HM: A Legacy in Neuroscience

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"The problem of neurology is to understand man himself." Walking by the Montreal Neurological Institute (MNI) and Hospital, one might give brief regard to these words coined by Wilder Penfield and prominently displayed on the edifice of the building. It is unlikely, however, that most passersby would have an accurate grasp of the groundbreaking work that has been undertaken by scientists at this institute – research that has delved into the inner workings of the human mind. During the 1930s, Penfield developed the surgical treatment of epilepsy by means of temporal lobe resection, and this procedure became a standard among many neurosurgical centres (Greenblatt, Dagi, et al. 1997). The MNI is also where Brenda Milner began her groundbreaking work in the field of neuropsychology, most notably with a patient who until recently was simply known as HM.

Nowadays, it is a rare occurrence that one can attribute significant advances in science to a single individual, especially one with no post-secondary education or formal training. However, no neuroscience textbook would be complete without mention of HM, a patient suffering from severe non-localized epilepsy and perhaps the most studied individual in the field (Corkin, 1984). H.M. was born in 1926, and at the age of 7 was involved in a bicycle accident that left him unconscious for 5 minutes. In addition, he suffered a laceration to the left supra-orbital region of his head (Corkin, 1984). At the age of 10, HM began exhibiting minor seizures, during which he would cross his arms and legs, open his mouth, close his eyes, and generally exhibit a lack of responsiveness. By the time he was 16, the seizures had progressed to major attacks. These general convulsions included tongue-biting, urinary incontinence, loss of consciousness, and ensuing drowsiness (Scoville and Milner, 1957). It is believed that the bicycle incident was linked to the onset of epilepsy, though the basic radiological studies and physical examinations available at the time showed normal findings (Scoville and Milner, 1957). This may, however, have only been a reflection of the state of imaging technology at the time and it is unclear whether modern neuroimaging techniques would have identified abnormalities. HM's family history shows a presence of epilepsy, which may be indicative of an unrelated causative factor (Corkin, 2002). Nonetheless, the etiology of HM's disorder still remains inconclusive.

In 1953, at the age of 27, HM underwent an experimental procedure in order to alleviate the severe epilepsy that had remained largely unresponsive to anticonvulsive drug therapy. At this point, he was having 10 petit mal seizures a day and at least 1 major seizure per week (Corkin, 1984). Electroencephalographic recordings indicated diffuse abnormalities; hence, the decision was made to surgically remove the medial temporal lobe structures, which were known to have epileptogenic qualities (Scoville and Milner, 1957). The bilateral medial temporal lobe resection extended 8cm posteriorly from the temporal tip, including the amygdaloid complex, temporal pole, and a large part of the hippocampal formation (Scoville and Milner, 1957). During the surgery, HM was fully conscious and talking (Corkin, 1984). The surgery succeeded in abating the severity of HM's seizures and he recovered from the surgery without any complications. However, there was one completely unexpected side effect of the surgery: severe anterograde amnesia, characterized by a loss of ability to formulate new memories (Scoville and Milner, 1957).

The beginning of the nineteenth century marked the onset of the memory debate in the neuroscience community. Specifically, scientists began to question where memory is stored and the extent of its localization in the brain (Greenblatt, Dagi, et al. 1997). In the early half of the twentieth century, Karl Lashley, a prominent neuropsychologist, conducted studies in rats that led to his theory of mass action. Removal of cortical areas of rat brains did not show any evidence of memory storage localization, but rather demonstrated that the extent of memory deficit is proportional to the amount of cortical tissue removed (Greenblatt, Dagi, et al. 1997). Opponents of this theory, notably Donald Hebb, proposed an alternate view. Hebb theorized that "assemblies" of cells work together to represent information and that these complexes are widely distributed. In the event of a localized lesion, the distributional nature and significant number of interconnected cells would ensure continued functioning (Milner, Squire, et al. 1998).

After performing the procedure on H.M. and recognizing the unexpected amnesic syndrome, William Scoville invited Brenda Milner to Connecticut to systematically evaluate HM's condition using neuropsychological methods. In 1957, Milner and Scoville published what would soon become a groundbreaking paper on memory. The surgeon and neuropsychologist described the results of testing of HM and nine other patients, who had been treated for psychosis using neurosurgical methods similar to those performed on HM (Scoville and Milner, 1957). HM was a unique case to consider since he did not suffer from psychosis, and his surgery was "frankly experimental" (Scoville and Milner, 1957). At the onset of extensive testing in 1955, memory deficits were immediately apparent – HM gave the date as March 1953 and his age as 27 (Scoville and Milner, 1957). Milner and Scoville (1957) also noted that "he reverted constantly to boyhood events and seemed scarcely to realize that he had had an operation." HM's IQ on the Wechsler-Bellevue Intelligence Scale actually improved from a preoperative score of 104 to a postoperative 112 due to the reduction in seizures (Scoville and Milner, 1957). In contrast, his score was determined to be 67 on the Wechsler Memory Scale, far below average for someone of his intellectual capacity (Scoville and Milner, 1957). A battery of tests confirmed Milner's suspicions: HM suffered from a complete loss of memory for all events occurring after the surgery, and a partial retrograde amnesia for three years preceding the surgery (Milner, Corkin, et al. 1968). Studies performed later in 1985 showed that this retrograde amnesia extended to include a period of 11 years prior to surgery (Corkin, 2002). Memories of his early life events and his pre-surgical personality remained unaffected.

Further testing also demonstrated the pervasiveness of HM's memory disorder. He was severely impaired regardless of the type of memory test, the nature of the stimulus, or the sensory modality through which the test was delivered (Milner, Corkin, et al. 1968; Corkin, 2002). He was unable to successfully acquire long-term episodic memory (events in a spatial/time context) or semantic memory (general knowledge and factual information); however, he had functional short-term memory (Milner, Corkin, et al. 1968; Corkin, 2002). HM was readily able to register new information within his immediate

memory span, but failed recall tests as soon as the information exceeded that time-span or his attention was diverted (Scoville and Milner, 1957). The evidence was progressively mounting for the role of the medial temporal lobe as a consolidation centre of long-term memory separate from short-term and working memory (Squire and Zolamorgan, 1991).

Since the surgery, HM has been examined and tested in a variety of other psychological domains. Milner was the first to demonstrate H.M's preserved learning capabilities in the form of motor learning tasks (Milner, 1970). This finding was achieved using a mirror-drawing task, in which HM exhibited learning without being able to recall any of the sessions in which he engaged in the learning (Milner, 1970). Additional studies have shown that HM withheld preserved residual learning capacities, such as perceptual learning and priming repetition (O'Kane, Kensinger, et al. 2004). Subsequent advancements in radiological imaging technology have allowed researchers to use magnetic resonance imaging to confirm the true extent of temporal lobe damage that HM had acquired. Corkin et al. (1997) found that the temporal lobe lesions were bilaterally symmetrical and included the amygdaloid complex, most of the entorhinal cortex, and approximately half of the hippocampal formation. The parahippocampal cortex was largely spared. The MRI results indicated that the extent of the lesions was less than Scoville estimated at the time of surgery (Corkin, Amaral, et al. 1997). Additional abnormalities included atrophy of the cerebellum and shrunken mammillary bodies. As the authors concluded, "these findings reinforce the view that lesions of the hippocampal formation and adjacent cortical structures can produce global and enduring amnesia."

HM has greatly advanced our understanding of the human brain and cognition. Studies conducted on him, along with the other patients given bilateral hippocampal zone excisions for psychosis treatment, have provided conclusive evidence that the medial temporal lobes are crucial regions for memory encoding. Given this evidence, HM has helped ensure that no other patient has had a bilateral resection from this critical area of the brain. The extent of HM's impairments due to the surgery prompted his surgeon, William Scoville, to campaign against continuation of the procedure (Corkin, 2002).

After the surgery, HM was cared for by his mother. Although quiet in social situations, he appeared at ease and still enjoyed puns and semantic ambiguities (Corkin, 2002). He would often apologize when interacting with other people for his apparent lack of manners, such as forgetting the names of individuals he was just introduced to (Milner, Corkin, et al. 1968). In 1980, HM moved into a nursing home due to the ailing health of his caregivers at home and was reported to have participated in the daily activities such as games, crafts, and poetry (Corkin, 1984). In the early evening hours of December 1, 2008, HM died as a result of heart failure at the nursing home he had lived in for decades.

It is essential that we not forget the humanity behind the person; many of the articles describing his psychological testing are also interspersed with anecdotal tales speaking to his continued sense of humour and social graces. While HM died completely unaware of his monumental contributions to the scientific community, even after his death, his brain will be preserved for further study. In this age of cutting edge technology and research it is easy to forget the humble roots of neuroscience. The loss of HM serves as a reminder of a time not very long ago when this field was in its infancy.

"Every day is alone in itself, whatever enjoyment I've had, and whatever sorrow I've had"

- Henry Gustav Molaison, aka "HM" (1926 – 2008)

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