Brenda Milner on **Early Clues to the Cerebral Organization of Memory:**

Mr. President, fellow Prizewinners, colleagues and friends, I am going to take you back a long way, to the early days of the Montreal Neurological Institute (MNI), where I still have the privilege to work, and where we just celebrated our 75th anniversary.

How did I come to be there in the first place? Well, you will not get far in any field without some luck along the way, as I am sure my colleagues would agree. We need it. And I had that luck in 1950, when my research adviser at McGill, Donald Hebb, gave me the opportunity of going to the Montreal Neurological Institute to do my Ph.D., studying the patients of the neurosurgeon Dr. Wilder Penfield, who founded the institute and whose pioneering work focused on the neurosurgical treatment of epilepsy, and particularly on temporal-lobe epilepsy, in which seizures arising from one temporal lobe of the brain may be extremely hard to control by pharmacological means. Very little was known back then about what the temporal lobes of the human brain did, though fortunately we had some guidance from work on the monkey and other experimental animals. And here you really have to cast your minds back and imagine what it was like then without the wonderful technical tools that we have now. It was impossible to know what was going on in the brain, or even what the brain looked like, until it was exposed at the time of surgery. All we had to go on preoperatively was a picture of the ventricles of the brain and of the plain films of the skull, but beyond that we were really relying on clinical skills (including any psychological tests that one was lucky enough to devise), as well as on the very beginnings of electroencephalography (EEG), the recording of electrical activity from the brain. The EEG is of course of major importance in tracking down the source of the epileptic discharge, and if the surgeon is going to operate on a part of the brain to treat epilepsy, it is very important that he should feel confident beforehand that he is operating on the correct side of the brain. And here I must emphasize that all the Montreal operations were unilateral (involving one hemisphere of the brain), with the assumption that the corresponding region on other side was working normally. You can get along with one eye, one kidney and so on, but you must not lose both of these paired structures, and so it is with the paired structures of the brain. So that was the diagnostic challenge.

In the human brain, the two cerebral hemispheres differ in their cognitive functions, with over 97 percent of right-handers having their language represented in the left hemisphere. It is more variable with left-handers, but for today I am going to assume that we are all right-handers with speech in the left cerebral hemisphere. Figure 1

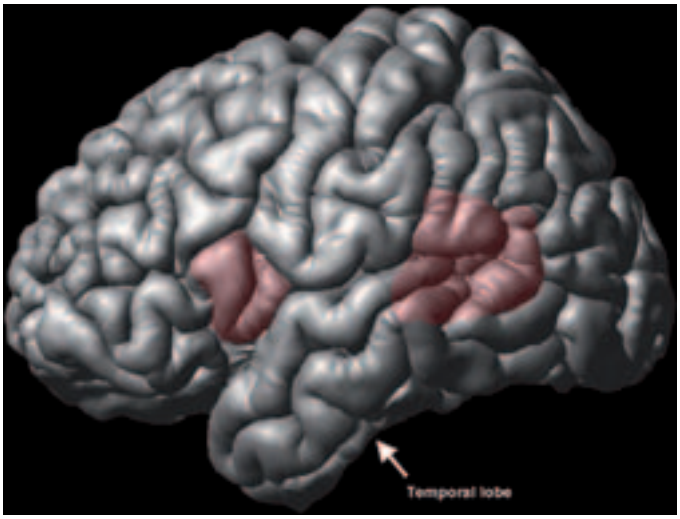

Figure 1

Lateral view of the left cerebral hemisphere, showing (in red) the anterior and posterior speech areas in the typical right-handed individual.

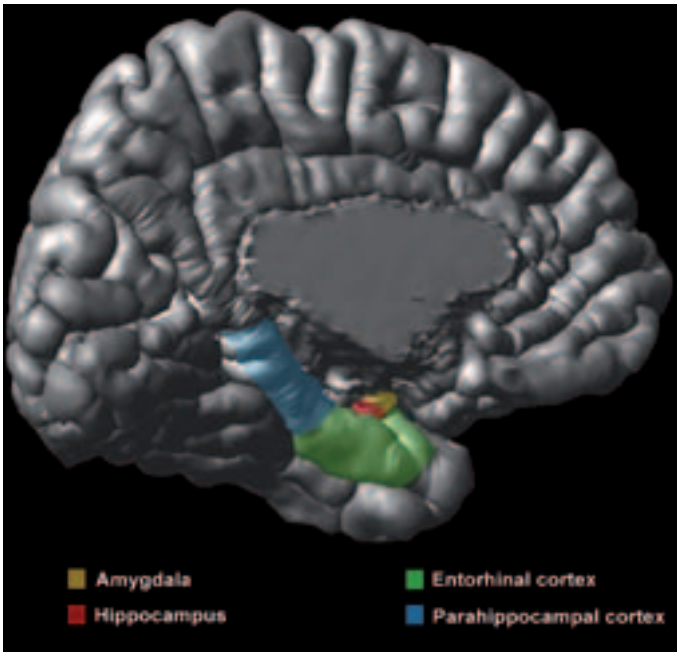

Figure 2

Medial view of the left hemisphere, indicating the various medial temporal-lobe structures.

shows the left cerebral cortex of the typical right-handed person, in which the red areas are forbidden territory for a surgeon operating for epilepsy, because this is elective surgery and damage to the primary speech areas in the adult can cause lasting language impairment. These patients are not faced with some life-threatening brain disease. They are trying to have the quality of their everyday life improved. So you must not have them paralysed afterwards, or speechless, or suffering major memory loss. That is the clinical situation. And so the typical anterior temporal lobectomy would be well in front of the temporal speech zone (shown in red), but by the time that I got to the MNI, in most cases, the removal would also include structures (shown in Figure 2), on the medial surface of the temporal lobe, including the hippocampus and neighbouring structures, because these are often the culprits in temporal-lobe epilepsy.

Initially, I was studying the cognitive changes in groups of patients having an anterior lobectomy from the left hemisphere, and comparing them with groups of patients having similar removals from the right hemisphere. And I suppose that is one of the areas in research where I could claim to have made some new contributions, because neurologists in those days tended to focus on the dominant hemisphere for speech, whereas I was always interested in the so-called minor hemisphere. This was partly because you can then use animal models; one cannot study language in monkeys, but other functions you can, and I got help from studies in the monkey for devising tasks, both visual and auditory, to explore the functions of the right temporal lobe in the human brain.

And so, how memory? I was not particularly interested in memory when I went to the MNI in 1950, because by then it had become an unfashionable topic, since, following Lashley's work on the rat, memory was thought to be a function of the whole brain, rather than of specific regions. But then the patients came to me, and especially the ones with injury in the left temporal lobe, and they would say: 'You know, I have a terrible memory'. And then I questioned them and found that they just had a bad memory for words, for what they had read and what they had heard. These were young adults, who should not have had bad memories like that. It's a disadvantage and it's annoying if you can't think of people's names when you are only 20 years old. And so they complained. And if the patient comes to you – this is the first rule – and complains that he has trouble with his memory, you don't say: "Go away, I'm not interested in memory, I'm working on the motor system", or "on visual perception"; you start studying memory. And so I began to study memory, which proved to be another great stroke of luck. What I found first was that patients with removals from the left temporal lobe did indeed have a selective impairment

of verbal memory. It did not affect their ability to recall the events of everyday life, such as what they had had for breakfast that morning; they were just not very good at recalling verbal information, whether read or heard. In contrast, patients with similar removals from the right temporal lobe had no trouble with verbal memory, and so they rarely complained of memory difficulty, because our society values verbal skills so much that you could get by, maybe not even notice, that you have a bad memory for other things. But what I found when I tested them, and this was quite new, was that these patients with right temporal-lobe lesions had an impaired memory for nonverbal material, such as faces, places and tunes. Thus, we saw a complementary specialization of the two temporal lobes of the human brain in memory processes. These results have stood the test of time. They were interesting to me then, and they are still of interest to me now.

In the midst of all this work, we got quite a shock, a disagreeable shock for the surgeon. A patient I shall call PB, an engineer from New Jersey, who had had a small removal from the left temporal lobe a few years before, now came back still having seizures, and Dr. Penfield then decided to complete the temporal lobectomy by removing the hippocampus and surrounding medial temporal-lobe structures, at this second operation. But after that, this patient, who was a very intelligent man, said: "What have you people done to my memory?" He was quite understandably bitter, because, from that day forward, he had what we would call a continuous anterograde amnesia, a forgetting of events as he lived them, of his life as he lived it. He had no idea whether his wife had been to see him that morning, what he had had for lunch, and so on. But fortunately I had tested PB extensively before the hippocampal removal and could show that the memory impairment occurred in the context of preserved high intelligence, including, and this is a very important point, an excellent short-term or "primary" memory, as I like to call it, following William James. What is primary memory? To illustrate, suppose I were to say to you now: "I am going to give you a short list of numbers and I want you to repeat them in the same order." You would all succeed with a list of five or six numbers (e.g. 62913), but with longer lists you would soon reach your limit. Thus, short-term memory is a limited-capacity system. It is what you can really keep on the stage of your consciousness, until your attention shifts. This primary memory capacity is intact in these amnesic patients, but the minute their attention is diverted (and life is constantly diverting us), they forget what happened just before. And so we have this patient PB, his intelligence unimpaired, his memory of the past seemingly intact, but from then on not building up new experiences. I think this has great relevance to the first question you are raising here, the relevance of our work to the humanities, because memory is a real

topic going back to antiquity. What we now call “episodic memory”, or the ability to recollect the past, is really the core of our being, of what we are as humans. We are our memories, and so you can imagine what it would be like if you lost that capacity. I think we can all imagine that. So this instance of postoperative memory loss was very disconcerting, to put it mildly.

At this point, Penfield and I asked ourselves: Why is this? And we speculated, in 1953, that perhaps what this patient had, unknown to us because we could not see into his brain, was damage in the hippocampal region of the opposite side, in the right hemisphere. This meant that when Penfield removed the left hippocampus, he effectively deprived the patient of hippocampal function in both hemispheres. We emphasised the hippocampus because PB had had a two-stage procedure, and it was only after the second operation, in which the hippocampus was removed, that we had this result. Shortly thereafter, we had a similar case of memory loss in a young man (FC), after a left temporal lobectomy that also included the hippocampus. We reported these findings at the American Neurological Association Meeting in Chicago in 1954.

And that is where we come to what is much better known in this story: The American neurosurgeon, Dr. William Scoville, working in Hartford, Connecticut, telephoned Dr. Penfield and said: “I think that what you and Dr. Milner are describing is what I have seen in a patient, in whom I have carried out my operation, also for epilepsy. And I would like to invite Dr. Milner down to Hartford, to study this patient and any other of my patients that interest her. I may say parenthetically that our hypothesis in the case of PB was proved true on his death 12 years later, when we did indeed find atrophy in the hippocampus of the unoperated right hemisphere, but of course at the time we made the suggestion, it was conjecture only.

We come now to the story that people read about these days: my visits to Hartford to study Scoville’s patient, Henry Molaison (HM), who died about a year ago, at the age of 82. As a young man, HM had suffered from a severe form of epilepsy, which failed to respond to any of the medications available at the time. This led Scoville to carry out an operation on the medial structures of the temporal lobes (Fig. 2) in an attempt to control HM’s seizures. Dr. Scoville was a very good surgeon, but a very bold one, and he believed, following Penfield’s work in Montreal, that the medial temporal region played a critical role in the genesis of epilepsy. But Scoville’s operation differed in two important ways from those carried out in Montreal. First, it spared the lateral neocortex and second, it was a bilateral procedure, removing the amygdala, the perirhinal and entorhinal cortex, and the bulk of the hippocampus, in both hemispheres. We know now, from subsequent magnetic-resonance-imaging studies, that Scoville’s description of this operation

was very accurate and that he did indeed spare the lateral cortex on both sides. This operation did in fact control HM's epilepsy to a remarkable degree, but it also left him with a continuous anterograde amnesia similar to that of PB and FC. Over subsequent visits to Hartford, I was able to delineate more precisely the main features of this profound memory loss.

HM was operated on by Dr. Scoville when he was 27, and I met him first when he was 29, in 1955. So I did not do the pre-operative evaluation, which was limited to IQ tests. And now we'll talk about HM. From the first, I found him a very friendly young man. But in all the time that I worked with him he never learned to recognise me, or know my name. He was always very polite and cooperative, while doing tests, but he never got to know me, nor any of the people from MIT who worked with him over the years. You have to think of me in 1955 as very naïve but very excited about what I might discover. I first established that HM had a normal short-term memory, as was the case with PB and FC. So I then gave him a three-digit number (584) and told him to remember it until I came back. I then left the room and had a cup of coffee with Dr. Scovillle's secretary. I came back 20 minutes later, and said: "What was the number?" HM replied: "five eight four". I was very surprised, and said: "That's very good. How did you do that?" And he replied: "Well 5, 8 and 4 add up to 17. Divide by 2, you get 9 and 8. Remember 8. Divide 9 by 2; you have 5 and 4; 5, 8, 4. It's simple!" I said: "That's very good! And do you remember my name?" and he answered "I'm sorry, the trouble is my memory." So you see immediately the dissociation between HM's inability to build up anything in long-term memory as soon as he is distracted and his amazing motivation. There is no question of poor motivation; these amnesic patients all try very hard, and they make up all these tricks to try to remember. But they don't succeed.

We come now to this question of examining the limits of this memory loss and also to trying to find an animal model. Given the general feeling at the time that memory was a function of the whole brain, you don't imagine that the entire scientific world was saying: "Oh, isn't this interesting?" They were all very sceptical, the neurologists in Europe being perhaps the least sceptical. But in North America the general view was that you could not possibly have seen these huge effects, these huge changes in memory, from such a restricted brain lesion. So it was important to show that monkeys with similar brain lesions to those of HM would have the same pattern of memory loss. And so I and my colleagues elsewhere were working hard on this problem.

The first idea was to teach the monkeys something, then to distract them with another task, on the hypothesis that they would forget what had happened before. And of

course we did not find this. And why not? Because on most learning tasks then in use with the monkey, it could take hundreds of trials for the monkey to know what the examiner wanted them to learn: to know that a picture of a triangle was going to have a bit of banana under it and that there would be nothing under the picture of a square. The monkeys have to find this out by trial and error, whereas you can say to a human subject "I want you to remember that", and then, a few minutes later, you can test their memory. This is a different task. My colleague, from NIH, Dr. Mortimer Mishkin (also a former student of Donald Hebb), would call learning over many trials an instance of "habit learning", or procedural learning, a different kind of learning from memory of a single experience. So we were a bit challenged in our search for an animal equivalent. The big advance came when Mishkin (following a suggestion from David Gaffan at Oxford) began to test memory in monkeys over a single trial.

Let me illustrate the procedure. If I were to show a picture of a blue bucket to HM and say "What is it?", he would reply: "A blue bucket". And then I would say "I want you to remember that, because, in a minute or so, I am going to show you two pictures, and I shall want you to tell me which is the new object." So you have to remember the object you have seen. And in this case HM would sit there, and you would see his lips moving as he said: "Blue bucket, blue bucket, blue bucket", and that's how he would keep it in mind. And then, after a short delay, I would show him two objects (the bucket and a ball) and he would know that the ball was the new object. Now imagine instead that you are the monkey and you cannot say "blue bucket". But normal healthy monkeys, with training, can learn very well to bridge considerable delays and succeed on such a task. We've got Michael Petrides here, who can attest to this. Monkeys like to choose the novel object; maybe babies do too, I don't know. So that is why we use a non-matching task "choose the new object". And what we found was that monkeys that had had the same surgical removals from their medial temporal region as HM, failed miserably on this delayed non-matching-to-sample task. They forgot the object they had been shown. These were wonderfully valuable data for which we had had to wait 20 years. It was in 1976 that Mishkin published this finding; it was in 1955 that we were publishing the work on HM. It took that long to get an insightful, meaningful animal model. But then memory research took off. It suddenly became extremely fashionable, and now it seems as if everyone is working on memory, and students find it hard to believe that memory was not a popular field as recently as 30 years ago.

But this is a history talk, so I want to take you back again, to my work as a young psychologist in the 1950s, when I was exploring the extent of HM's memory

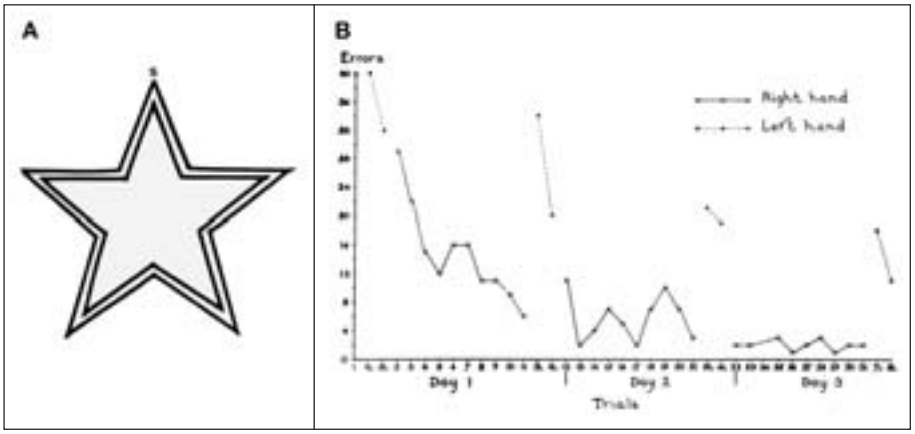

Figure 3A: *Five-pointed star used in the mirror-drawing task. The subject is instructed to draw a pencil-line, starting at point S and keeping within the double outline of the star. The subject's hand and the star are only visible as reflected in a mirror.*

Figure 3B: *Learning curve for the amnesic patient H.M., showing his progress over 30 trials, spread over three days.*

impairment and finding that he was forgetting everything. Yet you could not just say: "Oh, well he can't remember anything'", because I had not tested everything, and you cannot prove the null hypothesis. So, in search of a solution, I went over to the Psychology Department at McGill and picked up a couple of learning tasks (ones that I could carry easily). I took the night train down to Hartford, arriving at three in the morning, and having at most three days to work with HM. He failed some of my learning tasks, as I had predicted he would, but I struck lucky with one of them, which was a simple, really a very simple task, illustrated in figure 3A. It shows a five-pointed star with double contours on a simple 8 inch by 10 inch sheet of paper. You instruct the subject to start at the point S and to trace a pencil line, keeping within the narrow contours of the star, until he gets back to the starting-point. It sounds easy, except that he only sees his hand and the star as reflected in a mirror. Under these conditions we would all do badly at first, especially when we come to a point in the star; but the wonderful thing is that we learn with practice and eventually achieve a perfect performance. And now we come to what was the most exciting moment; I think that in all the years I've been working, this was the most exciting moment for me. Figure 3B shows you the learning curve for HM, depicting steady progress in

reducing his errors over three days of testing. (You can disregard the few interpolated trials with the left hand; HM is strongly right-handed.) From one day to the next, he still did not know me, nor recall that he had done the task before. Each day, we start again and we see this normal learning curve, and his beautiful performance on Day 3. At the end of Trial 30, he stood there in front of the apparatus, where he'd been working, and he said: "You know, this is funny; looking at this, I would have thought it would be rather difficult, but it seems I've done pretty well". He had absolutely no memory, no awareness of those 30 trials over three days of training that I had taken him through. For him, it was a new experience each time, and he was very proud of himself for having done so well on the last trial. And this really made me think: well this is a new kind of learning, a different kind of learning. Experimental psychologists had often thought that motor learning was different because it follows different rules from many other kinds of learning. Motor skills are acquired best when you are young and they are remarkably stable over time. You learn to ski in the winter and you can still do it the following winter. These are skills that you learn by doing. If you are trying to improve your stroke at tennis or golf, and then you ask yourself what you have learned today, and you try to analyse why your performance is better today than it was yesterday, not only can you not do so, it impairs your performance, because it is a totally inappropriate sort of question. You learn by doing. And HM's success demonstrated that this kind of learning, the acquisition of this motor skill, is quite independent of the medial temporal-lobe system that is so important for memory as we know it, thus showing the existence of more than one kind of memory system in the brain. I do not, myself, work on the motor system, but since then other scientists have gone on to show the importance of another part of the brain, the basal ganglia, for this kind of motor learning. We also know now that there are various kinds of perceptual learning that depend, for example, on the visual cortex and not on the medial temporal-lobe system. But this medial temporal system is critical for life as we live it, for re-evoking past experience, for looking back and looking forward. Looking back, if you remember events, you may just remember a fact, that this is the date something happened, or you may say that you have seen something before, without any awareness of when or where. But the kind of memory that makes our inner lives so rewarding is being able to recall the context of past episodes in all their richness. I can go back to Montreal and sit in a British Airways plane, as I expect to do in a day or two, and I shall sit there and think about this meeting today, and the new friends I have met, and the historic surroundings. That is episodic memory, and it depends on the integrity of these deep systems of the brain, which interact with the overlying cerebral cortex of both hemispheres. So this is what looking back does, and I think it does

engage the humanities. But, looking forward is the challenge, and I have to say that it is an incredible challenge to be given a lovely lot of prize money to do new research at the age of 91. You are impressed that I am still working at 91, but I am impressed that someone is giving me money at 91 to foster young people, to do research. I have spent a large part of my life delineating the complementary specializations of the two cerebral hemispheres of the human brain in memory processes. But there are huge tracts connecting the two sides (most notably the white matter of the corpus callosum), and neither hemisphere functions well on its own. My challenge for the future is to explore further how these two hemispheres work together, in health and in disease.