

## SPECIAL REPORT

## Trials & Tribulation

### The Hope for a Cure

By Mary Mashburn

Joan Talmage and her friend Wilma learned to play golf together in Mount Vernon, Ohio, heading out into the sunshine to talk and work on their game. Over the years, they kept in touch, even when Wilma and her husband moved hundreds of miles away.

When Wilma developed the progressive and fatal neuromuscular disorder amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, Joan talked to her frequently on the phone, listening to the details of Wilma's earliest symptoms, sharing the pain of her failing health. In 1997, several years after Wilma's death, Joan noticed a strange flapping of her foot when she walked the dog. She thought about the terrible muscle cramps she had been having in her legs. She thought about Wilma.

Joan Talmage knew that somehow, she, too, had ALS.

**Joan Talmage with  
her doctor, ALS  
researcher Jeffrey  
Rothstein**

Photo by Will Kirk



Her internist told her she was wrong, but the symptoms persisted, and eventually Joan saw a young neurologist who confirmed her fears. A family friend encouraged her to see Jeffrey Rothstein at Johns Hopkins, a leading ALS researcher

and clinician, for a second opinion. The test results were unequivocal: Joan, like her friend Wilma, would face the ravages of a disease with no cure, a disease diagnosed in only about 5,000 people a year in the United States.

Treatment options for ALS patients are few. The FDA has approved just one drug, Rilutek, and that only prolongs life by a few months. Inexorably, the motor neurons in the brain and spinal column die; the muscles they feed falter and then waste away, leading to paralysis of limbs and vital organs. Thinking ability and sensory perception are unaffected. About half of people with ALS die within three to five years of diagnosis; others may choose to live on a ventilator when they are no longer able to breathe on their own.

For someone with ALS, hope for staving off the disease hinges on a scientific breakthrough: a drug or drug cocktail that prolongs life or, better still, a gene therapy to stop the disease in its tracks or stem cell therapy to reverse the disease's progress. A clinical trial would likely be the only timely way to get such cutting-edge treatment. It is that hope that fills the waiting room in Hopkins's Outpatient Center with people like Joan Talmage.

Talmage and her husband, Jim, have been traveling from their retirement home in South Carolina to see Rothstein since 1997, first by plane when she could still walk, now by van as she relies on a wheelchair to get around. Sitting in the waiting room during a recent clinic visit, Talmage is, in a word, charming—her fashionably coiffed head tilting to better listen to the story of the man in the wheelchair beside her; her lambswool sweater and tweed skirt appropriate for lunch at the club. But despite the soft appearance, her blue-gray eyes are unflinching, the well-modulated timbre of her voice unflinching as she describes life with ALS.

For a time after her diagnosis, she could still play golf, using leg braces to help her balance. Last April, she fell at home, breaking both ankles. Her leg muscles continue to deteriorate, so she has moved from braces to walker to wheelchair. But she counts herself fortunate: "I ride my wheelchair to the club by myself for my three bridge games a week. I can still shower and dress myself. Life is still good to me."

When Talmage first came to Hopkins, she was asked whether she wanted to take part in a clinical trial for a new drug, Xaliproden, that held some promise for slowing the disease. She didn't hesitate: "I just thought, and my family thought, that maybe this would be a breakthrough."

To date, clinical trials for ALS treatments have offered more hope than positive results. The Phase III trial for Xaliproden was inconclusive; the positive effect demonstrated was not statistically significant enough for the manufacturer to seek FDA approval. Talmage received a placebo during the trial; when it ended, she was given the opportunity to take the drug because of her participation in the trial. Despite the disappointing results, she elected to take Xaliproden: It has few if any side effects, and there's a chance it might help to slow disease progression.

Rothstein's lab currently pursues two lines of research that hold promise for a more significant treatment for ALS. Since 1992, Rothstein has been tracing the role decreased levels of the protein EAAT2, which helps to regulate the nerve messenger glutamate, play in ALS. By developing a therapy to repair the body's inability to regulate glutamate, Rothstein believes, the cascade of nerve damage could be slowed or stopped. The other line of research--and the only hope for replacing the motor neurons that have already died--is stem cell therapy.

Rothstein and researchers like him don't lack for people eager to offer their bodies for research, despite the risks. And more and more, people with ALS and their families and friends also offer money --private funding for research unlikely to be funded by more traditional sources such as the National Institutes of Health.

"All our stem cell research is Project ALS funded," Rothstein notes, referring to a family foundation started in 1998 by three sisters. "You just can't go to NIH and say 'I've got a neat idea.' You have to say, 'I've done a lot of experiments that prove my neat idea is worth doing.'"

Because of private money, Rothstein now has the necessary data; he recently submitted his first grant proposal for stem cell research to NIH. The bottom line, he says, is that private funding "means we have the money to make sure a treatment moves faster to patients. If this goes to patients, we've shaved off at least two years, and if we're lucky, and it somehow leads to a cure, every year that we shave off, that's thousands of people saved."

But the money for novel research, and the willingness of patients to participate, can't distract from the basic safety and efficacy concerns of clinical trials. "When patients say they'll be guinea pigs, they're ignoring what I as a physician can't ignore: that we may find that it's a negative, that it will be very hurtful," says Rothstein. "I might put stem cells into a patient and two days later they're completely paralyzed, or worse, they'll suffer from the worst pain you could imagine and there's nothing I can do, because it's inside the spinal cord."

Still, Joan Talmage and her family, like so many others, hope for a breakthrough; they hope it comes in time. "Because of Wilma, I know what's going to happen down the road. You're going to die from this disease. There's no cure," says Talmage, her voice low. "I'd be selfish enough to hope a new treatment would work, but if it didn't, I'd hope my trying it would help the next person."

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