

Lasker Award Winner Mahlon DeLong

Mahlon DeLong, Professor at Emory University School of Medicine, shares the 2014 Lasker~DeBakey Clinical Medical Research Award with Alim Louis Benabid, Chairman of the Board at Clinatec Institute in Grenoble, France. DeLong and Benabid are honored for their work that led to the development of deep brain stimulation, a therapy that has helped relieve symptoms in thousands of patients with advanced Parkinson's disease.

The success you have achieved obviously involved lots of hard work but probably also some degree of luck. Could you talk about the interplay of those two in your scientific career?

At almost every step of my career, unforeseen opportunities have presented themselves. The first was a year I spent with Stanford professor Don Kennedy following my undergraduate studies. He advised me to "Go East, young man!" or at least that's how I remember it; I was thinking of staying at Stanford, but when I was admitted to Harvard Medical School, I couldn't resist going because I was looking for a change and a little adventure. At Harvard, I had the richest possible exposure to neuroscience imaginable. Following medical school, internship and residency in Boston, I had to find a place to begin my research and some way to avoid the draft for the Vietnam war. I was offered the opportunity of a lifetime to do neurophysiological research in the laboratory of Ed Evarts at the US National Institutes of Health (NIH), who had virtually pioneered the technique of single-cell neuronal recording in behaving primates. Because the most obvious parts of the brain had been already assigned for study by others in his lab, I was given the basal ganglia, which no one had yet wanted because it was not as exciting as the cerebellum, the frontal eye fields or the motor cortex. I could not have asked for a more interesting project.

In college at Stanford, your focus changed from physics, to history and finally to biology in your final year. As a young man, what attracted you to biology and to neuroscience in particular?

I had been narrowly focused on hard sciences and had never taken a course or read much about biology until my last undergraduate year when I became very interested in the brain and in behavior and took a very basic biology course. I was simply amazed at the beauty and complexity of biology. I never turned back and couldn't imagine how I could have overlooked it for so long. The neurosciences were made very real to me because of interactions with Stanford professors like Carl Pribram and Don Kennedy, who were very accessible to students. Neuroscience as a separate discipline didn't yet exist at that time. It was first appearing within other departments, such as physiology, anatomy and pharmacology. After my journey through undergraduate studies, I actually got my BA in history and spent a year abroad at the Free University in Berlin, having taken a crash course in German the summer before beginning studies.

At the National Institutes of Mental Health, you performed electrical recordings of the basal ganglia to better understand their role in controlling movement. What did you learn from these studies?

My time at the NIH was incredibly rich, because so many really amazing people had come there during the Vietnam era, in part to escape the draft but also since it was *the* place to go for research training. It was five of the best years of my life and an unprecedented opportunity to just do research without any clinical responsibilities. I began to figure out how to record single-cell activity in subcortical structures in behaving primates. We correlated cellular discharge with different aspects of movement, such as body part, direction and amplitude of movement. That was not trivial. Also I carried out the very basic studies identifying the neuronal specificity and somatotopic organization of movement-related neurons within the subnuclei of the basal ganglia. These studies provided the basis for subsequent studies of abnormalities of basal ganglia neuronal activity in disorders such as Parkinson's disease (PD).

Could you discuss how your anatomical understanding of the circuitry of the basal ganglia that you gained during your research paved the way for the clinical development of deep brain stimulation (DBS) in PD?

My research was focused initially on the role of the basal ganglia in the control of movement and later on the pathophysiology of PD and chorea, a form of involuntary movement which may occur following damage to portions the basal ganglia. Our basic studies provided the understanding of the networks responsible for movement and the knowledge of where to look in the animal models of these disorders. DBS was discovered by Alim Benabid at around the same time we were working on the MPTP primate model of PD. MPTP is a neurotoxin that is highly specific for the dopamine neurons in the substantia nigra and, when administered to animals, produces parkinsonism. It was later that we observed the amelioration of parkinsonism by lesioning of the subthalamic nucleus (STN). This suggested to us the importance of the 'indirect pathway', a circuit from the striatum via the STN to the output nucleus, the internal



Figure 1 Normal basal ganglia circuitry (left) and the changes that occur during parkinsonism (right). Red arrows show locations of surgical intervention for movement disorders.

segment of the globus pallidus (GPi) (Fig. 1). After this finding, we turned to lesioning of the motor area of GPi (a procedure called pallidotomy), which we carried out in patients for several years. We were quite amazed when Benabid reported his findings using DBS for the treatment of tremor. When Benabid targeted the STN in the animal model of PD and the patients with PD, it was a home run for DBS, since it provided immediate relief from all of the motor features of parkinsonism (tremor, rigidity and slowness and poverty of movement) and led to a renaissance of functional neurosurgery.

What role does the STN have in controlling the output of the basal ganglia?

It is obviously a big player, even though it isn't a large structure. What is most interesting to me is how misleading neurological and psychiatric signs and symptoms are about the function of certain structures. This is the paradox of functional surgery, which is that we can lesion the STN or GPi or stimulate them at high frequency and eliminate signs and symptoms of PD without causing obvious deficits. But what we observe clinically (parkinsonism and chorea) is not due to or reflective of the missing function of the basal ganglia but rather is the result of the abnormal activity of downstream structures whose activity is compromised and deranged by abnormal input from the basal ganglia. Removing the abnormal output enables the downstream networks to function more normally.

How did you arrive at the finding of the central role that the STN has in driving Parkinsonian symptoms?

We tested the idea that if the STN is excitatory and neuronal activity is increased in the STN and the GPi in PD, it could be playing a role, although we could not know how successful this would be. This concept was supported by anatomical, electrophysiological and metabolic changes. Our study in the primate MPTP model showed that lesioning or DBS of the STN eliminated parkinsonism and normalized activity in the GPi and throughout the network. As we now know, it's not really the increased rate of firing in the network but the abnormal pattern of activity and synchrony of discharge that is mostly responsible for the clinical features of PD.

How did improvements in neuroimaging techniques allow for some of the clinical applications of your findings?

Neuroimaging has helped in the planning for placing the leads for DBS, and we now are able to implant these under anesthesia in

the operating room thanks to guidance from magnetic resonance imaging. In the early days of these surgeries, patients needed to be awake for DBS electrode implantation so that surgeons could perform microelectrode 3-D mapping of the target nucleus and macrostimulation for assessing motor and sensory responses from the adjacent motor and sensory pathways.

Could you discuss some differences between pallidotomy and DBS in the treatment of PD?

Both are highly effective in treating tremor, rigidity and bradykinesia or akinesia. Both mimic the effects of dopamine replacement therapy with the drug levodopa. Both target the same sensorimotor area of STN or GPi. For lesioning procedures, however, such as pallidotomy, there is only one chance to get it right, and there are risks of permanent damage if the lesion is not well placed and of secondary bleeding or infarction. DBS is reversible and adjustable and, therefore, more forgiving. By an implanted pulse generator, similar to a cardiac pacemaker, it is possible to externally program and adjust the site of stimulation, the voltage or current, the frequency and pulse width. The ability to tailor and optimize stimulation is a big advantage of DBS over pallidotomy. Also, in general, pallidotomy is done only on one side, because of the risk of speech or swallowing difficulties, which are seen in some cases due to inadvertent damage to corticobulbar motor pathways mediating these functions, whereas DBS can be done safely bilaterally.

Could you talk about how your research on basal ganglia circuitry has paved the way for clinical approaches in neurological diseases apart from PD?

I think the concept that many neurologic disorders can be viewed as circuit or network disorders is fundamental to guiding our therapies, realizing that one can stimulate at multiple nodes along the circuit for the same disorder. The observed segregation of circuits involved in motor, cognitive and emotional or reward functions makes it possible to avoid side effects by targeting the specific circuit. Also, we now recognize that DBS is not really disease specific but rather circuit specific and that the targets for disorders that cause involuntary movements, such as chorea, are the same as that for PD or dystonia. The signature activity of the network determines the clinical features.

How has competition shaped your scientific career?

In my view, competition often leads to cooperation between different teams and expedites discovery and progress. I think most researchers can point out competitors but often are on good terms with them, respecting each other's abilities. I don't think competition has played a major role in my career. I was fortunate in that I entered this area of research at an early stage and found that just following your nose seemed to work very well. The individuals in my field had a very good sense of what others were doing and were more like members of a club than competitors. As we often said, jokingly, we were 'outnumbered by neurons.'

What are some key questions you see in the field of basal ganglia function that you think are the most pressing to address in the near future?

We still don't know exactly what it is that the basal ganglia do and how do they do it. We know that the basal ganglia are components of larger segregated circuits that receive input from the cerebral cortex and return output to the cerebral cortex via the thalamus. These circuits provide a mechanism for parallel processing of information related to motor, cognitive and emotional or reinforcement functions. We used to think that basal ganglia contribute to movement by controlling the speed and amplitude of motion, but more recently this hypothesis has come into question. Scientists also once believed that the basal ganglia played a role in the initiation of movement, but this has not been supported by physiological and clinical data, including the effects of lesioning or stimulation in patients with various movement disorders. The basal ganglia appear to be particularly involved in the learning of skilled motor acts and a type of learning called procedural learning, such as learning to ride a bike or to ski. Dopamine is very important in this type of learning, but how such learning is reinforced and transmitted to the cortex and other areas of the motor system is unclear. Although DBS is highly effective in treating movement and other neurological as well as some psychiatric disorders, the mechanism of action is still controversial. Understanding the nature of these disorders and finding better treatments are the highest priority.