Lasker Award Winner **Alim Louis Benabid**

Alim Louis Benabid, Chairman of the Board at Clinatec Institute in Grenoble, France shares the 2014 Lasker~DeBakey Clinical Medical Research Award with Mahlon DeLong, Professor at Emory University School of Medicine. 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.

During the early parts of your career, you had an interest in both medicine and physics. How do you think this dual interest led to your discovery of deep brain stimulation (DBS) as a therapy for Parkinson's disease and other movement disorders?

My interest in both medicine and physics has been present all along my career and has driven most of my choices. As a rule, I did my best to combine my clinical practice of neurosurgery with basic research, oriented towards fundamental neurophysiology and physics-based approaches. Neuroscience is the perfect field for combining those two types of interests. Neurosurgery gives access to important problems related to the function and dysfunction of the brain. Operative approaches are and must be combined with sophisticated methods of exploration, such as microrecording and imaging, both being based on physical principles (electrical methods) and data processing (imaging and data analysis). Recording and analyzing neural activity in the basal ganglia involves physical concepts such as electrical currents, frequency of spike discharge and electrical stimulation. My interest in these physical concepts is probably why I paid more attention to the frequency of electrical stimulation than some of my other colleagues and why I was intrigued by the brain responses to high-frequency stimulation.

How did the focus of your surgical techniques in patients with movement disorders move from the thalamus to the subthalamic nucleus?

In the 1980s, the thalamus and particularly the ventral intermedius nucleus (VIM) was the main target used by functional neurosurgeons to treat tremor, mostly in Parkinson's disease, but also in essential tremor. The method used was 'ablative surgery', meaning that the target was destroyed. This could be achieved by several means, such as induction of radiofrequency lesions (coagulation of the tissue due to heat produced by the passage of electrical current at several thousand Hz). The size of the lesion was more or less controlled by the intensity of current being delivered for a variable period. The evaluation of the 'correct' size of the lesion was based on the observation of the therapeutic benefit—the intensity of tremor—just after the lesion, and the upper limit by the appearance of side effects or complications. My neurosurgical practice was mostly oriented to the thalamus, and my concern was to find a less invasive, more precise and possibly reversible new method to alter the thalamus firing rate, so that lesioning by thalamotomy could be avoided. During intraoperative tests, we found that using stimulation around 100 Hz would induce equivalent beneficial effects as lesioning for Parkinson's disease and essential tremor, but that these effects were reversible. However, high-frequency stimulation or lesioning of the thalamus did not change the range of the improved symptoms in Parkinsonian patients: tremor may have been alleviated, but there were little or no beneficial effects on akinesia or rigidity. The publication in 1990 by Mahlon DeLong on the effect of subthalamic nucleus (STN) destruction in monkeys injected with the neurotoxin MPTP, which reported alleviated Parkinsonian symptoms, drew our attention because VIM high-frequency stimulation was solely limited to the alleviation of tremor. Making the lesion in the STN was considered at that time highly dangerous because of the risk of creating choreic hemiballistic movements. Having at hand six years of experience with high-frequency stimulation of the thalamus, which had shown the safety and reversibility of the effect, we could take the risk in 1993 of targeting STN in advanced Parkinsonian patients using high-frequency stimulation. This proved to be highly efficient, and this became what is currently the surgical therapy of choice for severe advanced Parkinsonian patients.

How did you determine the optimal frequency for stimulation of the STN in those early studies?

As a rule in experiments, in biology as well as in physics, parameters used for a given method are explored in the largest reasonable band of frequency which is available to the investigator. Usually neurosurgeons tested intraoperatively at 30 or 50 Hz because these were considered as classical excitatory frequencies of electrical stimulation. To proceed more systematically, I explored during these tests the entire range of frequencies that I had available at the time on my intraoperative equipment. The system I used offered a continuous range from 0 Hz to 100 Hz. In the first patients in whom we observed the dual effects of frequency, we found that at frequencies of 30 to 50 Hz we could not obtain anything but excitatory responses in the sensory (paresthesias) and in the motor (contractions) structures surrounding the VIM. Above 50 Hz, the results were starting to influence tremor, but above 80 to 100, it was clear that tremor

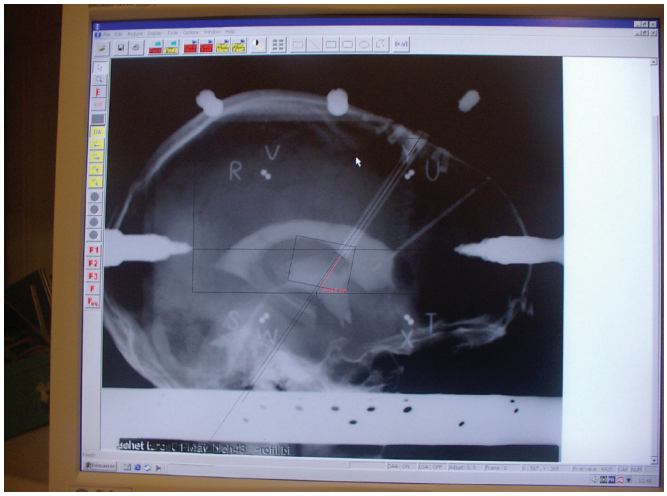

Figure 1 Targeting high frequency stimulation to the subthalamic nucleus to treat obsessive-compulsive disorder.

would be reversibly, rapidly and safely interrupted at the onset of stimulation and would return when stimulation was turned off. In later experiments, we used a stimulator with a much larger band of frequency, which allowed us to determine that the best benefit (total arrest of tremor) occurred at around 100 to 200 Hz, and even going up to 3,000 Hz would provide no additional benefit.

Could you talk about the relative role of serendipity and hard work in your scientific career?

Hard work and serendipity cannot be dissociated from each other. Hard work is the result of your commitments to a given task or a specific goal or to the completion of a specific project. It means that your attention is devoted full time to reaching the goals or finding solutions to the unsolved problem underlying your project. You set your brain to a high state of excitation, of accuracy, of attention. Then, in the flow of the daily events of normal activity, something might occur, quite often unrelated to your interest but presenting some aspects which may have a slight resemblance to the topics of your activity favorable to an association of ideas. This might then spark a sudden understanding or the occurrence of new ideas or changes in the usual orientation of your thoughts that may create the situation where, for an excited, available, prepared and expecting mind, it suddenly makes sense and leads you to a new creation, explanation, idea or theory. This is what is called serendipity, the random encounter between a random event and the prepared mind reaching for an expected solution. While exploring the effect of various frequencies in a routine procedure, the observation of the arrest of tremor met the underlying expectation in the back of my mind of a possible new solution for replacing the usual method of thalamic lesioning with high-frequency stimulation.

What role do you think mentorship has played in your scientific career? How important do you think having good mentors is to today's young scientists?

I was very privileged having Professor Jacques de Rougemont as a mentor; I spent more time with him that I spent with my father. He taught me neurosurgery, he taught me the behavioral and moral aspects of clinical practice and of relationships with patients, he was interested in my research, and he was able to provide advice. The mentorship is primordial and crucial for the development of individual young investigators. The mentor has to be directive and able to guide a young investigator along a difficult research path, should suggest new avenues of research and should rapidly observe and suggest ceasing experimental approaches which are not leading to valuable results in a reasonable amount of time. The mentor has to be a leader but also must be careful not to inhibit independent thinking; mentors must aim to find the right level of permissiveness.

What do you think about the application of DBS techniques to other disorders, such as depression?

The progress in the knowledge of brain circuitry during the last two decades has brought into perspective many targets potentially useful in treating a large number of disorders. For example, it may be applied to psychosurgery, literally the surgery of the psyche, a field of functional neurosurgery devoted to the treatment of mental disorders. The typical example is lobotomy or prefrontal leucotomy, initiated by Egaz Moniz (who won the 1949 Nobel Prize) for the treatment of psychoses. Based on evidence implicating the subgenual cortex CG25, Helen Mayberg and Andres Lozano have implanted electrodes bilaterally in CG25 (which is not far from where subcaudal lesions were formerly induced) in severe treatment-resistant depressed patients. The results have been very impressive, with acute benefits and immediate reversal when high-frequency stimulation was turned off. High-frequency stimulation in the STN has also been used to treat obsessive-compulsive disorders and in the pallidum and the thalamus to treat Tourette's syndrome (**Fig. 1**). These efforts have reopened the field of psychosurgery.

Could you describe your role in the advances in technologies that eventually allowed for chronic DBS in patients?

When my work was beginning, low-frequency electrical stimulation of the brain and spinal cord was already used to excite pain-suppressing structures. Therefore low-frequency electrodes and stimulators were already commercially available. This allowed us to start the clinical application of stimulation at high frequency by adapting the use of the stimulator to the maximum frequency available (100 Hz) without the need to develop a novel device. When it was clear that high-frequency stimulation would be the new method for functional neurosurgery, I had to work with companies to obtain several improvements in their devices, such as extension of the range of available frequencies from 100 Hz to several thousand and the possibility of having tetrapolar electrodes. The electrodes which were commercially available were monopolar, which meant that the tip of the probe had one contact. Having four contacts in a row (in a tetrapolar electrode) instead of only one expanded the length of the active area and provided four choices instead of one to obtain the best location of the active contact within the target and therefore provided a better selectivity. I also developed for DBS as well as for brain tumor biopsies a robotized neurosurgical hand regularly used in my department and in many others.

Could you talk about the role that you played in getting clinicians to apply DBS to many different disorders?

Besides the introduction of high-frequency stimulation as an innovative method to replace radiofrequency lesioning and to induce adaptable and reversible inhibition of cellular targets, I have worked to promote this method and convince our community that the results were sound and solid. I have directly acted to initiate its application to STN and then for several diseases such as epilepsy, and obsessive-compulsive disorder. I have developed a less invasive approach through the endoventricular route for high-frequency stimulation of periventricular targets such as the hypothalamic nuclei for obesity and cluster headaches.

What do you think is the biggest problem in movement disorder research that still needs to be addressed?

Neuroprotection is clearly the new frontier in movement disorder research and therapy. The long-term clinical studies have so far failed to prove that high-frequency stimulation has been able to slow down the evolution of the disease. So-called 'earlystim' clinical protocols have only proven that it was safe to stimulate STN much earlier than it was so far accepted. At the experimental level, we have published that in MPTP-treated monkeys, high-frequency stimulation of the STN could protect neurons in the substantia nigra. To test this hypothesis in humans, one would need to perform STN stimulation at the very beginning of the disease, which is not easily ethically sustainable given the surgical risk, even if low, in patients who are still minimally impaired by the disease.

How important do you think new technologies are for the advancement of science and medicine?

There have been so many advancements in computing capabilities; big data management; miniaturization of electronics, devices and batteries; and new sources of energy compatible with implantation of biological devices and fuel cells. More recently, there has been an explosion of biological imaging at the nano level as well as whole-brain imaging. It is impossible to generate a reasonable picture of future technological development without being sure to be wrong. The consequence of that is that when building projects and setting new protocols as well as imagining new tools and devices, we should be confident that what has not yet been developed will eventually be created.