

RESEARCH

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Special Report

Three strategies to beat Parkinson's

Mathias Germain

[Photo caption] At Clinelec, an applied research laboratory, patients' movements are studied to observe the effects of Parkinson's treatments

[Photo credit] DUNG VO TRUNG/LOOKATSCIENCES

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Parkinson's disease attacks neurons that produce dopamine, a neurotransmitter essential for controlling mobility. Patients suffer from slowed movements and shaking on a daily basis. Treatments exist for temporarily relieving these symptoms. But recent discoveries by French teams go further. They open up avenues for stopping the degeneration of neurons: stimulation of neurons with infrared light, treatment of a protein anomaly that causes the disease, and use of a viral vector to deliver therapeutic molecules.

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1. ALIM-LOUIS BENABID

“Infrared light re-energizes neurons”

Interview The French neurosurgeon looks back on a fruitful scientific adventure that started with deep brain stimulation to treat Parkinson’s symptoms and has led to a discovery that could stop the progression of the disease. Mathias Germain

At 73, Alim-Louis Benabid has plenty of ideas for new projects. Full of enthusiasm, he is getting ready to test a method involving illumination by near-infrared radiation on patients suffering from Parkinson’s disease. This technique may be able to stop the progression of the illness. In animals, the results are very encouraging. Benabid, a native of Grenoble, has remained at the cutting edge of research, twenty years after his discovery of high-frequency electrical stimulation for the treatment of Parkinson’s symptoms, which has helped more than 100,000 patients throughout the world. In 2014, this work earned Benabid the Lasker Prize (awarded by the Lasker Foundation since 1946 to clinical and basic researchers) as well as the 2015 Breakthrough Prize in Life Sciences (created in 2013 by the founders of Facebook, Google, and 23andMe).

Benabid’s work is not limited to Parkinson’s. In 2009, with the support of the CEA and the Edmond J. Safra Foundation, he created Clinec, a highly unusual laboratory bringing together in one location physicians, biologists, mathematicians, and robotics specialists, among others. With one strategy: draw new resources from basic research in order to develop innovative treatments that serve patients.

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“Infrared light re-energizes neurons”

>>> **RESEARCH:** How did you discover the effects of high-frequency deep brain stimulation?

ALIM-LOUIS BENABID: It was while preparing to operate on a patient suffering from essential tremor, a neurological disease, that I observed the effects of high-frequency electrical stimulation. The operation destroys a small part of the thalamus, the VIM or ventral intermediate nucleus, which eliminates the tremor. Low-frequency electric stimulation is used to accurately identify this nucleus, which measures around 10 millimeters. The excitation of this nucleus triggers tremor in the patient; the surgeon then knows that the target has been localized. In modulating the parameters of this stimulator, I observed that the patient stopped shaking when I increased the frequency of stimulation above 100 hertz [1]. This was a real surprise because, at the time, electrical stimulation was known for its excitatory rather than its inhibitory effects.

His key dates

- **1987.** Discovery of the effects of high-frequency deep brain stimulation on Parkinson's disease.
- **1988-2006.** Director of the Inserm Preclinical Neurobiology research unit.
- **1989-2005.** Head of the neurosurgery department at the Grenoble University-Hospital Center.
- **1993.** Treatment of first Parkinson's patient using deep brain stimulation.
- **2009.** Launch of the Clnatec laboratory project in Grenoble.
- **2011.** Clnatec laboratory is operational.
- **2014.** Awarded the Lasker Prize.
- **2015.** Awarded the Breakthrough Prize.

Did you immediately realize the relevance of this observation for the treatment of Parkinson's symptoms?

A.-L.B.: Yes, because shaking is among the three major symptoms of Parkinson's disease. In 1990, the focus was on the subthalamic nucleus, part of the basal ganglia in the central nervous system and whose role in movement control had recently been demonstrated by Mahlon DeLong, at Emory University in Atlanta, Georgia, and by Tipu Aziz at Oxford University in England, then by Abdelhamid Benazzouz at the Université de Bordeaux. Thanks to this work, we were able to apply this technique in patients quite rapidly; the first patient underwent surgery in Grenoble in 1993. This quick application is explained by the fact that we did not have to invent new equipment. Most importantly, deep brain stimulation offers the advantage of being reversible, modulable, and non-destructive [2]. Today in France, 17 neurosurgery departments use it for Parkinson's disease with, in the most active departments, around 50 operations per year.

In concrete terms, what does deep brain stimulation entail?

A.-L.B.: The principle is to implant very fine electrodes in the subthalamic nucleus of each hemisphere. This is done using stereotaxy, an imaging technique that enables defining a very accurate position in space and performing minimally invasive surgery. The two electrodes are connected to a battery, like a pacemaker, situated near the clavicle, under the patient's skin. The stimulation is high frequency, 130 hertz, with a voltage between 1 and 4 V, depending on the patient. It's a personalized treatment. As soon as the system is in place, the result is spectacular: the patient stops shaking and no longer has any of the movement disturbances that appear after several years under medication.

At what stage in the disease is deep brain stimulation indicated?

A.-L.B.: This is a second line of treatment. In the beginning, when the disease is diagnosed, the patient is given medication, which compensates for the deficit of dopamine in the brain. Parkinson's disease is due to the destruction of neurons that produce this molecule, which is an essential neurotransmitter for the neurons of the basal ganglia, which include the thalamus. Without dopamine, the neurons of these ganglia can no longer correctly perform their role in neurotransmission. This leads to disturbances in movement control, such as slowness in the movement of the limbs (akinesia), muscular rigidity that blocks the joints, and shaking of the hands and feet in a resting state. These disturbances also affect the face, in particular the muscles involved

in speech. The symptoms of the disease appear when around 70% of the substantia nigra have been destroyed.

What effect does the medication have on the patient?

A.-L.B.: In the minutes after the patient takes the medication, the symptoms are reduced. The patient's situation improves, to a nearly normal state. It's so effective that people speak of a "honeymoon" for the patient. But after several years of treatment, the patient begins to have complications due to repeated use of the medication.

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Each time the patient takes a pill, it's as if the dopamine receptors, located at the synapses of the neurons, were hit by a hammer, and they end up losing their functional flexibility. After five to ten years, depending on the patient and the treatment doses, the dopamine receptors no longer respond in a flexible, harmonious way, but in binary fashion; they are either "on" or "off", like a switch. When they are "on", the treatment is effective. On the contrary, when they are "off", the patient's movements are slowed. His or her treatment is modified at that point, and the doses are taken closer and closer together. Patients find themselves between a rock and a hard place: intensifying treatment causes dyskinesia, involuntary and uncontrolled movement, during the "on" period, while during the "off" period, patients are rigid and blocked in their movements.

Is that when deep brain stimulation is considered?

A.-L.B.: Yes, especially stimulation of the subthalamic nucleus. It eliminates all of the symptoms of the shaking, akinesia, and rigidity triad. At the very beginning, the effects of high-frequency electrical stimulation are as spectacular as for medication. But it should be noted that this treatment is not appropriate for all patients. And response to medication is often a predictor to response to stimulation.

Do we have a good idea of how deep brain stimulation acts on neurons?

A.-L.B.: All we know is that it works... We don't understand the mechanisms. We do know that this stimulation interferes a great deal with the neuronal circuits that use dopamine and that it does not create lesions or organic modifications [3]. Everyone is trying to understand how it works. As I see it, a series of mechanisms act conjointly and simultaneously. Note that electrical stimulation is not a phenomenon that acts only at the end of an electrode... It has a diffuse action. In these zones of the brain, there is great variety in cell type: there are different categories of neurons that function with different types of neurotransmitters, synapses, fibers, and so forth. And we come into these zones with our "electrical storms"! So we influence a lot of things. I have proposed that we speak of functional inhibition, because it's clear that the neurons that we stimulate don't function together anymore, so they seem inhibited. Cameron McIntyre, at Case Western Reserve University in Cleveland, who has done a lot of work on these questions, speaks of an "informational lesion" [4]: stimulation interrupts the passage of abnormal signals in brain nuclei. This appears to produce a jamming effect.

How long do the beneficial effects of deep brain stimulation last?

A.-L.B.: If the stimulation is stopped, the beneficial effects last no longer than one or two seconds! The effects are totally reversible. That's one of the reasons for the method's success, making it possible to target zones considered untouchable, like the subthalamic nucleus. Hemorrhage in this nucleus causes hemiballismus, resulting in involuntary abnormal movements in which the proximal parts of the limbs are projected forward in a very abrupt, and exhausting, manner. Cases of death by exhaustion have been reported... As long as the stimulation is maintained in place, the beneficial effects continue... The problem is that we're only acting on the symptoms. In the meantime, the disease continues to progress. Other neuronal circuits are also affected by degeneration, for example in the autonomic nervous system. Consequently, problems affecting digestion, the heart, and the blood vessels develop. That is, as degeneration progresses, a set of new symptoms appears that affects different areas of the body and that doesn't respond to pharmacology or high-frequency brain stimulation.

The Holy Grail: Prevent dopamine-producing neurons from degenerating

Until now, no treatment has been able to block the development of the disease.

A.-L.B.: That's the challenge. Several lines of research are being conducted to find treatments. Specifically, researchers are looking at how to prevent dopamine-producing neurons from degenerating. Obtaining this neuroprotective effect has become the Holy Grail of neurologists. Everyone is out to find it. And there are a lot of possibilities, like gene therapy. In 2010, working with John Mitrofanis at the University of Sydney, we discovered something very interesting: illumination using near-infrared radiation.

What does this involve?

A.-L.B.: Similar to electrical stimulation, we use a system placed inside the brain. But to stimulate the neurons, this technique diffuses near-infrared radiation, that is light with wavelengths between 600 and

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1000 nanometers. Our work has shown that exposing dopamine-producing (dopaminergic) neurons to this type of radiation stimulates their metabolism.

Was this discovered by chance, like deep brain stimulation?

A.-L.B.: No, the scientific literature provided clues. Studies showed the benefits of light, especially infrared light, on states of cellular stress. John Mitrofanis's colleagues performed experiments on cells in culture subjected to various forms of stress or inflammation. Given that near-infrared light can penetrate organic tissue to a depth of up to 3 cm, it occurred to us that we could expose sick mice to find out whether external radiation could act inside their brains.

Clinattec aims to create innovative biomedical systems

How did you carry out this experiment?

A.-L.B.: We performed this experiment on mice by injecting them with a toxin, MPTP, which attacks dopaminergic neurons in the substantia nigra. The mice then have the same symptoms as in Parkinson's disease. Some of these animals were exposed to lamps diffusing near-infrared radiation. The result: we observed that the exposed animals had much less neuron loss in the substantia nigra than the others, between 35 and 45% [5]. Encouraged by this finding, we launched a series of experiments aimed at applications in humans.

Can an external source of infrared radiation reach the substantia nigra in humans?

A.-L.B.: No, radiation diffused by an external lamp does not penetrate to sufficient depths in the brain to expose the two parts of the substantia nigra. This structure is at a depth of 10 to 12 centimeters, so we had to use our imaginations to devise a way to proceed. That's where my experience with electrical stimulation was useful. I had developed minimally invasive techniques to deliver stimulation in the very center of the brain. We used these techniques in mice [6], then in monkeys.

What is the technical setup?

A.-L.B.: In schematic terms, we implant an optical fiber connected to a laser source, which is in turn connected to a battery that is exactly the same as the one used for deep brain stimulation. The fiber is implanted toward the third ventricle, a cavity situated between the two cerebral hemispheres, right on the median line, at the level of the two nuclei of the substantia nigra on the left and right, which contain dopaminergic cells. The target is no longer the subthalamic nucleus, but the substantia nigra.

What results do you obtain?

A.-L.B.: A few months ago, we obtained results for an experiment lasting several weeks in monkeys. We had brought on the illness in them using MPTP. Those animals who correctly received the infrared light had behaviors that were practically identical to normal behavior, with very minimal neuronal loss, or even no neuronal loss. This is a rather incredible result.

Nonetheless, their neurons were damaged by the MPTP toxin, not by Parkinson's disease...

A.-L.B.: That's true, these animals aren't patients, this isn't Parkinson's. But MPTP is one of the most widely used models of the disease. Furthermore, we've also started experiments with other models that mimic Parkinson's disease, with the hope of demonstrating that, here again, we can slow or stop neuronal loss. This may very well be the beginning of an exciting scientific adventure!

This time, do you know what is happening in the neurons of the substantia nigra?

A.-L.B.: Yes, even though much remains to be elucidated, we have a better explanation of the mechanism than we do for deep brain stimulation. We have known for a long time that the death of a cell, and a neuron in particular, is associated with degradation of its mitochondria, which are the energy factories in cells. Mitochondria contain enzymes, such as cytochrome C oxidase, that are light sensitive. It's a bit like chlorophyll in plants, which absorbs light and produces energy. In the case of mitochondria, cytochrome C oxidase absorbs light in wavelengths close to infrared light. This phenomenon stimulates the electron transport chain. And that increases production of ATP, the molecule that provides the energy necessary for the chemical reactions of cellular metabolism. In other words, infrared radiation re-energizes the dopamine-producing neurons in the substantia nigra that Parkinson's attacks.

This prevents them from dying. The effect is thus neuroprotective.

Is the system used in animals applicable to humans?

A.-L.B.: It will have to be adapted. In principle, the model is identical to the one we've produced. But the optical fiber will be longer, to reach the back of the third ventricle in a human brain. All of the materials used must be as durable as possible in an organic environment. And the system will have to meet even more stringent standards for safety and biocompatibility. The prototype used in animals was produced at Clnatec, in Grenoble, with the collaboration of Leti, a CEA laboratory specialized in micro- and nanotechnologies. We're currently developing a system that we could use in humans, with the hope of starting the clinical trial phase in the near future.

You've just mentioned Clnatec. Tell us more about this surprising laboratory!

A.-L.B.: It's a dream that we've been able to achieve. I wanted to bring together in time, space, and action different disciplines, where the best ideas would meet the best skills. Over the course of my career, at the hospital, in the laboratory, at the medical school, I've observed that the structures people work in are far from each other, resulting in slow, viscous relations that discourage attempts to achieve goals together. Clnatec was born of my meeting with Jean Therme, Director of the CEA's Technological Research Center. We're convinced that bringing together medical research and technological research may change the fate of millions of patients suffering from neurodegenerative diseases, cancer, and quadriplegia. Clnatec does just that. It is a place where mathematicians, biologists, physicians, engineers, technicians, animal specialists, and administrators work together with the goal of creating innovative biomedical systems, from the basic concept through to treating patients. Patient safety is a priority.

What sort of equipment does Clnatec have?

A.-L.B.: Clnatec opened its doors in 2011. It's a 6500m² building including a technical platform where high-tech systems are developed, an animal laboratory for preclinical experiments, and a clinical wing with six rooms fitted with the best equipment. It contains a vast operating room equipped with robots piloted from an adjacent control room and a powerful MRI instrument that can be moved into the operating room and used for brain imaging during surgery, or during the injection of medication. The first patient with a brain tumor was operated on in October 2013. Clnatec is unique in France.



The Clinatec laboratory in Grenoble is developing an exoskeleton known as EMY. The structure is controlled by thought and could help quadriplegics.

What major projects are underway?

A.-L.B.: One of the most ambitious is the development of an exoskeleton controlled by thought for quadriplegics. This is a BCI or “brain-controlled interface” project that relies on two implants measuring cortical activity, algorithms for interpreting brain signals pertaining to movement intentions, and the exoskeleton, which weighs 70 kg including the computers and batteries. We call the exoskeleton EMY (Enhancing Mobility). These components have been tested and approved under French regulations relative to medical equipment. An application for a clinical trial was submitted four months ago to the French National Agency for Medicines and Health Products Safety and to the Ethical Research Committee. Once we get the green light, we will be ready to carry out testing in humans. Miniature tools for making molecular and cellular imprints of cancerous tumors, or for delivering medication in the very center of tumors, are also being developed.

Miniaturization, robotics, the brain... doesn't your research generate false hopes, or on the other hand, opposition?

A.-L.B.: Of course, there was some opposition to the development of Clinatec. And I've been accused of practicing “transhumanism”... a term you hear often these days. But I have only one ambition: to serve patients and improve their daily lives. We are in no way trying to transform human beings. Our work complies with many regulatory systems and we have support from monitoring organizations. It's perfectly normal that new technologies give rise to ethical debates and raise questions for society. Clinatec is not an ivory tower. While people have expressed their fears to us, patients have also asked to participate in our work. We have to be careful here, too, and not promise miracle solutions.

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