Chapter 1

The Amnesic Syndrome

A neurologist does not forget his first encounter with the amnesic syndrome. The patient is normal in so many ways that a conscientious doctor can be embarrassed by his failure to recognize that a patient has a profound problem. The person is alert, aware, responsive, and fluent. He has lost none of his social graces. He can calculate and reason. He does not complain of memory difficulty. Only if the physician does a simple bedside test of word retention will he recognize that his patient is severely disabled. Although the patient can register information, he cannot recall it minutes or sometimes seconds later. In other words, the patient has lost the ability to learn and remember (anterograde amnesia). Further investigation will then reveal that the patient has to some extent also lost memories for events preceding the onset of the amnesia. When the retrograde amnesia is severe, years of memories can be erased. If there is cognitive abnormality other than amnesia, it is minimal compared to the memory disorder.

By and large the amnesic syndrome is due to damage to one of four brain regions: the medial portions of the temporal lobes, the medial aspects of the thalamus, the fornices, or the basal forebrain. In certain diseases more than one of these regions can be affected. Severe and persistent amnesia usually indicates that there is bilateral disease.

1.1 Inferomedial Temporal Lobe (Hippocampal Region)

In an attempt to treat patients with intractable epilepsy and schizophrenia, Scoville performed bilateral resection of the inferomedial temporal lobes. The surgery left 10 of his patients with an amnesic syndrome. The patients who had developed the amnesic syndrome were among those who had undergone bilateral resection of the hippocampus and parahippocampal gyrus. Those patients, who had undergone hippocampal sparing removal of the amygdala and the uncus, had not developed amnesia. The idea that the hippocampus plays an important role in memory developed from study of these neurosurgical patients.

The association of the amnesic syndrome with bilateral damage to the hippocampal region has subsequently been confirmed in patients with herpes simplex encephalitis, autoimmune encephalitis and cerebral infarction [1,2]. We have seen the amnesic syndrome result from a global ischemic process affecting the hippocampi (Figure 1.1), One carefully studied amnesic patient had survived for two and a half years after having suffered generalized status epilepticus. At autopsy the anoxic injury severely affected the hippocampi but largely spared the rest of the temporal lobes [3]. This and similar cases demonstrate that lesions, which are restricted to the hippocampi proper, suffice to cause the amnesic syndrome.

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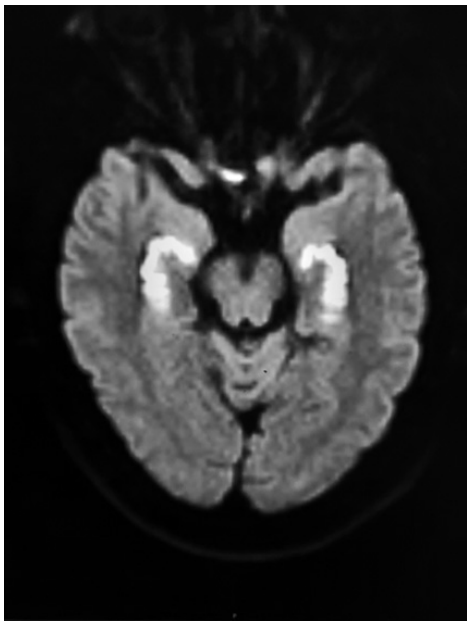

Figure 1.1 Bilateral hippocampal infarction after a hypoxic ischemic event. (Diffusion weighted MRI)

Study of transient global amnesia (TGA) provides additional information about the relationship of the hippocampus to memory function. Many patients during or after TGA show restricted diffusion in the hippocampus on magnetic resonance imaging. The typically punctate abnormality may be on either the right or the left. It occurs most often in the CA1 region of the hippocampus. Although TGA is a diagnosis made clinically, the presence of the imaging abnormality may support the diagnosis when the history is not clear [4,5,6]. The pathophysiology of TGA is unknown. Nevertheless, the location of the imaging finding provides further evidence that a hippocampal disorder can interfere with memory function.

Degenerative brain diseases, which eventually cause global cognitive impairment, can begin with a relatively isolated loss of memory. In such cases the amnesic syndrome can last for years before other cognitive problems, personality change, and aphasia emerge. Although imaging in such cases eventually shows prominent medial temporal lobe atrophy, the scans can be unimpressive early in the course of the disease, when amnesia is already prominent (Figure 1.2).

The evidence amassed from these varied conditions shows that the hippocampus is a critical region for memory function.

1.2 Medial Thalamus

Victor and colleagues studied brains of patients with Wernicke disease [7]. Those whose clinical manifestations had included amnesia (Korsakoff psychosis) always had bilaterally symmetric medial thalamic lesions, mainly in the dorsomedial nucleus. In some patients a single artery supplies the medial thalamus bilaterally. Embolism to or occlusive disease of that vessel can cause bilateral thalamic infarctions with a persistent amnesic syndrome (Figure 1.3).

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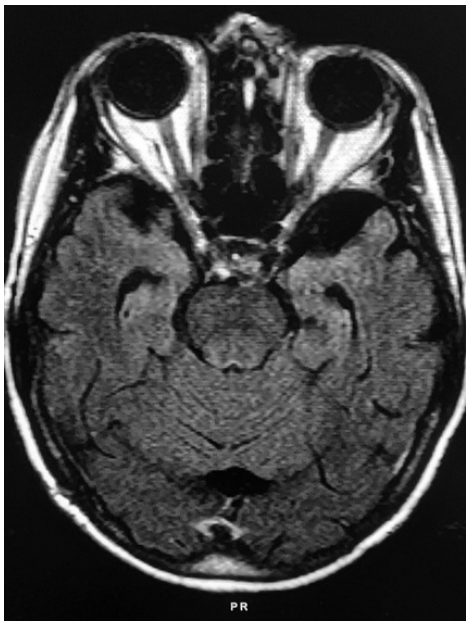

Figure 1.2 Brain MRI of a patient who had isolated amnesia as a manifestation of bitemporal atrophy. Over the years she gradually developed profound global dementia and severe generalized cerebral atrophy.

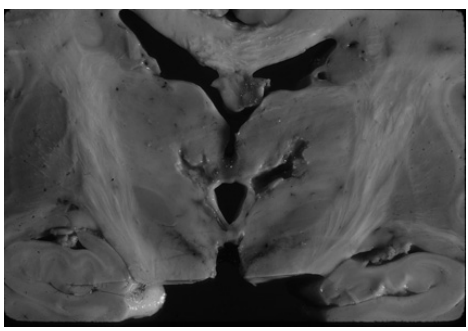

Figure 1.3 Symmetric thalamic infarcts which caused the amnesic syndrome.

This association of medial thalamic lesions with loss of memory in cerebrovascular disease supports the conclusions drawn from study of Wernicke–Korsakoff patients, namely that the medial thalamus is important for memory function.

1.3 Fornix

Because diseases which damage the fornix often affect other parts of the brain, it had long been uncertain whether isolated fornix lesions can cause amnesia. When a tumor affects the fornix, nearby areas are often affected by infiltration and/or edema. Trauma disrupting the fornix ordinarily affects neighboring structures. Infarction of the fornix is often accompanied by infarction of the genu of the corpus callosum. Involvement of the fornix in Wernicke disease is always accompanied by other forebrain lesions. Since nearby structures are involved in these various diseases, one could not know whether fornix damage alone can cause the memory trouble.

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However, we now have MRI case reports in which simultaneous infarctions limited to the columns of the fornix have been shown to be the cause of the amnesic syndrome [8]. It is believed that occlusion of a single subcallosal artery, which supplies the right and left columns of the fornix, causes these symmetric infarctions. Although they often lack clinical and/or radiologic detail, accumulating reports of such cases strongly suggest that fornix lesions can severely disrupt one's ability to learn and remember [8].

1.4 Basal Forebrain

Many investigators have recognized that patients with an anterior communicating artery aneurysm can develop an amnesic syndrome as a result of rupture or surgery. The underlying injury is in the basal forebrain [9,10]. This region includes the area of the septal nuclei, the olfactory tubercle, the sub-commissural regions, and parts of the amygdala. Non-aneurysmal cases with a discrete basal forebrain lesion can also leave a patient amnesic (Figure 1.4).

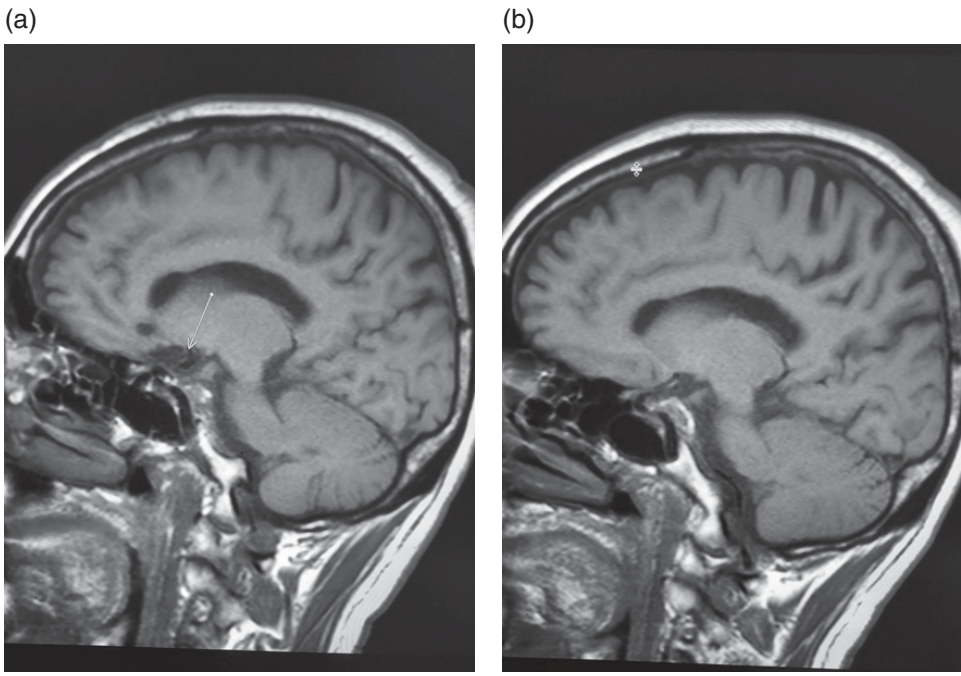

Figure 1.4a Amnesic syndrome due to left basal forebrain damage subsequent to surgery for an anterior communicating artery aneurysm.
Figure 1.4b The paracentral area on the right side is normal.

1.5 Multiple Territories

A permanent amnesic syndrome is typically due to bilateral lesions which are more or less symmetric. There are exceptions:

An 85-year-old physician had suffered a right posterior cerebral artery distribution infarction affecting the medial temporal and occipital lobes. Four years later he developed the amnesic

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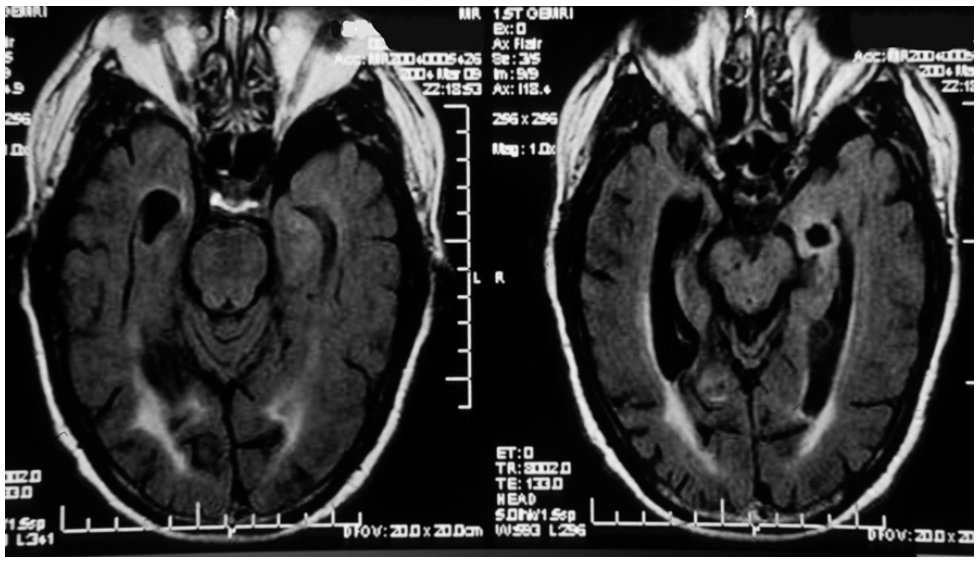

Figure 1.5 Recent left amygdala-anterior hippocampal hemorrhage superimposed on an old right posterior cerebral artery distribution infarction. This combination of lesions caused an incomplete amnesic syndrome.

syndrome when hemorrhage occurred in the area of the left amygdala. On an office visit one month after the hemorrhage he stated: "I hope that I'm not seeing patients." By the time of this visit he was frustrated by his memory trouble: "My memory is shot." His wife explained that, since his hospital discharge, he had been the honored guest at a special lecture attended by many of his former residents and fellows. He had no recollection of this occasion at all.

In this patient the amnesic syndrome resulted from the superimposition of an amygdala/anterior hippocampal hemorrhage on a preexisting, contralateral, inferomedial temporal lobe lesion (Figure 1.5). This case demonstrates that, although the lesions causing lasting amnesia are bilateral, the identical territory need not be affected on each side. Another example would be the emergence of amnesia when a new hippocampal lesion is superimposed on an old contralateral thalamic lesion. When amnesia does occur after sequential damage to differing territories of right and left brain, the cause is not always cerebrovascular disease. In one of Penfield's surgical cases, unilateral removal of the medial temporal lobe resulted in the amnesic syndrome. Autopsy revealed the contralateral lesion, hippocampal sclerosis [11].

1.6 Anatomy and Memory

At first one may be surprised that the amnesic syndrome can result from lesions in so many different regions of the brain. Actually, developmental and evolutionary relationships show that the territories under discussion are closely related. For example, the great arch of the human fornix is less of a puzzle when one looks at a platypus brain. In this mammalian brain (with a relatively smooth cortical surface) the hippocampus is a dorsomedial structure [12]. It gives rise to the fornix, which projects directly ventrally to septal gray, adjacent to which are the thalamus and hypothalamus. In the human embryo one can likewise confirm the proximity of the hippocampus, fornix, thalamus, and basal forebrain. It is only with the

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expansive growth of neocortex (isocortex) that relationships are distorted. Sulci and gyri develop. The hippocampus is pushed back from the dorsomedial position above the corpus callosum to the inferomedial temporal lobe. The fornix follows as it is similarly forced back and thus elongated. Hence, in higher mammals the fornix has to run a long path forward from the medial temporal lobe to the basal forebrain and diencephalon. Exactly why normal memory function requires these regions to be intact we do not know. However, embryology and comparative anatomy show that these structures are intimately associated.

1.7 Unilateral Lesions

Occasionally, amnesia develops after unilateral damage to an appropriate region, most often the hippocampus or medial thalamus. In such cases there was always the possibility that there were bilateral lesions, that there had been a preexisting lesion contralaterally. In the era of magnetic resonance imaging, however, a preexisting, sizable, contralateral lesion can be excluded. Compared to amnesia caused by bilateral lesions, amnesia following unilateral stroke is likely to be incomplete and is likely to improve over days to months. Some have suggested that unilateral stroke on the left side of the brain is more likely to cause amnesia than is stroke on the right [13].

1.8 The Mammillary Bodies

Lesions of the mammillary bodies commonly occur in Wernicke disease. Early writing about this disease suggested that these conspicuous lesions were the cause of the memory deficit of the Wernicke–Korsakoff syndrome. Careful study of Wernicke disease eventually showed that mammillary body lesions occur in the absence of the amnesic state and that profound memory loss can occur when there are no mammillary body lesions [7]. In that series of patients, the consistent association of Korsakoff psychosis with symmetric medial thalamic lesions indicated that it was bilateral diencephalic damage that caused the amnesia. It is noteworthy that animal experiments provide no convincing evidence that mammillary body lesions cause an amnesic syndrome comparable to that observed in humans. In sum, mamillary body lesions are irrelevant to the amnesic syndrome [14,15].

1.9 Memory and Amnesia

Amnesia is most evident on tests of memory for personal events or memory for facts. The former type of memory is referred to as episodic memory and the latter as factual ("semantic") memory [16]. If one cannot remember that he was the honoree at an annual lecture a month earlier or that his daughter visited him yesterday, the patient is said to have a problem with episodic memory. If a patient cannot remember that Tokyo is in Japan, he has a problem with factual memory. If he remembers Laureno, with whom he has worked for decades but cannot remember that Laureno is a neurologist, the patient also has a problem with factual memory. Since many facts are learned in a biographical context there can be ambiguity as to whether a memory is "episodic" or "factual."

Additional comment on memory for facts is appropriate. Because we usually do not know what facts a patient has learned in the hours, days, or weeks prior to development of amnesia, it is hard to know whether very recently acquired facts have been forgotten. Certainly, factual memory is affected in anterograde amnesia. In severe cases the patient will not remember anything (including facts) which you discussed with him 30 seconds

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earlier. Much of one's store of facts is "overlearned" information that has been stored for decades. This kind of information seems more resistant to loss in retrograde amnesia.

A remarkable aspect of the fully developed amnesic syndrome is the patient's failure to complain of memory trouble. This lack of insight is striking because the disability is severe. As with other neurologic abnormalities there can be a partial defect. There can be a partial impairment of memory and there can be a partial impairment of insight into the amnesia. (Note the case of the physician presented above.) Insight is less impaired when amnesia is caused by a unilateral lesion than it is when the disease is bilateral. With amnesia due to bilateral lesions, loss of insight is more consistently seen in thalamic than in hippocampal disease

1.10 Terminology

When Korsakoff described the amnesic syndrome, often referred to as Korsakoff psychosis, it was clear that he was describing a syndrome, a clinical constellation, not a manifestation of a specific disease. Thus, from a historic point of view, Korsakoff would be a perfectly appropriate label for the amnesic syndrome regardless of cause. Although Korsakoff wrote that his patients were not all alcoholic, today the eponym carries the connotation of alcoholism and malnutrition for many physicians. Hence, it is best to use the adjective Korsakoff only when the memory disorder is due to Wernicke disease and to use the term amnesic syndrome in other situations. Some have used the alternative term "amnestic syndrome." This usage would be appropriate. However, it should be avoided because the word "amnestic" carries special meaning in the field of immunology. To lessen the chance of confusion and for that reason alone the word "amnesic" is preferable to the alternative adjectives, "amnestic" and "Korsakoff."

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