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ALSAlert

A NEWSLETTER FROM THE ROBERT PACKARD CENTER FOR ALS RESEARCH AT JOHNS HOPKINS

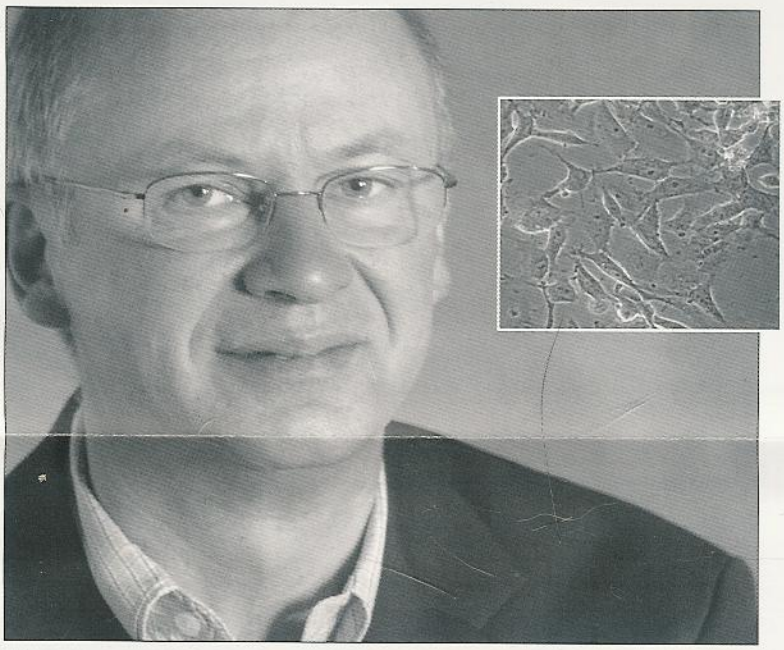
www.alscenter.org

Fall 2006

Excitotoxicity, We Have Ways of Making You Talk

Excitotoxicity. It's a miserable process, this quick chemical cascade—one repeated in strokes, in epilepsy and, yes, ALS. It follows the same steps as nerve cells when they're stimulated, but exaggerates them in a harmful way. Excitotoxicity is certain death to nerve cells.

Questions about the process have dogged ALS researchers. What brings it on? And why, in that disease, is it almost entirely restricted to motor neurons?



When astrocytes whispered secrets of neuron control, Robberecht listened.

Now Belgian scientist **Wim Robberecht** and his colleagues are gathering answers from unsuspected areas. Their work, so new that the journal article isn't yet published—though it's been presented at scientific meetings—is sure to cause talk, in part because it opens virgin territory for ALS therapy. Excitotoxicity is likely an early event in ALS, making it a logical target. It's where Riluzole works, for example, just not in the best way.

So what's been found? First, Robberecht's team has shown that motor neurons vary in excitotoxic vulnerability. Further, that vulnerability can be regulated. Also, whatever does the regulating apparently isn't from motor neurons themselves but from astrocytes, a neuron's neighbor cells.

Early on, the team cultured motor neurons from Wistar and Holtzman rats, two different strains. Then came the first surprise: While neurons of both strains were dotted with the usual receptors that respond to the neurotransmitter glutamate, those in Wistar rats were hair-trigger responsive, Robberecht says. Tests on whole animals showed what that means: Wistar rats are far more vulnerable to glutamate-releasing nerve insults such as stroke. A closer look told why. A small protein subunit in the sensitive rats' receptors—one that damps chemical changes that mark excitotoxicity's start—was in short supply.

What, then, controls supply?

"Astrocytes," says Robberecht. "Somewhere in the soup of molecules secreted by astrocytes, we believe, there's a factor that signals a motor neuron to make this protective subunit for its receptors."

The idea that astrocytes can control motor neuron structure and, thus, their vulnerability is a major find. The hair-raising part comes, however, when the team tested ALS model animals. Control apparently disappears. "In SOD1 rats," says Robberecht, "astrocytes lose their ability to alter the motor neuron receptors in a protective way." ALS, then, may keep astrocytes from being motor neurons' intimate caretakers.

Robberecht's team aims to find how. Meanwhile, he's enthused over ongoing Packard studies of the stem cells that spawn astrocytes: "If you put healthy astrocytes into the spinal cord, could they perhaps correct the mistakes?"

Vantage Point

One great thing about medical science is that it *moves*. You don't sit forever at a plateau. And the moment a shift begins—like a breeze stirring—little can compare with the optimism it brings. Optimism's important; it's pushed many a scientist to the finish.

Now, at the Center, we sense such a shift. The two studies reported in this issue are part of it. One, by Wim Robberecht's team, fleshes out a major role for astrocytes in ALS. Until recently, astrocytes were the nervous system's undercaste cells. Even though they're a hair's width away from motor neurons—suggesting a real relationship—they were seen as scaffolds, a sort of supportive putty for nerve cells. Later, some speculated they helped with nutrition.

But new work shows astrocytes are major players: Sometimes, like neurons, they release the nerve transmitter glutamate. They help maintain synapses. They tie motor neurons into the nervous system. And in Robberecht's work, we see them help motor neurons resist changes in environment—stressful, damaging changes.

Most important, we get the first suggestion that in ALS, something's wrong with the normal conversation between astrocytes and motor neuron receptors.

It's no surprise to us that this new work could dovetail with that of Nicholas Maragakis and Mahendra Rao, who've used Center grants to culture healthy astrocytes from stem cells. Those cultures make studying astrocytes easier and create plenty of cells for trial therapies.

Then, on page 3, Don Cleveland offers perspective for Center studies. By showing that ALS looks to have two phases, an early, gearing-up phase, then full-fledged disease, his work implies that whatever happens to astrocytes happens early on. That makes us want to pour energy into his and Robberecht's efforts. The best therapies stop things from snowballing.

Jeffrey D. Rothstein

Jeffrey D. Rothstein, M.D., Ph.D.
Director, The Packard Center

Tales of Honor

As a girl, **Liz McFarlane** vacationed with family and close friends in Maine. One night, as she and the others constructed a fort out of chairs and beach towels, Steve, a friend's father, sitting cross-legged, read them a story. "We were spellbound," recalls McFarlane.

In 1998, when Steve was diagnosed with ALS, it was the first time McFarlane had seen the disease strike someone she knew. She still felt a tug seven years later, when she became a senior associate director for development for the Packard Center.

McFarlane has found that, like Steve, most ALS patients embrace life and refuse to give up. She's also struck by their candor with her. "It's a high form of intimacy, an honor to be allowed into peoples' lives at their worst moments."

Liz McFarlane: "Meeting with grateful patients and their families is the best part of my job."

Formerly at the University of Maryland as its law school's director of development, McFarlane found her work there had a different feel. Fund raising drew on a built-in affinity for the school. And, even as a development director for the Johns Hopkins Wilmer Eye Institute, McFarlane found that people benefiting from advances in ophthalmology were eager to give back. But with ALS, patients and families face obstacles at every turn.

And yet, she says, donors' generosity abounds—from the simple, spontaneous help of enthusiastic high-schoolers to formal memorial endowments. Their support for the Center is based on positive experiences and the Center's drive to find a cure.

Still, raising funds for a fledgling organization is daunting. It takes at least $3 million a year to keep the Center afloat. The Center can grant out as much money as it raises, minus about $500,000 in operating expenses. Meanwhile, with $4 million in the endowment, interest covers only one research grant.

ALS is a far more complicated disease than McFarlane imagined. But, in her view, it's also more compelling. So is each person's narrative. And, though she can't always control the sadness, "it doesn't stop me. It only makes me want to work harder."

SAVE THE DATE

1st Annual Packard Center 5K & Fun Run for ALS Research

May 5, 2007, 8 a.m.

Power Plant Live! Pavilion, Downtown Baltimore

Sponsorship opportunities available.

Info: Amy Kearney, 410-735-7681

No More Family Secrets

Summers in Vermont were magical for Heidi Erdmann, especially the year she turned 15. That's when she met Curtis Vance, a dishy 17-year-old whose smile and adventurous spirit won her over. By midsummer, they were a couple.

Come fall, the sweethearts went their separate ways. But they spoke and saw each other often. In 1994, Erdmann relocated to Vermont and decided to stay, to be with Vance.

Things were going well for both of them until one day in August 1998, when Vance, then 25, suddenly couldn't lift his right leg. Puzzling symptoms mystified doctors before they made the ALS diagnosis.

That November, when doctors at Massachusetts General Hospital learned that Curtis' maternal grandmother had died at 39 of a strange neurological disease, they dug deeper.

Unknown to Vance, his great-grandmother had shared her family journal with doctors at Mass General. Researchers there both identified the mutation—A4V, on the SOD1 gene—and traced it back to Vance's maternal ancestor, Samuel Farr, who died in 1865 of an unknown debilitating illness. They came to call it Farr's disease, before Lou Gehrig made it famous.

Hearing the family name, "Farr," they told Vance, "We've been waiting for you."

ALS has struck half of every generation of the Farr family. So distraught was Vance's great-aunt that she urged her family not to have children.

Vance, however, refused to take the news as a family curse. Instead, he advanced familial ALS research, becoming an eager volunteer for clinical trials. In October 1999, he and Erdmann launched the Curtis R. Vance Foundation to promote education and funding for a cure.

Heidi and Curtis Vance. "We lived half a century in one year," Heidi says.

"As much as we cursed ALS," says Erdmann, "we grew fond of its teachings. Curtis said the diagnosis actually gave him time to appreciate the little things. We learned how to live while we prepared to die."

The disease progressed rapidly. Still, on Nov. 27, 1999, the couple married before 500 people in Danville, Vt. "We wanted to be united for all eternity," says Heidi. Twenty-one days later, Curtis died.

The years following his death were dark indeed for Heidi. But, later, she met a man—Paul McCann—who helped her through her grief, and in 2003, they married. Today, the family's foundation continues to raise funds for ALS research, including $2,000 for the Packard Center.

RESEARCH UPDATE

ALS's One-Two Punch

Two separate phases mark the disease

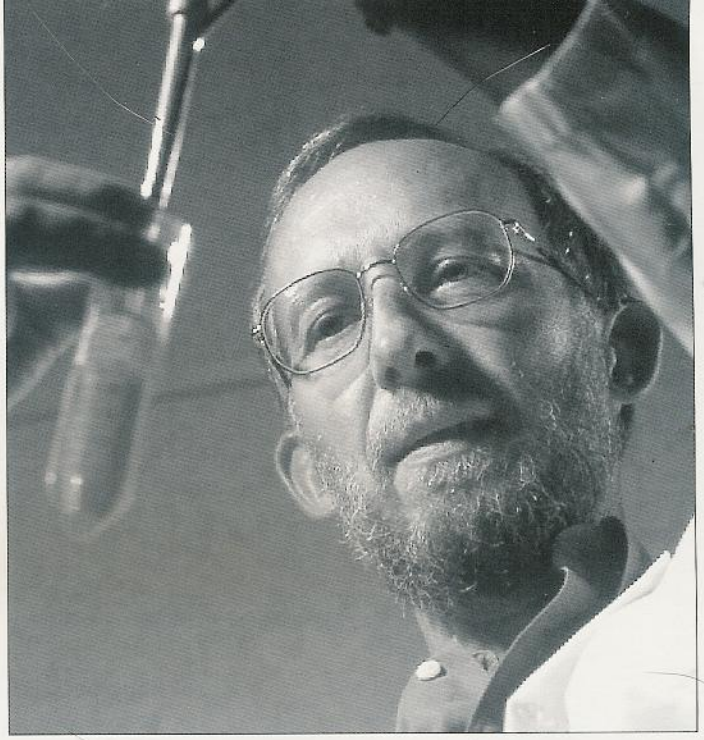
At the Center's spring symposium, researchers clapped hard for a half-minute after **Don Cleveland** spoke. That's something rare. Time is tight at this meeting and the hundred-or-so ALS scientists, grad students and guest experts know that any delay cuts into the question session or the talks to follow. This time, though, they didn't care. Admiration for what Cleveland's team discovered—a significant find—and for the elegant science behind it electrified the room.

For some time, ALS's basic questions have driven Cleveland—ones that can clear away the underbrush on the path to therapy. His team focuses on where ALS starts and how it progresses. They want to know if its early stages and full-fledged disease are part of the same process or are separate and, if so, how.

Last June, in a *Science* article, Cleveland's work clearly suggested that what starts ALS and what keeps it going are distinct. "Knowing ALS has two separate phases more narrowly focuses our search for therapy," says Cleveland, a neuroscientist at the University of California, San Diego. "It also dangles the idea before us that, with the right drugs, stem cells or gene therapy, ALS could become a manageable chronic disease."

Basically, the team observed ALS mice and, one cell type at a time, subtracted that cell's ALS mutation to see what happens. It's akin to pulling out parts under a car's hood to find what makes a horn stop blaring. Cleveland's team first chose motor neurons, using sophisticated molecular techniques and selective mouse breeding to isolate and shut off the mutant SOD1 gene in those cells only. Though the technique isn't totally efficient—only about 30 percent of the SOD1 genes were muffled—the results, Cleveland says, are telling. Disease onset was slowed by 50 days, on average.

By contrast, when mutant genes of the microglia—the immune cells of the spinal cord—weren't expressed, the scientists found little change in disease beginnings. Once it starts, however, what happens is dramatic. Cancelling mutations in microglia almost doubled mouse lifespan.

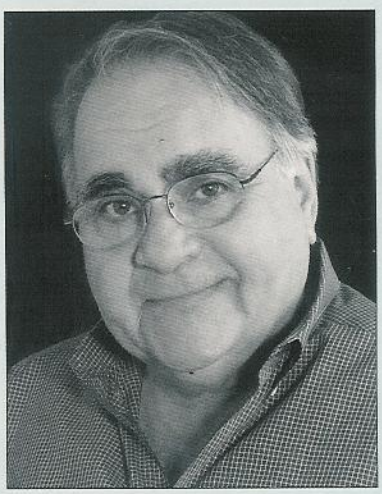


Elegant science marks Don Cleveland's evaluation of different cell types.

"This shows us that at least two cell types contribute to the ultimate toxicity that damages the nervous system," Cleveland explains. Motor neurons matter for disease onset and its early phases. And microglia? Once ALS starts, they're activated; they come to help out. But the mutant gene they carry sets things awry; instead of helping, they actually speed the disease along.

"The benefit to mice was so robust," he adds, "that targeting microglia now makes sense."

FROM THE CLINIC



What about caregivers? Devoted as we are to a cure for ALS, the Packard Center rightly focuses on the disease itself. That doesn't mean, of course, that we lack concern for caregivers or patients.

One Center advantage is our easy access to Johns Hopkins' respected ALS clinic and to a variety of clinicians. So here we talk with **J. Shep Jeffreys**, Ed.D., an assistant professor in Hopkins' psychiatry department and an expert on caregiver issues. Jeffreys is a licensed psychologist, wise about grief associated with chronic or terminal disease. His book, *Helping Grieving People—When Tears Are Not Enough,* is a handbook for care providers. He also offers coping strategies through audiocasts: wwwgriefcast.com.

Look for part two, on patients, in the winter issue.

So you're a rare soul if a loved one has ALS and you don't feel grief?

Well, it would be unusual. A significant grief process begins as soon as someone close gets an ALS diagnosis. Actually, it can start beforehand, with the unsettling symptoms.

Explain what happens.

Caregivers show typical responses when a disease is terminal. They enter a special living/dying interval, drawn into a narrowed world of the patient and other supporters—family, friends. For many, it's a time of "the new normal." Mom isn't able to cook our favorite meals, for example. At first that's abnormal; then it becomes the usual. You redefine what's normal. It's a way to cope.

Along with that goes grief: You mourn that things are changed, that your loved one is less available.

Do caregivers know they're grieving?

Not usually. They know they're dealing with sadness, sometimes depression, anger. But they don't necessarily equate that with grief. There's fear too: *If genes play a part in ALS, maybe I'm at risk!* Or *How will I cope when my wife can't speak?* Such fears can bring on guilt. *I'm not a good daughter/spouse/friend. I should give more time, not think of myself.* We roast ourselves in it. But guilt is often part of loss. It may stem from resentment that life is curtailed. Or from having to have outside help, or because you're upset that ALS drains the finances. Feeling guilt is totally normal. It's how we humans respond. There's nothing bad or crazy or rotten about it. It's just what we do. It's part of the grief process.

What helps?

Not feeling guilty about guilt, for one. For another, you or someone else must sensitize others to the fact that you need breaks, need help with meals, cleaning, shopping. This isn't a time for independence.

A FRIEND INDEED

One Good Turn Deserves Another

Life at the top has never been lonely for George Gordon, managing partner at New York Life Insurance Company's Greater New York division. That might be because his wife, Ilene, has worked by his side since he started his career 34 years ago. And it's telling that his office door is always open.

Not a day passes that the man responsible for roughly 500 employees isn't talking to them—from support staff to agents. He wants them to understand the intricacies of the policies they're selling.

At the same time Gordon wants employees to feel comfortable discussing anything with him. "We don't lose agents because they aren't making sales," says Gordon. "They stop working because of personal problems. If things aren't going well for you at home, nothing else matters."

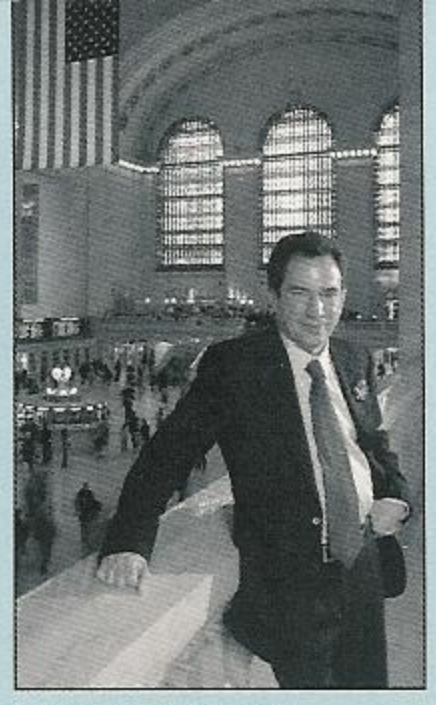
At 60, Gordon isn't shy about sharing his mistakes and triumphs to help others going through a rough time.

With the same openness and grit, Gordon wrote a letter to his employees announcing his greatest personal challenge: living with ALS. Diagnosed in December 2005, Gordon wrote: "I am hopeful, and I am counting on you to continue to strive for excellence."

Gordon's colleague Sal Farina, managing partner of the Long Island office, was especially saddened by the news. He'd heard about ALS from his sons, whose teacher at Northport High School had been diagnosed with the disease. Beyond sponsoring a table at a Northport High event in Gordon's honor, Farina wanted to find a lasting way to recognize his longtime mentor—the man who always sent plants and congratulatory notes as Farina advanced in his career.

He asked Phil Hildebrand, executive vice president of New York Life, permission to send out a solicitation letter for ALS research in Gordon's honor. And what began as a $3,000 fund-raising goal morphed into well over $48,000 in checks for Packard Center research. Hildebrand, who shares Farina's admiration for Gordon, raised additional funds to make it an even $50,000.

And, for once, observes Farina, grateful colleagues from New York Life's family could reciprocate Gordon's generosity and support.



George Gordon, the approachable executive.

THE BIG BOARD

Olympian Feats

In the summer of 1999, as Anne Martin packed for vacation, the phone rang. "I have terrible news," said her good friend and mentor, Bob Packard, from San Francisco. "I have ALS."

"What's ALS?" asked Martin.

From that moment, Martin searched the Internet, troubled by how little was known about ALS and the lack of a streamlined approach to finding a cure.

Meanwhile, Packard flew to Baltimore for a confirming diagnosis from Johns Hopkins neurologist Jeffrey Rothstein. Packard, then 41, learned he had an aggressive form of ALS and, though saddened, left inspired by Rothstein's resolve to find a cure.

Martin and Packard spoke daily about how to build momentum for ALS research. They knew it would require millions of dollars and come too late for him. Still, recalls Martin, "Bob wanted something positive to emerge from the despair."

Financial savvy—and drive—came naturally to both of them. Packard, an investment banker with Deutsche Bank (Alex. Brown & Sons), and Martin, Deutsche's senior banker in media and technology, had overseen high-profile financing and mergers together for eight years. She'd taken a leave of absence from her job just weeks before Packard broke the news.

By July of 2000, Packard, aided by family and friends, had raised more than $3.5 million through the Robert Packard Foundation, established in December 1999. Taking over for Packard as president, Martin joined forces with the Emily Davie and Joseph S. Kornfeld Foundation, led by Chris Angell. Together they launched the Packard Center, a novel collaboration of scientists that now also bears his name.

One month later, Packard died, but Martin, married and with new twin sons, poured more energy into the new Center. "Building the right team and reputation for good science," she says, "was vital."

Martin understands teamwork. She carted off medals at the 1985–1987 World Rowing Championships and was on the 1988 U.S. Olympic rowing

Anne Martin champions Bob Packard's mission

team. There she met rower John Pesc tore. They married in 1989 and move to San Francisco.

Today, Martin works at Yale Univer sity's investments office and flies to California for the annual Packard Cu golf tournament she helped launch in 2003. The tourney has raised more than $1.4 million for ALS research. A chair of the Center's board of governors, Martin is hopeful. "The Center is demystifying ALS and is pinpointi real therapies." Bob Packard, she add would have agreed.

ALS Alert

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