (*TS*), and monkeys with conjoint amygdala-hippocampus lesions (*A + H*) were tested on progressively longer delays presented in sequence from 8 seconds to 10 minutes (left) and then on the same delays presented in a mixed order (right). The A + H group was severely impaired. The TS group did not differ from normal. (B) Average score for two pattern discrimination tasks learned in succession by normal monkeys (*N*), monkeys with temporal stem lesions (*TS*), and monkeys with conjoint amygdala-hippocampal lesions (*A + H*). Circles show individual scores for all monkeys. The TS group was impaired. The A + H group was normal as measured by trials to criterion and mildly impaired as measured by errors to criterion.

(TS versus N: $U = 0$, $P < .05$ for both trials and errors) (*11*), but monkeys with A + H lesions were only mildly impaired (unimpaired in trials to criterion—345 for the A + H group and 310 for normal monkeys—but significantly impaired in errors to criterion—110 and 99, respectively, $P < .05$) (Fig. 2B).

These results, taken together, provide a basis for rejecting the hypothesis that temporal stem damage causes amnesia. Lesions of this region caused no discernible impairment of memory on a task that reliably reveals an impairment in amnesic patients. Temporal stem lesions did, however, disrupt visual pattern discrimination learning, presumably as a result of damage to afferents and efferents of area TE (*12*). By contrast, monkeys with conjoint A + H lesions were markedly impaired on a task sensitive to amnesia in humans, confirming previous observations of monkeys with A + H lesions using the same task (*7, 13*). Yet, if performance by the A + H group in delayed nonmatching-to-sample is taken as evidence that they are amnesic, how are we to understand the rather good retention exhibited by the same monkeys during day-to-day acquisition of visual discrimination tasks?

We suggest that neuropsychological facts of human amnesia, as we now understand them, provide an account of human memory impairment that is consistent with these findings in monkeys. It is now clear that human amnesia is a selective impairment that does not encompass all forms of learning and memory. Thus, amnesic patients retain the capacity to acquire perceptual-motor skills (*14*), and they also retain the ability to acquire cognitive skills such as mirror-reading and the ability to solve certain puzzles (*15*). These findings have suggested a distinction between two kinds of learning and memory, one independent of the medial temporal brain structures damaged in amnesia and one dependent on these structures (*15, 16*). The usefulness of this distinction to the study of monkeys with medial temporal lesions has recently been explored in detail (*4*). Evidence was presented that pattern discrimination learning, as it occurs in the monkey, is in many ways analogous to human skill learning and should therefore not be affected by medial temporal lesions.

Our findings thus bring us a step closer to establishing an animal model of human amnesia. Now that a behavioral profile has been identified that signifies bitemporal amnesia in monkeys, it will be possible to determine precisely what parts of the limbic system must be damaged to produce the syndrome (*17*).

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11. To determine whether damage to the upper bank of the superior temporal sulcus, sustained during the surgical approach to the temporal stem, might have contributed to the pattern discrimination deficit, we prepared one monkey with a lesion limited to the bank of the superior temporal sulcus. This monkey learned the two pattern discriminations in an average of 345 trials, which was within the range of the normal group.
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18. Supported by the Medical Research Service of the Veterans Administration and by NIMH grant MH24600. We thank D. Amaral for his help in evaluating the lesions and R. Philips and J. Kurz for assistance with histology.

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