You Say You Want a Revolution?
By Wise Young, M.D., Ph.D., and Patricia Morton, Ph.D.

Editor’s Note: From their roles directing the W.M. Keck Center for Collaborative Neuroscience at Rutgers University, Wise Young and Patricia Morton have been on the front lines of spinal-cord-injury research for most of their careers. In this article they lean on lessons from the past, their own experience, and events still unfolding as they raise questions about the future of all scientific research.
We are in the midst of a scientific revolution, changing from the long-established practice of teaching patients to live with disability to the new field of regenerative medicine that utilizes stem cells and other approaches to regenerate tissues and restore function. As with all revolutions, regenerative medicine is encountering opposition on many fronts and for many reasons. Some objections are moral, others scientific. Some people object to a particular approach because they think it is scientifically unsound, while others have a vested interest in a different methodology or a favored cell or mechanism. The lack of sufficient funding will fuel these attacks because projects and careers are at stake.

This revolution raises new questions and requires new strategies. For example, scientists are trying to figure out which lessons from the past will inform the future. In their 2013 book *Decisive: How to Make Better Choices in Life and Work*, Chip and Dan Heath identify several ways that people get trapped when making decisions: “Research in psychology has revealed that our decisions are disrupted by an array of biases and irrationalities: We’re overconfident. We seek out information that supports us and downplay information that doesn’t. We get distracted by short-term emotions. When it comes to making choices, it seems, our brains are flawed instruments. Unfortunately, merely being aware of these shortcomings doesn’t fix the problem, any more than knowing that we are nearsighted helps us to see. The real question is: How can we do better?”

One of the shortcomings that Chip and Dan Heath stress is the human tendency to get trapped in binary (either/or) thinking. This raises a query: What are some ways in which moving beyond binary thinking could change the future of science? Let us suggest four areas to consider.

**Collaboration and Competition**

It’s the lone researchers who generally explore scientific frontiers, but groups of people with various areas of expertise come together to consolidate advances. As new knowledge arises, these groups solidify standards that provide the platform for the next frontiers.

The battles between Jonas Salk and Albert Sabin to find a vaccine for poliomyelitis are well documented. Each scientist was driven and fervently believed in his approach. Funding from the National Foundation for Infantile Paralysis fueled the competition, and secrecy hid fundamental
errors that openness might have quickly revealed. The competition strengthened each researcher’s commitment to his approach, but it perhaps caused a significant delay in finding a vaccine when both Salk and Sabin initially ignored the findings of Dr. Dorothy Horstmann, the woman who discovered the actual path of the viral entry.²

On the other hand, an effective model of collaboration functioned between 1993 and 1996, when the National Institutes of Health (NIH) funded work on the Multicenter Animal Spinal Cord Injury Study (MASCIS). Eight leading spinal-cord-injury laboratories in the United States worked together to develop and validate the first standardized rat model of spinal-cord injury. In addition to developing the model, MASCIS scientists developed outcome measures such as the Basso, Beattie, Bresnahan (BBB) locomotor scale and white-matter sparing, both of which became standards in the field. The first project of its kind funded by the NIH, MASCIS proved that people in different laboratories can work together to develop approaches and to standardize procedures, thus enhancing the work of each of the individual researchers.

The current model of individual principal investigators competing with each other for funding, and the consequent lack of collaboration, not only is expensive and inefficient but also forces scientists into undesirable binary thinking that invariably accompanies competitive endeavors. What your competitor is doing automatically becomes off-limits. A much better approach to developing new scientific discoveries would be to offer increased funding of projects that both enhance collaboration and stimulate individual initiative.

**Biology and Technology**

*Biotechnology* has become the buzzword of the 21st century; an entire industry has arisen around the term. But biology and technology don’t always work well together. One example is the dichotomy between the electrical stimulation and cellular transplantation approaches to restoring function to people who are paralyzed.

Implemented by engineers who think in terms of electrical current, voltage, and resistance, a whole field has been built around functional electrical stimulation (FES)—using computers to deliver electrical signals to muscles and treating human muscles like robotic components. The film *RoboCop* exemplifies the thinking and limitations of this approach. In contrast, cellular transplantation is the
brainchild of biologists, who think in terms of synapses, neurotransmission, and metabolism. As with FES, an entire industry has grown up around the concept of cell transplantation. Fueled at the end of the 20th century by the discovery of stem cells, this field has been dominated by paranoia and fanciful thinking illustrated in the film *Star Wars: The Clone Wars* (2008).

Biology and technology must work together in practical and realistic ways to restore meaningful function based on the best available technology and understanding of biology. A recent example provides a clear illustration of a fruitful marriage between biology and technology. Each field provides a best-of-class solution to the problem of restoring function after spinal-cord injury.

Many researchers have shown that the spinal cord can regenerate. For example, Lu et al.\(^3\) demonstrated that rivers of axons can grow across the transection site of a rat spinal cord if you implant mesenchymal cells to form a bridge, inject the response-element binding protein cAMP to motivate neurons to grow the axons, and induce the neurons on the other side of the gap to express growth factors and “come hither” signals. Likewise, Liu et al.\(^4\) showed that silencing a single gene called PTEN can stimulate rivers of axons to grow across the injury sites in mouse spinal cords.

The problem was that the rats and mice did not recover motor function even though thousands of axons grew across the injury site and made connections with neurons above and below it. It was fairly obvious why function did not recover. The regenerated axons were new, and they probably were not connecting to the neurons in the same way the old axons had. Thus, the brain had no idea which “buttons” to push to move specific muscles or how to interpret incoming signals.

Much evidence suggests that intensive locomotor training is needed in order to restore function. In fact, the most successful mobility training programs for those with spinal-cord injury are those that involve prolonged repetitive activation of desired movements as often as six hours a day, six days a week, for six months or more. Such intensive training is not only expensive but also unavailable to the majority of those who would need it.

Why is such intensive training necessary for functional recovery? It turns out that learning requires repetitive activation of synaptic connections. In Donald Hebb’s\(^5\) book, *The Organization of Behavior: A Neuropsychological Theory* (1949), he proposed that timing of synaptic activation is responsible for learning. Specifically, Hebb said, “When an axon of cell A is near enough to excite cell B and
repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.” Sometimes rephrased as “Neurons that fire together, wire together,” the Hebbian principle has become a leading theory of neuronal learning. The formation and consolidation of synapses or connections requires synchronized activity from sensory and central sources. Intensive exercise can achieve such synaptic consolidation, while desynchronized activation weakens it.

Electrical stimulation is one way to induce synchronized activity for spinal-cord injury. Today most people carry in their pocket or purse more computer power than what once filled an entire room of mainframes. Brain-to-machine interface has demonstrated the ability to control and deliver electrical stimulation synchronized to desired activities and thereby increase synaptic consolidation and learning of regenerated fibers. Therefore, a combination of cell transplantation and electrical stimulation is the best way to restore function when neither can do it alone.

Regenerated axons are not a repaired nervous system but a new one in which new neuron-to-neuron and neuron-to-muscle connections must be learned. Initial studies show that transplanting umbilical-cord-blood stem cells in combination with intense physical therapy restores walking in people with spinal-cord injury. But the cost would be prohibitive for large numbers of people to participate in months-long walking programs. However, what if people could receive cell transplants and walk two hours a day in addition to undergoing electrical stimulation that allows them to continue to “walk” while they sleep? Injected stimulators such as the rice-size BION raise this possibility.

**Hope and Realistic Expectations**

The story of stem-cell advocacy is relevant to the balance between hope and realism. Celebrating the passage of stem-cell legislation in New Jersey in 2003, Commissioner of Health Fred M. Jacobs, M.D., J.D., proclaimed that stem-cell medicine was the most significant paradigm shift in the 40 years he had been practicing medicine. Newspapers heralded the advance, and community advocates believed that with the exception of restrictions imposed by President George W. Bush, the way was clear for miraculous cures for devastating diseases. 6
In a movement called Quest for the Cure, impatient activists worked together to pursue stem-cell legislation at the state level. In December 2003 New Jersey passed S1909/A2840, and California’s Proposition 71 followed in November 2004. Each of these bills, and others that followed, provided avenues for funding stem-cell research within its respective state. During a subsequent backlash, other states increased restrictions on—or entirely prohibited—fetal and embryonic stem-cell research.

On March 9, 2009, excitement filled the room when, in front of many disabled and ill people and their families, newly elected president Barack Obama signed an executive order lifting restrictions related to human embryonic stem cells. The president proclaimed, “Today, with the Executive Order I am about to sign, we will bring the change that so many scientists and researchers; doctors and innovators; patients and loved ones have hoped for, and fought for, these past eight years: we will lift the ban on federal funding for promising embryonic stem cell research. We will vigorously support scientists who pursue this research.” Later, when the order’s official guidelines were released, scientists were disappointed to discover that the new policy was more restrictive and onerous than the previous one. Even more disappointing was the fact that no increased funding was to follow.

Two years earlier, Shinya Yamanaka’s discovery that skin cells can be reprogrammed to become embryonic stem cells called induced pluripotent stem (iPS) cells had changed the field and had made it unnecessary to harvest fertilized eggs in order to obtain embryonic stem cells. To date, no iPS cell has been tried in humans because of fears that these cells can produce tumors. However, the discovery established the principle that pluripotency is genetically programmed. Further recognition of the discovery’s significance came when Yamanaka received the Nobel Prize in 2012 for Physiology or Medicine.

The suppression of embryonic-stem-cell research did lead to a renaissance of studies of adult stem cells. This soon resulted in over 4,500 clinical trials involving stem cells in the United States. The field of stem-cell therapies has turned 180 degrees from embryonic stem cells because pluripotency is not as desirable as originally thought. In fact, most scientists and clinicians consider pluripotency to be a dangerous property that must be eliminated before cells can be transplanted. For example, Geron Corporation obtained permission from the Food and Drug Administration (FDA) to transplant
embryonic stem cells into people with spinal-cord injury, but only proving that less than one in a billion transplanted cells were pluripotent.

Pluripotency—the ability of make many kinds of cells—is a dangerous property if not controlled. Stem cells that find their way into the spinal cord to make a hair or a toenail or to penetrate a tissue—but end up causing a tumor—are harmful to the point where the human body has evolved to suppress pluripotency. An adult stem cell can behave like a stem cell only if it finds a niche of cells that tell the stem cell exactly what to do, which is why it is so difficult to grow stem cells in culture. Nature has developed ways to reduce the dangers of stem cells by forcing them to produce the correct type and number of cells in response to tissue requirements.

Hype comes from ignorance. When embryonic stem cells first were discovered and grown in culture, we did not understand stem cells and the implications of pluripotency. Scientists were excited about the possibility of growing any and all sorts of tissues from embryonic stem cells. The public regarded embryonic stem cells as a panacea. Religious conservatives believed that allowing embryonic stem cell research to proceed would lead to the practice of killing fetuses to treat adults. With more knowledge and greater understanding of the biology of stem cells, we now have a more balanced approach to stem cell therapies.

Real hope comes from knowledge and understanding. For example, we know from animal studies—and hopefully soon from clinical trials—that the spinal cord can regenerate. At the same time, our expectations are tempered by the observations that animals do not recover function after regeneration and that intensive exercise and training are needed to restore function. But lest overhyping hope sow the seeds of its own destruction, hope must be coupled with honest realism. In the absence of understanding, scientists would do well to under promise and over deliver.

Compassion and Caution

Each potential treatment raises the question: When is “too soon,” and when does an overly conservative approach perpetuate human suffering? Are large animal studies always required before people can be studied, and to what extent are double-blind randomized trials de rigueur? What data are sufficient to move forward with clinical trials? When is a situation so critical that immediate action is essential?
The present Ebola virus disease (EVD) epidemic has brought this debate into focus. As deaths mounted, ZMapp (Mapp Biopharmaceutical, Inc., San Diego), a potential treatment untested in clinical trials, was given to six patients. Three lived, and three died. According to the World Health Organization (September 2014 Fact Sheet N103), the average fatality rate for untreated EVD is 50 percent, with a range of 25 to 90 percent. So, what, if anything, was learned? Did a sense of urgency overcome scientific rigor? Should it have? Now one idea is that the blood of EVD survivors might impart immunity to patients, and transfusions are being given without meticulous study.

The question of timing raises the important issue of whether there should be different standards for situations like the AIDS epidemic of the 1980s and the present EVD crisis—in which death is a highly probable outcome—or for conditions like spinal-cord injury, in which people are paralyzed but stable. Should victims of the former have fast-track access to untested potential treatments while victims of the latter are made to wait through a full clinical-trial process? Should there be different criteria for children as the enterovirus D68 (EV-D68) respiratory illness spreads across the United States?

One danger arising from delay in committing resources and manpower is the burgeoning industry of false promises. Whenever new possibilities arise, such as stem cells and clinical trials, so-called clinics spring up like mushrooms and offer these treatments—or claim to offer them—without waiting for trial results. For instance, the black market for the blood of EVD survivors was flourishing almost before the newsprint was dry. Unscrupulous opportunists lie in wait to take advantage of the desperation of the afflicted and their families.

Under what circumstances should compassion supersede caution? Should the definition of “compassionate use” be expanded to offer people the option to obtain treatments approved by the FDA for Phase III trials but at non-trial sites by companies in exchange for cost of the therapy? It behooves the scientific community to develop guidelines to balance the urgency of impending death with the dreams of those who would be healed.

Another principle advanced by the Heaths in their book Decisive is that of multitracking options—that is, keeping all options on the table. Politics, fear, and mistrust raise the “slippery-slope” argument, which too often results in the closure of pathways that may be beneficial. For example, would we have safe nuclear power today if fear had shut down nuclear research? Would adult stem
cells have been discovered or well understood if all embryonic-stem-cell research had been terminated, as some people wanted?

There will always be tension between mechanical and biological approaches, between hope and hype, and between caution and risk—the struggle surrounding whether to test something new as early as possible despite the inherent danger or to wait too long at the potential expense of human lives. Debates about funding short-term immediate therapies or long-term potential breakthroughs will continue to rage. Are we open to radically different changes, such as shifting from developing each vaccine from scratch to the “chassis approach,” used by VaxCelerate, which cut time and money for a Lassa fever vaccine from several years and billions of dollars to four months and less than a million? Critics will continue to question practices such as spending money and using manpower on heart transplants from pigs and baboons; isolating stem cells from urine; 3-D “printing” of organs; DARPA’s ElectRx program, which may give humans self-healing powers; and quality of life issues like that raised by Ezekiel Emanuel in his recent article “Why I Hope to Die at 75”: How long is too long to live?

As we look to the future, we can learn from past revolutions. Experience enables us to anticipate. During the battle over polio vaccines, Dr. Thomas Rivers reminded the researchers, “Nothing is sacred in science; you give up the old when you find something new that is better.” When we fail to follow promising leads, we freeze ourselves to the obsolete, shut-out the critically important, break our foundational commitment that science exists to help people. Every path will be bumpy, and many roads will be dead ends. There always will be scientific and moral questions without easy answers.

But the greatest ethical travesty would be to stop the science.
Bios

**Wise Young, M.D., Ph.D.** came to Rutgers University in 1997 and is founding director of the W. M. Keck Center for Collaborative Neuroscience, the Richard H. Shindell Chair in Neuroscience, and a distinguished professor. In 2006, he organized a 24-center clinical trial network in China and ran trials to assess promising therapies for chronic complete spinal cord injuries. Phase II trials using umbilical cord blood mononuclear cells injected into the spinal cord, lithium, and intense locomotor therapy show promising results. He plans Phase III trials in China, India, Norway, and the U.S. Young established methylprednisolone as the first treatment for spinal cord injury, developed the first standardized rat spinal cord injury model, and founded the *Journal of Neurotrauma* and the National and International Neurotrauma Societies. Young received his B.A. from Reed College, his Ph.D. from the University of Iowa, and his M.D. from Stanford University. After a surgery internship at New York University and Bellevue Medical Center, he joined the neurosurgery department at NYU, where he became director of neurosurgery research in 1984.

**Patricia Morton, Ph.D.**, director of Planning and Development for the W. M. Keck Center for Collaborative Neuroscience and an Assistant Professor at Rutgers University, was recruited by Wise Young to assist in developing the Keck Center and Spinal Cord Injury Project. She organized the first New Jersey Neuroscience Symposium, the inaugural symposium for the New Jersey Commission on Spinal Cord Research, and was a founding member of the commission. She coordinated the state-by-state advocacy group, *Quest for the Cure*, which increased funding for spinal cord injury research. Morton has been instrumental in building collaborations between research organizations, corporations, and government leaders, and deals extensively with spinal injured persons and their families. She leads a seminar on spinal cord injuries, stem cells, and clinical trials: *"Pushing the Frontiers, Raising the Ethical Questions."*
References:

1. Heath, Chip, and Heath Dan, *Decisive: How to Make Better Choices in Life and Work*. New York: Crown Publishing, 2013.

2. Oshinsky, David, M., *Polio: An American Story*. New York: Oxford University Press, 2006.

3. Lu P, Blesch A, Graham L, Wang Y, Samara R, Banos K, Haringer V, Havton L, Weishaupt N, Bennet D, Fouad K, Tuszynski MH. *Motor axonal regeneration after partial and complete spinal cord transection*. J. Neuroscience 2012. 32(24): 8208-18.

4. Liu K, Lu Y, Lee JK, Samara R, Willenberg R, Sears-Kraxberger I, Tedeschi A, Park KK, Jin D, Cai B, Xu B, Connolly L, Steward O, Zheng B, He Z. *PTEN deletion enhances the regenerative ability of adult corticospinal neurons*. Nature Neuroscience. 2010. 13(9):1075-81.

5. Hebb, Donald O., *The Organization of Behavior: A Neuropsychological Theory*. New York: John Wiley & Sons, Inc., 1949.

6. Harold, Eve, *Stem Cell Wars: Inside Stories from the Front Lines*. New York: Palgrave Macmillan, 2006.

7. Weintraub, Karen, *The Trials of Stem Cell Therapy: Stem Cells: Plenty of Hope, but Halting Progress*. New York: New York Times, September 16, 2014.

8. CBS News (Sept. 24, 2014)

9. *The Atlantic* (Oct., 2014): [http://www.theatlantic.com/features/archive/2014/09/why-i-hope-to-die-at-75/379329/](http://www.theatlantic.com/features/archive/2014/09/why-i-hope-to-die-at-75/379329/)