Deep impact in the brain

Deep brain stimulation may sound like something out of a science fiction movie, but it's actually an accepted procedure used to treat the tremors and muscle spasms of Parkinson's disease. A battery-powered pulse generator in the patient's chest sends programmed electrical impulses to a tiny pacemaker-like electrode implanted deep within the brain. The electrode delivers mild shocks that alter neuronal signals. The tremors stop while the device is on and resume as soon as it's switched off.

Levels: Dartmouth researchers, led by neurosurgery resident Kendall Lee, M.D., Ph.D., may have discovered why this relatively new treatment is so effective: deep brain stimulation (DBS) seems to increase dopamine levels in the stimulated regions of the brain.

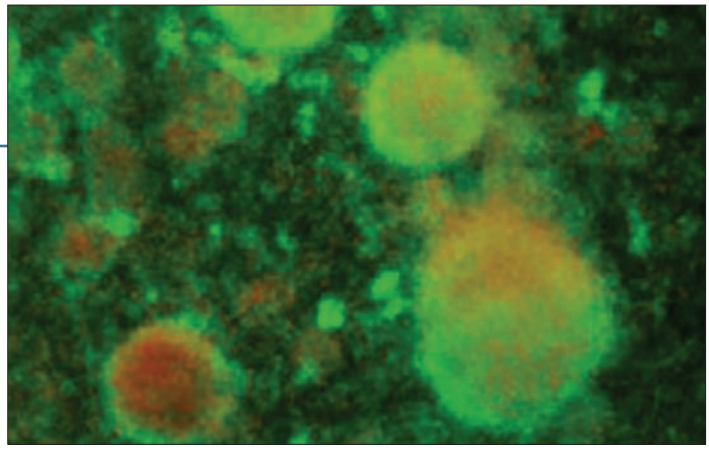
Dopamine is a neurotransmitter, a chemical-signaling molecule in the brain. Patients with Parkinson's have very low levels of dopamine, and this deficiency is responsible for the disease's symptoms of tremor, rigidity, stiffness, slowed movement, and walking problems. Typically, Parkinson's is treated with drug therapy, which often causes undesirable side effects and can lose effectiveness over time, or ablative surgery, in which affected parts of the brain are removed. DBS seems to be more effective than either of these treatments, but no one has understood how it works. Scientists suspected, but had been unable to prove, that DBS increases dopamine levels.

Neurosurgery section chief David Roberts, M.D., a DBS expert, encouraged Lee to do experiments that might help to solve the mystery. In February, Lee and colleagues published their findings in the *European Journal of Neuroscience*. Their paper explains that they showed for the first time that, at least in rats, DBS does increase dopamine levels. Using a technique called amperometry, they measured small changes in electrical current created by different levels of dopamine and detected a sustained increase in the neurotransmitter in the stimulated regions of the brain.

"This is exciting because knowledge such as this can be used to design the next generation of deep brain stimulators," says Lee. He hopes scientists will be able to develop even more effective stimulators by using different parameters, changing the location of the electrodes, or incorporating sensor systems.

Influence: These findings may also be important in understanding how to use DBS to treat other diseases, too—such as epilepsy, depression, bipolar disorder, and perhaps even eating disorders. Just as many of the drugs used to treat these disorders do, DBS, too, may influence the release of neurotransmitters.

Now that Dartmouth researchers have a mechanism to test for even the smallest changes in neurotransmitter levels, they and other scientists plan to continue to explore the possible applications of DBS. "We are just at the beginning of understanding deep brain stimulation and its utility," concludes Lee. KRISTEN GARNER



COURTESY BRUCE STANTON

This micrograph shows the macrocolonies of bacteria that infect CF patients' lungs.

Insight into common CF infection

The breath you'll take before you get to the end of this sentence is probably something you take for granted. Not so someone with cystic fibrosis (CF). Potentially fatal pulmonary infections with the bacterium *Pseudomonas aeruginosa* are common in CF patients. The reason why—long poorly understood—was recently explained by a team headed by Dartmouth physiologist Bruce Stanton, Ph.D., in a paper in the *American Journal of Physiology*.

CF is a lethal genetic disease caused by production of an abnormal form of a protein called cystic fibrosis transmembrane conductance regulator (CFTR), which controls chloride transport in many organ systems. Of CF's assorted symptoms, lung infections are among the most life-threatening. Inhaled bacteria are normally eliminated from the lungs after being trapped in mucus that is cleared by cilia. CF impairs this mucociliary clearance activity, allowing pathogenic bacteria to colonize the lungs. *P. aeruginosa* is the most virulent pulmonary pathogen for CF patients, resulting in chronic pulmonary infections that often culminate in death from respiratory failure.

Postpone: "The longer you can postpone infection," says Stanton, "the better. Aggressive treatment of early infections with antibiotics and physical therapy can help to minimize infection."

But why is *P. aeruginosa* so successful in colonizing the lungs of CF patients? To answer this question, Stanton and colleagues in several other departments tested the effect of *P. aeruginosa* on CFTR function. They cultured epithelial cells from the airways of CF patients and of healthy subjects. In both groups, exposure to the bacteria inhibited CFTR-mediated chloride transport. Bacterial filtrates produced the same effect, suggesting that a product secreted by the bacterium rather than the bacterium itself was responsible. Thus patients with CF, who already have greatly diminished CFTR activity and mucociliary clearance, are further compromised by infection with *P. aeruginosa*.

What are the clinical implications of these findings? "Pseudomonas infection complicates treatment of CF," Stanton explains. "Our findings suggest that it may be necessary to block the effect of the bacteria on CFTR before [using medication to restore] CFTR function. We are attempting to identify the bacterial product so that we can design ways to block its actions." JOSEPH E. MELTON, PH.D.