

THE NEW YORKER

NOVEMBER 10, 2003

ANNALS OF MEDICINE

THE REEVE EFFECT

Can an actor's determination to walk again change the way medical research is conducted?

BY JEROME GROOPMAN

The home of the actor Christopher Reeve is in the middle of horse country. He lives in Westchester County, down a winding country road that takes you past several estates with stables and riding tracks. At the end is a sprawling farmhouse set on a hill and surrounded by spruce and oak; a graded incline provides wheelchair access to the front door.

It has been eight years since Reeve broke his neck at an equestrian competition in Culpeper, Virginia. After his horse, Buck, stopped suddenly in front of an obstacle, Reeve flipped forward and suffered what doctors call a "hangman's injury": a fracture of the upper cervical vertebrae. Death by hanging often results from suffocation, and Reeve was heard to say, "I can't breathe."

The crushed vertebrae caused massive hemorrhaging within Reeve's upper spinal cord. The location of a spinal-cord injury determines its consequences. Indeed, a minute difference in the trajectory of Reeve's fall would have left him in dramatically different circumstances. An MRI scan that Reeve received after his accident suggested that if he had landed with his head one-sixteenth of an inch to the left he would have died instantly. An impact slightly more to the right would have left him with a concussion, and he would have been back on his feet within weeks.

Reeve's injury left him paralyzed from the shoulders down. He was unable to breathe on his own, and doctors at a Virginia hospital immediately placed him on a ventilator. Reeve was informed that his injury was permanent, and that he would no longer feel sensation in ninety per cent of his body.

Upon arriving at Reeve's front door, I was greeted by an assistant—he employs several—and led to his office, where he sat waiting in his wheelchair. On a shelf behind him were pictures of his wife, Dana, and his three children, and a large blue button that read "PROUD YALE PARENT." His daughter Alexandra is the captain of Yale's polo team. The Reeves are clearly not a superstitious family.

This spring, an experimental electrical-stimulation device was implanted in Reeve's diaphragm, and he now breathes without a respirator for hours at a time, so his speech has become more fluid and his voice more resonant. He gasped only occasionally. Reeve weighs two hundred and seventeen pounds and is six feet four, and even in his motorized wheelchair he looks imposing. The most striking change in his appearance has nothing to do with his accident. Reeve has alopecia areata, a condition that causes patchy hair loss, and in February he had his head shaved.

"I was told from the very start that it was hopeless, that it was impossible for me to regain movement below the shoulders," he began. "But every scientist should remove the word 'impossible' from his lexicon." Not only does Reeve want to cure himself; he is determined to transform medical research, which he feels is constrained by excessive caution. "Research should not be reckless," he said, but it

does need to be fearless. “If you don’t add courage to the equation, the scientific aspect will go to waste.”

In his 1998 autobiography, “Still Me,” Reeve writes that he has a controlling, perfectionist nature. As an actor, he would obsessively analyze his scripts, looking for moments that could trip him up. Before the Culpeper contest, he walked the cross-country course three times and drew a map, with extensive annotations. In our meeting, he displayed a similar tendency—his words were as carefully chosen as those of a Presidential candidate.

Soon after we began talking, Dana, who is an actress, carried in a tray with some lunch—turkey with sliced cucumber. (Reeve can eat whatever he likes.) As a nurse assisted him with his meal, he described the progress he has made since he began a regular, intense physical-therapy regimen, in 2000. “I am able to use the biceps of my right arm against resistance,” he said. “My left arm is weaker. Perhaps my strongest and most remarkable recovery has been in my legs.” I noticed that his lower body did not appear to be as shrunken as that of the typical quadriplegic.

During our conversation, Reeve was largely immobile. The only movements I saw were hand gestures; he would lift his index finger and point it, often without any hesitation or visible effort. He saves greater physical exertions for his therapy sessions. I asked him if he could move his legs. “A bit,” he said, adding that he now exercised regularly in a swimming pool. “I can push myself off the side with my legs. And I can make a snow-angel movement with my arms.” The buoying effect of the water, Reeve explained, helped him make the slow, sweeping motion.

“One day, I expect to get up from this wheelchair,” he said. This claim, which Reeve has made often in speeches, has not been well received by certain scientists and advocates for the disabled. Some critics attribute his words to a state of denial; others have been more caustic, calling him a spoiled celebrity who raises false hopes. The columnist Charles Krauthammer, who is wheelchair-bound and has a medical degree, wrote an angry appraisal of Reeve after the actor appeared in a television commercial touting advances in spinal-cord research; the ad used computer imagery to make it appear as if Reeve could walk again. Calling the ad “disgracefully misleading,” Krauthammer wrote, “In Reeve’s view, reality is a psychological crutch. His propaganda to that effect undermines those—particularly the young and newly injured—who are struggling to face reality, master it and make a life for themselves from their wheelchairs.”

Reeve is aware that his intention to recover has been dismissed, even denigrated. Yet he is not as naïve as some of his doubters think. Reeve has a dogged intelligence, and in the past eight years he has developed a nuanced understanding of the biology of spinal-cord injury; he has learned how the scientific establishment sets priorities and conducts its research; and he has deciphered the ways that different branches of the government permit or bar innovative medical treatments. Reeve knows that his fame gives him unique access to the media, to politicians, and to fund-raising dollars. By exploiting these resources, he has set out to change the way things are done in the clinic, the laboratory, and the government. He believes that only by causing a revolution in all three realms does he have a chance.

It is perhaps easy to view Reeve’s quest as one driven by hubris; it is far from certain that he will walk again. However, the steady, incremental progress he has made is extraordinary and, to many scientists, confounding. Indeed, the results have been so encouraging that mainstream researchers are reconsidering the dogma that long-term paralysis is irreversible—and paralyzed patients around the world are beginning to follow Reeve’s lead.

The spinal cord is about an inch in diameter and has a soft, jellylike texture; it is protected by the long chain of vertebrae. The cord houses millions of nerves, which transmit crucial signals between the brain and the rest of the body. Extending from each nerve cell is an axon, a comparatively long, threadlike projection that can convey signals to a neighboring nerve, creating a pathway. Some of the nerve

pathways that pass through the spinal cord help control muscle movements and regulate blood pressure; others allow us to feel pain, touch, and temperature.

When a fracture dislocates the spine and shatters the vertebral bones, small hemorrhages from broken blood vessels seep into the viscous tissue of the spinal cord, resulting in swelling. Since the cord is contained within the bone of the vertebral column, there is little room for expansion, and the circulation of vital oxygen and nutrients is cut off. Nerve cells within the cord are starved. As these cells die, they release toxic chemicals, particularly glutamate, an amino acid that overexcites the surrounding nerve cells, causing inflammation. That is why Reeve was given an intravenous dose of methylprednisolone, a steroid, shortly after the accident. In a 1990 study, a team led by Dr. Wise Young, a neuroscientist at Rutgers University, showed that a prompt dose of methylprednisolone could limit inflammation and spinal-cord damage.

Even after methylprednisolone therapy, many surviving nerve cells in the damaged spinal cord begin to die. This process is poorly understood, but it is believed that the cells, programmed to sense a hostile environment, self-destruct. A bruised spinal cord resembles a landscape after napalm: one axon after another has been turned into a severed stump. Where cells once resided, large cavities develop that fill with fluid. Over time, the inflammation subsides, but scars form, further distorting any surviving nerve pathways.

Reeve spent thirty days at the hospital in Virginia. “In 1995, it was considered a miracle that I survived,” he said. His heart stopped beating on the way to the hospital; in the days after his resuscitation, he developed pneumonia, a urinary-tract infection, two ulcers, and skin lesions. He considered committing suicide, but Dana helped change his mind. “Chris had to make his own decision,” Dana told me. “I was very clear that I was in it for the long haul. I said, ‘You’re still you, and I love you. Let’s give it two years, and if in that time life is too agonizing let’s reevaluate.’ ”

Reeve was transferred to the Kessler Institute for Rehabilitation, in West Orange, New Jersey. Like all new patients at Kessler who have suffered a spinal-cord injury, Reeve was given an instruction manual to orient him to his new life. “I read the manual in its entirety, and there was nothing in it about an injury like mine,” he said. Patients like Reeve were not expected to live long.

With Dana’s help, he began to investigate different approaches to rehabilitation. “I was the link to the outside world,” she said. “I was like a chief of staff. We were bombarded with information and offers of help. Once he was able, he grabbed the reins and took over.”

Nearly everything that Reeve read asserted that patients like him could not improve. He eventually discovered, however, that a few physicians and neuroscientists had taken a contrarian position. One was V. R. Edgerton, a neuroscientist at U.C.L.A. Edgerton had theorized in the early eighties that the spinal cord could function independently of the brain. This was at odds with the prevailing view that the spinal cord was merely a cable connecting brain and body. “When scientists think they know how something works, it becomes difficult to get new ideas accepted,” Edgerton told me. Virtually no decent scientist would study spinal-cord injury. “The dominant view was: it’s a hopeless situation,” he said. Spinal-cord-injury research was considered “the graveyard of neurobiology.”

Edgerton began experimenting with cats whose spinal cords had been cut with a scalpel midway down their backs. The injured cats were placed in a harness and put on a treadmill. The idea was to make the cats mimic normal walking, to see if inducing such repetitive activity could reawaken circuits that Edgerton believed had been shut down by the injury. The experiment was a success: after using the treadmill for three to six months, most of the cats could walk again.

Later work in Edgerton’s laboratory showed that glycine and GABA, amino acids that inhibit communication between neurons, flood the spinal-cord area after an injury; with repetitive activity on the treadmill, the levels of these amino acids fall. “Another interesting aspect was that only those

networks that you train improve,” Edgerton told me. When the cats were trained expressly to stand up, they were unable to walk, because they had not been taught how to step forward.

In a paper, Edgerton called the neural structure in the lumbar spinal cord a “central pattern generator.” This generator was like a small computer, he suggested. Not only did it govern subconscious motor activity like walking but it had a form of memory, which could be reactivated through rehabilitation.

“He couldn’t sell this idea anywhere,” Reeve said of Edgerton’s argument. “But he kept at it at U.C.L.A., and it made perfect sense to me. It doesn’t take much brainpower to walk. Walking is almost autonomic.”

In the late eighties, Dr. Anton Wernig, a neurophysiologist at the University of Bonn, in Germany, decided to find out if Edgerton’s results with cats could be reproduced in humans. For his study, Wernig selected patients who had severe but not total cord damage: their ability to move was markedly limited but they were not completely paralyzed. As he began to recruit patients, including quadriplegics, he met with resistance from other physicians. “They said, ‘Why the hell do you want to have them walk?’” he recalled. “I realized that if there is no interest in experimenting with people with spinal-cord injury, there will be no data.”

Wernig’s experiment was inspired by the observation that when newborn babies are held upright, their toes touching the ground, they spontaneously move their feet in a stepping motion. To him, this suggested that there was an innate “program” within the human spinal cord for walking; perhaps this program could be retrieved, like an intact file on a damaged hard drive.

Wernig spent the next several years refining ways to help patients perform patterned activities on a treadmill: optimizing the harness, foot weights, and, most important, the speed at which the paralyzed person steps. Some of Wernig’s patients underwent therapy within a few weeks of their injury; others had been injured years earlier.

In 1995, Wernig published a controlled study that included thirty-three patients who had been wheelchair-bound for an extended period. After completing Wernig’s regimen, twenty-five patients were able to walk independently, seven could walk with help, and one did not improve. Of the control group, which received traditional physical therapy, only one was able to walk unassisted.

Reeve was excited when he heard about such daring research. He decided that he was going to begin aggressive physical therapy, but he soon realized that his body wasn’t ready. “It took most of the summer of 1995 to become stabilized enough to do *any* form of exercise,” Reeve told me. “I was quite fragile. By October, 1995, I was able to begin therapy at Kessler.” The doctors at the rehabilitation clinic introduced him to a process known as “e-stim.” Reeve lay on a bed, electrical wires attached to the muscles in his buttocks, thighs, and calves. A computer program sequentially stimulated these muscles to re-create the sequence of contraction and relaxation involved in physical exertion. Reeve was retraining his body to perform work.

More important, Reeve began riding a specialized stationary bicycle while electrodes stimulated his lower body to perform pedalling motions. This exercise, which gave him a cardiovascular workout and increased his bone density, offered a crucial combination of patterned activity and electrical stimulation. In 1998, Reeve began working on a treadmill without electrical assistance. With the help of physical therapists, he was placed in a harness and his torso was held steady while aides guided his feet on the treadmill. This patterned activity was aimed at reawakening the preset circuitry for walking within his spinal cord.

Despite these efforts, there was no clear change in Reeve’s condition. In retrospect, he attributes the lack of progress during the first five years of his injury to his own inconsistency in exercising. He had thrown himself into a number of creative projects, such as writing his autobiography and directing “In

the Gloaming,” a film for HBO. When he wasn’t working, he was often too sick to exercise. Like most quadriplegics, he suffered life-threatening medical complications that required prolonged hospitalizations. He developed blood clots behind his knees; he required treatment for a collapsed lung. “Once, I was dropped while being transferred back from the bike to the wheelchair, and my humerus snapped like a matchstick,” Reeve recalled. To stabilize his arm, doctors inserted a titanium rod extending from the top of his shoulder to his elbow.

Reeve kept pursuing a contrarian but scientifically grounded approach to recovery. “My faith is in science,” he told me. In 2000, he began a more consistent exercise regimen on the electrical-stimulation bike. When he first started on it, he could pedal for only five minutes; now he was pumping for a half hour or more.

Within several months, Reeve began to show improvement. One summer night, when Dana cuddled next to him in bed, he realized that he could sense her touch. In September, he was talking to Dana and making an emphatic point when, suddenly, his left index finger rose up.

“Are you doing that on purpose?” Dana said.

“No,” Reeve said.

“Why don’t you try?”

He did, and he moved his finger again. (Or, as Reeve put it, with clinical detachment, “It responded.”)

In November, at a conference in New Orleans, Reeve met with John McDonald, an ambitious spinal-cord researcher at Washington University in St. Louis. McDonald agreed to supervise his therapy, and that winter, for the first time since his accident, Reeve entered a swimming pool. Around this time, Reeve found that he could wiggle the toes on his left foot. “The sequence didn’t make any sense,” he said. “So I thought, Why shouldn’t I try everything?” In 2001, Reeve discovered that he could move his right leg slightly when lying on his back. His left leg revived next. Finally, Reeve’s arms started to respond; he still can’t lift them while sitting up, but his exercises in the pool are making them stronger. His workouts are now so rigorous, he told me, that he often feels muscle burn afterward.

Reeve’s drive to heal himself is so relentless that he doesn’t allow himself to experience elation at these achievements. “I say to myself, ‘Now, what’s next?’ I know I have a long way to go.” He paused. “It’s much like being an astronaut. They know the drill and all the possible contingencies so well that the flight is almost anticlimactic. Neil Armstrong even calculated what he would say when he landed on the moon. They spent hours deciding what his phrase should be. They didn’t want astronauts to let their emotions get the better of them.”

Upon achieving a milestone, he says, his mind is filled not with wonder but with data that he can “report back to mission control.” When I asked him about the thrill of floating in a pool again, he responded dutifully. “The first time I went in, I felt grateful, and I felt muscles in my lower back release and I entered a very relaxed state of mind,” he said.

When Reeve is in the pool, he puts his legs up against a side wall while a therapist stands behind him, pushing against his shoulders. “He really has to dig in to resist me,” Reeve told me. “My therapist ends up standing with one leg in front of the other, knees bent, to have a solid base of support to offer maximum resistance.” At Reeve’s request, the therapist goads him, saying, “You’re pathetic!” or “What happened to your legs? They didn’t show up this week?”

McDonald sounds far more ebullient than Reeve does about his progress. “The adage was you’re going to get most of your recovery in the first six months, and if you haven’t gotten it by then, you’re over,” he told me. “As far as I know, no human being has *ever* been reported to have substantial

recovery after two years when he had no recovery in the beginning. Chris shattered that myth. That's really the take-home message, that a very delayed but substantial recovery is possible, even in the worst-case scenario."

McDonald's association with Reeve has allowed him to create a flourishing rehabilitation institute in St. Louis. Forty patients are now undergoing treatment. McDonald recently started a pediatric program. "I credit Chris with leading me down this path," he told me.

In 2001, McDonald began studying groups of paralyzed patients. He discovered that patients who used the electrical-stimulation bike had fewer pressure sores, blood clots, and infections. "The best way to avoid skin breakdown is put two inches of muscle on your buttocks," McDonald said. "The best way to build bone density is to put radial forces on bone. The bike is the best way to do that."

McDonald also conducts research on animals. In one experiment, he severed the spinal cords of rats, then implanted an electrical-stimulation device in their hind limbs. The device produced a gaitlike behavior in the animals. The animals with the device were dissected; compared with animals in the control group, they showed a sixty-to-eighty-per-cent increase in the development of cells that mature into neurons. McDonald believes that a similar process of nerve regeneration is taking place inside Reeve's body. McDonald's research, which will be presented at a meeting of the Society for Neuroscience this weekend in New Orleans, is some of the first documented evidence that functional electrical stimulation can inspire neurons to regenerate.

Claims about Reeve's recovery were initially met with skepticism by scientists. Some wondered whether he was simply what is called "an outlier"—a rare case that is nearly miraculous but essentially irrelevant to understanding the biology of the problem. To counter such doubts, McDonald and Reeve have rigorously documented both his progress and that of other patients who are undergoing similar treatment. "I made at least four visits to Washington University, and then also Dr. McDonald came here at least three times," Reeve told me. "So I'd say I've had a minimum of seven evaluations."

In 2002, after Reeve regained sensation in his left foot, his neural pathways were studied using MRI imaging. At the same moment that the bottom of his left foot was touched, his brain was scanned, in order to determine what part of the cerebral cortex registered the sensation. To assess his motor function, he voluntarily moved his index finger while inside the MRI machine. Reeve's restored perception and movements were shown to be controlled by the same parts of the cortex used by healthy adults. "My brain did not need to reorganize to get the functional recovery that I have had," Reeve said. Some of Reeve's neural pathways controlling muscle movement might have remained intact despite the severe trauma, and exercise finally reawakened them. Possibly there had been regeneration in the spinal cord, and the new nerve cells had made the right connections. McDonald can't explain it precisely; Reeve's case remains mysterious.

"No one is sure yet what is the exact explanation," Reeve said, then grinned. "If I were a mouse, they could sacrifice me and take a look. But let's wait a few years before we contemplate something like that."

In other tests, Reeve's foot was placed on the shoulder of a physical therapist; his knee was then bent to a ninety-degree angle. He pushed and straightened out his leg against the therapist's resistance. McDonald used an electronic device to gauge how quickly Reeve's muscles responded to the therapist's command to push. The "conduction velocity" for this voluntary contraction of his quadriceps was normal.

"You know what's remarkable?" McDonald told me. "I just recently saw him, and he's continuing to progress. He hasn't even plateaued." Reeve's bone density, he noted, is also now in the normal range.

His muscle strength is around eighty per cent. The key challenge that remains, McDonald said, is for Reeve to develop the coordination and balance to use his muscles effectively.

When I updated Anton Wernig on the progress Reeve had made—in particular, his ability to push off with his legs and make snow-angel movements in a pool—he said it was “shocking.” He was also cautious: it was still difficult to prove that all the changes were related to the rehabilitation program. “We have no information on people like this,” he said. “We would need a control group to absolutely show that the recovery could not be spontaneous.”

McDonald also recognizes that an experiment of one has limited value. Accordingly, he now has clinical results on muscle mass and bone density for twenty patients treated in St. Louis with patterned-activity therapy. He will soon be submitting the data for publication. Exercising on the electrical-stimulation bike three times a week for an hour restored patients’ muscle mass and strength substantially. Bone density increased to a level where fractures were unlikely. McDonald believes that one reason paralyzed people have never regained significant movement is that their bodies are so severely atrophied; even when nerve pathways do reawaken or regenerate, there is no muscle left to do the work.

McDonald will also soon report that the twenty patients have experienced a significant restoration of sensation. “They have some proprioception,” he said, meaning that they know where their body is in space. “And they can feel pain, which is important in avoiding injuries.”

One of McDonald’s youngest patients is Jessica Hill, who just turned six years old. She was born prematurely and developed meningitis. The infection led to a stroke in her spinal cord; the blood vessels that feed the cord tissue shut down. “When we brought her home from the hospital, she was paralyzed,” her mother, Leann, told me. “She had nothing from the nipple line down, no feeling, no movement. She was like a wet noodle, just hung down straight.”

The Hills live in St. Jacob, Illinois, across the Mississippi River from St. Louis. Kevin Hill does road maintenance for the neighboring city of Troy, and Leann is a housewife who works part time in a restaurant. “None of the doctors would give us anything for the future,” Leann said. “There was nothing about exercise, nothing about making her muscles stronger, nothing about what her potential might be. The doctors were from the old school. The therapist would just stretch her limbs so that her muscles wouldn’t tighten up.” When Jessica was two years old, the Hills saw a television program about John McDonald and the St. Louis clinic. McDonald agreed to enroll the child.

Initially, Jessica was placed in a Big Wheel tricycle, with her legs strapped to the pedals. Her parents pushed her around the house to simulate bike exercise. Later, Leann and a neighbor rigged a motor to a stationary bicycle. They also got a treadmill, strapped Jessica in a harness, and weighted her feet to show her how to step and walk. “We did the treadmill as many times a day as we could,” Leann recalled. Insurance would not pay for the treadmill, she added, so the family held a benefit to cover the cost.

After six months of intensive patterned activity, Jessica exhibited twitches of spontaneous movement in her hips. Then she began responding to touch. “At first, when we tested her by giving her little pinches over her chest, she couldn’t feel anything,” Leann said. “Then she could just feel it towards her belly button, and then farther down. Now she can feel stuff everywhere.”

Jessica has also started to move her limbs. “When she sits over the edge of a table, she can swing her legs back and forth,” Leann told me. “In the pool, she can lift her feet up and down. Jessica can also crawl across the floor on her own, propelling herself by her legs.”

I asked Leann what she thought about Christopher Reeve. “Every step that he makes, that he moved a finger or moved a toe, for us, we know how incredible that is. That would be like me running a marathon. Seeing the progress he is making, it keeps us going.”

Critics note that Reeve has financial resources that far exceed those of ordinary families. I asked him how he pays for the team of eighteen people, from nurses to physical therapists, who regularly assist him. (His annual medical expenses exceed five hundred thousand dollars a year; his insurance covers two-thirds of that.) Before the accident, Reeve explained, he was a member of three unions, and his disability benefits were unusually large, totalling some four million dollars. He also receives free equipment from manufacturers who hope to draw attention to their products; one company gave him an electrical-stimulation bike, which cost a hundred thousand dollars, for home use.

Reeve is unapologetic about mobilizing his resources to sustain his life and spur his recovery. He points out that he has worked tirelessly to encourage bold scientific research. To help ordinary families, he argues, exotic experiments need to become everyday procedures. And Reeve believes that too many researchers lack a sense of urgency.

As Reeve became acquainted with the scientific community, he grew frustrated by the widespread careerism. “Professors with tenure submit a grant application to get a little bit of money to try to have a little bit more success, which would then get them another grant and then another few years to achieve another little bit of success, but not to launch a major preemptive strike to get rid of the whole problem,” he said. Later, he added, “I want things to happen quickly. I certainly want to benefit within my lifetime. I don’t want to get out of this wheelchair at the age of seventy-five. I am fifty-one, and am now very healthy, and would like to be out of the chair very soon. I’m not willing to resign myself to being an advocate for research that will benefit people only after I’m gone. I’m not that noble.” He laughed, but it wasn’t a joke.

Reeve has begun to confront scientists directly, speaking at major conferences about his concerns. Recently, he gave a speech at a meeting of neuroscientists, and said, “I would really like it if, on your way home from the laboratory one evening, you would stop by a rehabilitation center, and watch those people lying on mats, trying to move an arm, or even just a finger, or trying desperately to sit up. And then take that vision back with you to work the next morning.”

Such exhortations don’t always charm his audience. “You know, a lot of the scientists were very offended by that speech,” he recalled. “They were offended that I would tell them how to do their work. They were offended by the implication that they didn’t care. But what I’m saying is that some are not working fast enough.” Reeve doesn’t mind if he comes across as irritating or even bullying. “I have nothing to worry about with respect to their reactions. My injury taught me to throw caution to the winds in terms of what I say. It’s extremely liberating, actually. Because, really, what do I have to lose? There is not much more you can do to me.”

Last month, the Lasker Foundation, which is dedicated to the promotion of scientific research, gave Reeve an award for “heroic advocacy for medical research in general and victims of disability in particular.” In his acceptance speech, Reeve said that the award had offered him “encouragement to be even more annoying and difficult in the future.”

When I spoke to scientists, many complained that Reeve’s impatience could lead to premature conclusions or faulty data. Nobody, however, would speak on the record. “He has gotten impatient when he’s heard the answer ‘We don’t know enough,’ ” one researcher said of Reeve. “You can almost hear him say, ‘Well, you’re not the one on the respirator.’ And yet doing something just because someone’s situation is desperate—that’s not acceptable.” *Nature*, the scientific journal, published a news article last May about how researchers felt pressured by Reeve and other advocates. When I showed him the piece,

his tone was icy. “If we push, that’s our prerogative,” he said. “And scientists, of course, have the right to push back.”

Early on, Reeve realized that it would take more than rhetoric to move the scientific establishment in the direction he wanted. Science is fuelled by money. Soon after the accident, he began working with the American Paralysis Association, a charity; by 1999, it had become the Christopher Reeve Paralysis Foundation. He now leads the organization, which offers more than thirteen million dollars in grants each year. Reeve has used this power to change the way spinal-cord research is conducted.

One of the vexing problems in the field, he told me, is that few researchers use the same animal models or techniques. Some work on rats; others experiment on mice or cats. Some cut the spinal cord with a scalpel or micro-scissors; others crush the cord with metal weights. Thus, results often cannot be compared—or reproduced.

To remedy this, Reeve’s foundation did two things. It assembled a working group of experts in the field and required that they collaborate rather than compete. “They have to share all the information, share the successes, share the failures,” Reeve said. The foundation is also associated with the Reeve-Irvine Research Center, at the University of California, Irvine. Equipped with all available animal models, the laboratory is dedicated to doing comparative studies and reproducing data.

Reeve is not afraid of arguing with the scientists on his foundation board about their decisions. He recently protested when he felt that a grant proposal was misguided. Some scientists think it is absurd that a layman can help determine funding decisions, but Reeve believes that he is simply making sure that scientists stay focussed on improving patients’ lives. “I heard a very distinguished scientist say, ‘You can never do enough basic science,’” he told me. “These are the kinds of people I’m no longer willing to fund. We used to fund this particular researcher, but we dropped him.”

Even more controversial, Reeve believes that researchers need to stop being so timid about giving experimental therapies to humans. In the United States, a new therapy is typically tested on animals for years before it is tested on humans, and even then it is administered to a slowly growing group. Most scientists think that this approach protects patients, but Reeve believes that it often harms more than it helps—by slowing science to a crawl. In our conversation, he described how, in a commencement address at an Ivy League medical school, he had told the students the story of Hans Keirstead, a professor at Irvine. Keirstead, who was working with human embryonic stem cells, had designed a treatment protocol that shortened the three stages of a traditional clinical trial to two stages. “I said to the audience, ‘This is how these young guys are thinking. This is a young scientist who really wants to make a difference. What he did was truly commendable,’” Reeve recalled. Afterward, he went on, “This tenured professor said to me, ‘That is very disturbing. It’s very upsetting, because that’s rushing things, and if one mistake is made it could set the whole field back ten years.’”

Reeve replied, “It might be upsetting to you, because it’s not the way you are used to thinking. But it’s not upsetting to me as a patient. Because, let’s face it, nothing of any significance has ever been achieved without reasonable risk.”

Although Reeve promotes risk-taking science, he is mindful of the need to protect a patient’s safety, including his own. Throughout the late nineties, he was desperate to be freed of the ventilator. He worked to strengthen the muscles of his neck and shoulders through therapy, but it did little to allow him to expand his thorax and breathe without the machine. Around 1980, doctors began experimenting with a pacemaker that causes the diaphragm to contract. But implanting the pacemaker involved complex surgery that sometimes resulted in infection, and even death. Reeve decided that, in his case, the protocol was too dangerous.

Last February, he went to Case Western Reserve University School of Medicine, in Cleveland, where the F.D.A. had approved a clinical trial of a next-generation pacemaker inserted via laparoscope—a much less traumatic procedure. Surgery was performed on Reeve, and it was a success. When I met with Reeve in June, he was on the ventilator fifteen hours a day; by October, he required it for only five hours a day. (He keeps his ventilator by his side at all times, in case the pacemaker malfunctions.)

One consequence of this procedure has to do with Reeve's sense of smell. Immediately after his accident, for reasons his doctors cannot explain, many ordinary odors struck Reeve as overpowering. One day at Kessler, he told me, Dana brought him some Chinese food, which he loves, and he had to insist that she take it away. "This is what it must be like to be a dog," he recalled saying. "Everything smells fifty times as intense." Over time, Reeve's sense of smell became less acute, almost vanishing. On the first day of the pacemaker's functioning, however, Reeve found that this sense had suddenly returned. "They put something under my nose," Reeve said, shifting to a stage whisper—a rare return to his old theatricality—"and I said, 'Coffee.' After coffee, it was an orange, and then peppermint."

I asked Reeve how he became the third person enrolled in the pacemaker experiment. "I applied early in 2002, and they said no," he said. "I was rejected from the study for more than a year. And the reason was that they didn't want to fail with somebody of my public profile." (Anthony DiMarco, the study's principal investigator, disputed this, but Raymond Onders, his co-investigator, said, "I can't deny that.") After the doctors practiced on one more patient, they agreed to test Reeve's fitness for the procedure. "I had to prove under fluoroscopy that my diaphragm moved in response to electrical stimulation of the phrenic nerve in order to qualify," he said. "And I passed with flying colors."

If the delay in his surgery had been related purely to safety concerns, Reeve would have been sympathetic. But the idea that career interests were involved made him angry. "I didn't take that very well," he said tersely. "It comes back to this underlying fear in the scientific community of setbacks. What will it cost if they make a mistake? Not only the cost of institutional reputation but also the cost to the scientist's career."

Last month, I spoke with Hans Keirstead, the young researcher at the Reeve-Irvine Research Center. Keirstead has been working with the Geron Corporation, a California biotechnology company focussed on stem-cell research. In 2001, the Bush Administration forbade the National Institutes of Health to fund research on human embryonic stem cells, unless the stem-cell lines had been acquired prior to the ruling. Using one of these existing lines, Keirstead has developed methods that cause the stem cells to mature into a form of glial cell known as an oligodendrocyte. Glial cells nurture and support the nerves in the spinal cord.

To test how these cells might contribute to recovery from spinal-cord injury, Keirstead has developed an experiment with rats. He crushes each animal's spinal cord with a metal rod. Seven days after the injury, Keirstead transplants human embryonic stem cells that have matured into glial cells to the wounded area. He has found that rats that receive these glial cells can consistently support their weight and occasionally step forward. Injured rats that did not receive treatment could do neither.

Reeve makes a point of visiting vanguard scientists like Keirstead. In recent years, his improved health has allowed him to stay in contact with researchers around the globe; last January, he attended a conference in Australia and was struck by the audacity of foreign scientists. "We are rapidly falling behind other countries," he told me. For example, a Spanish team is doing highly promising experiments involving glial cells that are found not in the spinal cord but in and around the nose. Olfactory nerves, which register smells, continually regenerate throughout adult life; they are the only nerves in the human body with this capacity for self-renewal. When the axons of nerves in the olfactory bulb are severed, fresh connections quickly regrow.

Dr. Almudena Ramón-Cueto, a researcher at the Spanish Council for Scientific Research, in Valencia, reported in 2000 that when rats with severed spinal cords had glial cells from their olfactory system implanted at the site of injury, the animals recovered markedly. Seven months after their spinal cords had been cut, all the rats who received the cells showed significant improvement in their ability to climb a small ramp. They also regained sensation, retracting a hind limb in response to light skin contact.

When researchers subsequently examined the site of injury, they found an opaque white tissue that bridged the separated spinal-cord stumps. The Spanish researchers suggest that the olfactory glial cells might wrap themselves around regenerating axons, protecting them from destructive molecules. After the Spanish group's paper was published, seven different laboratories performed studies confirming that olfactory glial cells facilitate spinal-cord regeneration.

Reeve is even more excited by the work of Dr. Hongyun Huang, a Chinese neurosurgeon. Huang, making a leap that Reeve applauds and others condemn, has injected olfactory glial cells into the spinal cords of nearly four hundred paralyzed patients, including three Americans. Huang obtained the glial cells from aborted human fetuses. (Such fetal-tissue research is banned in some U.S. states, and the Bush Administration supports a federal ban.)

The speed with which Huang has moved to clinical trials has stunned many in the West. Some scientists, such as Ramón-Cueto, think it is important to do more research first; she is determined to do primate trials of her method before proposing human studies. Given that scientists do not yet fully understand why glial-cell implantation works in rats, the F.D.A. would also likely have been wary of greenlighting Huang's study.

Early results have been promising, however, and nobody appears to have been harmed. In October, Wise Young, the researcher at Rutgers, travelled to Beijing to examine Huang's patients. "I saw this with my own eyes," he told me. No one should view Huang's protocol as miraculous, Young said, "but it is bringing back sensation and some motor function." All the patients in Huang's study had chronic injuries, he said; on average, they had been paralyzed for two years. "One very puzzling thing is that many of the patients are recovering function within three to five days, which is too fast for regeneration," Young added. "There may be some other mechanism of recovery that we don't understand."

Since news of Huang's success leaked out on Internet discussion groups, thousands of desperate patients have contacted him. Huang has set up a program that allows Americans and other non-Chinese to visit Beijing for one month, for surgery and preliminary rehabilitation. The cost is twenty thousand dollars; six thousand people, Huang says, are now on a waiting list for the program.

Young, who has created a Web site, Sciwire.com, to dispel rumors overstating the promise of new methods, tells patients who ask about Huang's trial to wait for more data. "But there is no way you can talk these people out of doing it," he said. "You can tell them, 'Wait another year until the paper has come out' and 'Maybe he'll come to the States,' but they say, 'Hey, I don't want to wait three or four years to try this.'"

As an actor, Reeve was a political activist, involved in the Creative Coalition, which battled Jesse Helms and other opponents of the National Endowment for the Arts. He now petitions Congress to increase the budget of the National Institutes of Health and pushes for full federal funding of stem-cell research.

With George W. Bush in the White House, Reeve is unlikely to get his way. So he intends to bypass the federal government and get bills passed in states before the next Presidential election. "What we are working on at the foundation, which I believe is going to turn the tide, is a series of state initiatives," he told me. "The example was set by California last September, when the governor signed a bill that allows scientists to conduct research on stem cells from any source. That means umbilical cord, adult stem

cells, embryonic stem cells left over from I.V.F. clinics.” California offers millions in state grants for medical research. The New Jersey Senate recently passed a similar bill, Reeve noted. “It is awaiting passage in the Assembly. We think that can be accomplished. And, regardless of who is running for President, he wouldn’t be able to do anything about it. Furthermore, one of the core Republican beliefs is states’ rights.”

Reeve’s emerging strategy resembles that of a venture capitalist. He relentlessly networks with scientists to determine which laboratories are doing inventive work and which clinical trials have had tantalizing preliminary results. His foundation invests in research projects around the globe, some of them high risk. Although many investments may fail, one or two may yield major returns.

Not long ago, Reeve returned from a trip to Israel, where he visited the Weizmann Institute of Science. In a novel and controversial experiment, a specialized type of human blood cell is being implanted in the spinal cords of acutely injured patients within fourteen days of their accidents. “Things move much faster there,” Reeve said. “We shouldn’t have to go abroad to enter into experiments like this.” He spoke feelingly about one man, an Israeli Arab, whose injury is similar to his own. After the treatment, the man was able to walk with the support of parallel bars.

I later spoke with Dr. Michal Schwartz, the scientist leading the project. She was encouraged by her early data, but she emphasized that the findings were preliminary and that no conclusions should be drawn from them. When I sat with Reeve in his office, however, he became so excited discussing such “pioneering research” that he spoke animatedly for four hours, and his rhetorical vigor and robust appearance made it impossible not to be caught up in his vision.

When I was first introduced to Reeve, I had placed my hand gently on top of his. At the end of the afternoon, I asked him if he had truly felt it. “Of course!” he said, surprised. Then he paused, and for the first time his voice was infused with emotion. The warmth of human skin, he said, was the sensation he valued most. “Feeling my children’s touch again—that’s been the most amazing thing.” □