Mark Pollock:  
**FAILURE IS PART OF THE PROCESS**

“Ever tried. Ever failed. No matter. Try again. Fail again. Fail better.” That’s the well-used quote from Irish writer Samuel Becket, often now a mantra for entrepreneurs, for writers, for golfers. Scientists, of course are quite familiar with failing.

Trinity College in Dublin, Becket’s alma mater, hosted an exhibition this year called Fail Better. It was, indeed, a celebration of trying and not succeeding, leading to better tries, better results. And sometimes better failures. Among the exhibits at the show was “Superman’s Wheelchair,” featuring Christopher Reeve’s power wheelchair. It was flown in from the Reeve Foundation offices in New Jersey at the behest of Dubliner Mark Pollock, a member of the Reeve Foundation’s Board of Directors.

Pollock suggests Reeve’s empty chair represents both the failure to cure paralysis and the compulsion to pursue progress. Indeed, one could say the fail began in 1994 when a horse missed a jump, a doctor could not fix a broken spine, when an army of therapists could not find a way to help the doctor, or the patient.

Pollock is not one to dwell on the failure aspect of pushing boundaries. He encourages a healthy disregard for risk, and for reaching toward the impossible. When he was 22, Pollock lost his sight. Twelve years later he became an adventure athlete and the first blind person to race to the South Pole. “I spent 12 years filling my life with experiences that would sweep the blindness to the side,” Pollock wrote.

A year and a half after the race, Pollock fell from a second story window. It nearly killed him. “I broke my back and the damage to my spinal cord left me paralyzed. Now I am inspired by the vision of another explorer –

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“Exercise is the number one key ingredient for a happier, healthier and longer life.” That’s the word from Dan Cummings, a C6 quadriplegic who credits his aggressive rehab program for recovery of walking, with a walker.

Cummings, injured in a shallow water diving accident in 2000, wanted more than the outlook his therapists presented him. “They gave me a wheelchair and wanted to teach me how to live in it. But I wanted more.” He had to travel from Boston to California to find a program that matched his ambition; Cummings spent four years at Project Walk, in Carlsbad. “I went in say a ten,” he said. “I came out at about a 90.”

Cummings moved back to the East Coast and began to wonder, why is there no intensive therapy closer to home? So in 2008 he created Journey Forward, a Boston non-profit that offers aggressive rehab and training. This year, Journey Forward became the newest Community Fitness and Wellness program within the Reeve Foundation NeuroRecovery Network® (NRN).

The NRN is a network of leading rehabilitation centers that cooperate to provide and develop therapies to promote functional recovery and improve the health and quality of life for people living with paralysis.

The Journey Forward approach matches that of the NRN; Rehab is long-term. “Traditionally, after the first six months of a spinal cord injury, people are given little to no hope of increasing their independence,” says John Walters, co-founder and Program Director of Journey Forward, recruited by Cummings to help start the program. “We don’t believe this is true; given the correct stimulus, some people with SCI can improve, and many continue to get better. Physical therapy for most people is a short-term program of doctor-prescribed rehab; what we’ve come to know is that spinal cord injuries take much longer to recover.”

Walters says rehab must be considered a lifelong recovery process. “Instead of working just on people’s strengths, we focus on a full body recovery. That includes working on your weaknesses, too.”

Journey Forward geared up quickly, Walters says, with the latest in exercise and rehab technology, including a robotic gait trainer (Lokomat), functional electrical stimulation bikes and other specialized exercise gear such as an anti-gravity treadmill. Not wanting to simply be a stand-alone facility, Walters says he and Cummings “wanted to be part of something bigger, to push innovation and to be part of the evolution of the activity based therapy industry.” That led them to the research-based NRN. “Being involved with the NRN, and the team of scientists and clinicians in the network, this provides us with tremendous expertise.”

Once accepted in the program, the Journey Forward staff was trained first at the Kessler Institute, an NRN site, and later at the University of Louisville (the main NRN hub).

Aligning with the NRN gives the program credibility, said Walters, especially among other health care institutions in the Boston area. Spaulding Rehab in Boston has begun referring patients, he said. And the Journey Forward team is working with Boston College to see how aggressive rehab might affect hospital stays, or how it might reduce secondary health issues such as pressure sores.

It’s not all about walking but about recovery toward health and independence, says Walters. “Recovery could mean just the little things – recovering enough to get a driver’s license, perhaps being able to move from a power chair to a manual. For everyone who comes into the program, there are the benefits of exercise in promoting overall health and prevention of secondary complications.”

“Through exercise and activity,” says Cummings, “a person has the opportunity to live a long, healthy life.”

Journey Forward sees about 40 clients a day. For the most part, insurance does not cover this sort of long-term rehab. “We do what we can to convince insurance companies that this should be paid for,” says Cummings. “We think they will realize it’s going to save them money in the long term.”

NRN Community Programs
Courage Kenny Rehabilitation Institute, Minneapolis, MN
Frazier Rehab Institute, Louisville, KY
NextSteps Chicago, Willow Springs, IL
NextStep Fitness, Lawndale, CA
Neuroworx, South Jordan, UT
Journey Forward, Boston, MA
Christopher Reeve. I am traveling in his tracks.”

Pollock is intensely dedicated to recovery, with aggressive physical therapy, exoskeleton walking and electrical stimulation. Conventional wisdom says Pollock will always need his wheelchair. He’s not betting on convention. Wrote Pollock: “I believe a cure for spinal cord injury is possible. Success is our objective. And we know that in our pursuit of a wildly ambitious goal, the potential for failure travels with us. If there is no risk of failure, it’s probably not worth pursuing.”

“Of all the things I have ever done this has the greatest chance of failure over success. ... We don’t know where the cure is. Out there, somewhere, like the South Pole, I am making the most educated guess available in this world at this time and I am pointing myself in what we hope is the right direction.”

For more about Pollock see www.MarkPollock.com

Error is an Option: Other Fails From Fail Better

The Mars Climate Orbiter: this $125 million project failed in flight because one team used the metric system, the other the imperial. Said NASA in 1998, “People sometimes make errors.”

The common fuse: failure is built in to sacrifice a minor component to protect larger system. Another built-in failure: the K1 Syringe: After one use, it won’t work again, thus preventing contamination.

Transorbital lobotomy: just 50 years ago, ice pick-like devices were used to treat psychiatric illness. Treatment fail. Ethical fail.

Fail often: James Dyson worked up 5,127 prototypes before his vacuum cleaner made the grade.
Lukas Bachmann, Ph.D.

This was while Bachmann was at the Zurich lab of Martin Schwab, a member of the International Research Consortium on Spinal Cord Injury, which is the heart of the Reeve Foundation’s scientific program. Bachmann, who recently moved from Europe to California to join the Consortium lab of Sam Pfaff at the Salk Institute in San Diego, embodies the mission of the Consortium program: to collaborate and share, and thus speed the path toward repair and recovery of spinal cord injury.

The Consortium, created in 1995, is a cross-lab collaboration comprising seven major research programs, two in Europe, one in New York and four in California. Each program is led by a senior scientist, or Principal Investigator. The PIs meet twice a year and share details of their work to a degree that rarely happens in the competitive world of research. A key feature of the Consortium, and perhaps its greatest success, is the Associates program. Each lab in the group includes two or more Associates – younger scientists who have obtained or will soon obtain their doctorates, and who are beginning a career specialty in spinal cord research.

The Associates work closely with the PIs, and handle the day-to-day workload of various Consortium collaborations. The Associates get the research done, but importantly, most stay in the SCI field after leaving their Associate positions. The Consortium program, over the years, has seeded the field with dozens of first-rate scientists who start their own labs and in turn, train their own post-docs in SCI science.

In Bachmann’s 2013 literature debut, he used well-established brain stimulation techniques (used clinically for Parkinson’s disease treatment) to insert a probe into the brain of a lab animal, lining it up to stimulate specific areas of the mesencephalic locomotor region (MLR). This is an important control center for locomotion, an area of the ancient core of the brain, conserved across species from fish and salamanders to higher mammals.

The probes were in place before the injury. After four weeks of paralysis, equivalent to a chronic injury in humans, they switched on the stim. It was successful beyond expectation. “A very impressive effect,” says Bachmann. In rats with severe, incomplete spinal cord injuries, MLR stimulation immediately improved the locomotor performance and resulted in the reappearance of fully or partially functional hind limb movements. Even in animals with the most severe injuries, with just 2.5 to 11 percent spared white matter, MLR stimulation restored movements in the paralyzed legs under gravity-released conditions (e.g., swimming).

Bachmann specifically set out to improve function after long-term spinal cord paralysis. “Most experiments – stem cells, anti-Nogo, riluzole, Cethrin, etc., these are directed toward acute injuries. Our intention was to develop a chronic, or sub-chronic model, to see if we could improve function in the chronic state.” That they did.

So what’s happening here? Bachmann’s working hypothesis is that the stimulation of the brain region associated with locomotor function activates what is called a central pattern generator (CPG) in the undamaged circuitry in the spinal cord. This, indeed, is the same circuitry that affects movement recovery when the spinal cord itself is stimulated, and thus is the theoretical basis of epidural stimulation and the widely known early success with four human subjects at the University of Louisville. What about combining the upper and lower stimulation? “I predict that were MLR stimulation combined with what Reggie Edgerton and his group are doing [spinal cord stimulation below the level of lesion], it would be additive or synergistic,” says Bachmann. “One could say we are pulling on the same rope.”

Bachmann joins Pfaff lab Associate Ariel Levine, M.D., Ph.D., who you might say has had her hands on another part of that rope. She recently was co-author with Sam Pfaff and colleague Christopher Hinckley and others for a paper in the top-tier journal Nature Neuroscience about identifying specific circuits in the spinal cord, the ones that automate certain motor activities and behaviors. Levine’s work is relevant to spinal cord injury because targeting these cellular networks, or what her paper calls motor synergy encoders (MSE), has the potential to activate significant movement in people living with paralysis.

“The idea has been around for a long time,” says Levine. “It is very appealing that the spinal cord holds programs for certain kinds of movements that the body may do all the time – such as locomotion, reaching for an object, or pulling a hurt limb towards the body.”
Levine and her team at Salk found a group of cells deep in the dorsal horn of the spinal cord that seem to hold the program for movement. “We call them encoder cells,” she says. “Functional studies of these MSE neurons revealed an orderly circuit organization; we speculate this helps to simplify the selection of the appropriate programs.”

Is an encoder cell anything like the cells that form the central pattern generator (CPG), the source of spinal cord automaticity Bachmann tapped into? Similar, yes. But not exactly the same. CPG networks are typically involved in rhythmic activity for major behaviors such as locomotion and breathing. An encoder cell network, says Levine, is involved in a wider variety of behaviors, including the movement involved in withdrawal from pain, or of the motion of bringing a fork to one’s mouth, but also for behaviors such as locomotion.

CPG and MSE cells appear to act together to shape motor activity. Levine speculates that it may be possible, as these spinal networks are further understood and mapped, to refine the signals that activate movement, and directly control the stimulation by way of the MSE nodes.

Bachmann and Levine, now colleagues, will have much to talk about. Another Consortium member with her hands on the rope is Pri Shah, who recently left the Consortium lab of Reggie Edgerton at UCLA to run her own lab within the Lorne Mendell group at the State University of New York, Stony Brook. Mendell is also a Consortium member.

Shah’s path has been a long one. She was trained as a physical therapist in her native India. After having worked in a neurological clinic she felt that “something was missing.” Any number of conditions were treated with the same PT therapies. “There was no difference in what we offered patients with stroke, or spinal cord injury, or MS. The doctor said to me, ‘This is what we have.’”

Shah decided that wasn’t enough. She wanted to learn more. Two years later, she enrolled in a doctorate program the University of Florida and eventually found her way to the lab of Andrea Behrman, Ph.D., one of the pioneers of activity-based recovery, locomotor training and co-founder of the Reeve Foundation’s NeuroRecovery Network. After studying metabolic function of muscles in animals, Shaw became interested in the scientific underpinnings of locomotor training, thus leading her to apply in 2008 for a post-doctoral fellowship in Los Angeles at the Edgerton lab. She eventually became an Associate, and became an expert in upper extremity recovery and stimulation. “There I expected to use my clinical background to bridge the neurobiology side and the clinical side. These two areas of expertise don’t always talk to each other.”

The move to UCLA was a good one for Shah. “Getting to the Consortium was the richest experience of my career. I got to know the big thinkers in the field, the senior investigators, to see how they came up with their ideas. It’s just amazing to see the senior scientists, the PIs, share their ‘hot bread data,’ the new, unpublished data that’s ‘just out of the oven,’ says Pri. It’s also great to work with other Associates, she says, all specialized in various areas of expertise.

“Every study at UCLA asked the question, ‘how can we enhance function after spinal cord injury,’” says Shah. The same goes for New York. “We want to know what rehab strategies can we develop to help with motor function.” Specifically, Shah and Mendell are gathering data on forelimb recovery, and how this ties in to the thalamic nuclei, a part of brain that processes sensory information.

Shah was lead author of a recent new research paper in the journal *Brain* that asks whether lower limb motor function be improved after a spinal cord injury by boosting functional activity of the upper limbs. The answer is yes – animals trained on all four limbs, so called quadrupedal step-training – had improved limb movement and better coordination than animals with lower limb training alone or no training.

Says Shah, “We propose that training the forelimbs significantly impacted the hind limbs through a link of interseg-

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Albert J. Aguayo is a scientist whose discoveries in the 1980s showed that spinal cord nerves could regenerate if they were provided with a favorable environment; this led to major discoveries by labs around the world regarding the extrinsic factors that restricted regeneration. Originally from Bahía Blanca in Argentina, Dr. Aguayo graduated in medicine from the National University of Córdoba and moved to Canada in 1960 where he trained in clinical neurology and neuroscience. He was the founding Director of the McGill Centre for Research in Neurosciences and is now Emeritus Professor at McGill University in Montreal.

Zhigang He is a member of a new generation of scientists; his primary work helped pioneer research to boost the intrinsic capacity of neurons to regenerate. Dr. He received his Ph.D. from the University of Toronto and was a postdoctoral fellow with Marc Tessier-Lavigne at the University of California, San Francisco. He is now Professor of Neurology at the Program in Neuroscience at Harvard University.

The following conversation, facilitated by Sam Maddox, describes the career development of two eminent researchers and illustrates the process of discovery as it builds upon the collective knowledge of the field.

Q: Let me start by thanking you both for participating in this conversation. Readers will enjoy meeting you and understanding more about your work. Could each of you start by telling me a little bit about how you decided to become a scientist?

Albert: When I was very young I never thought I was going to become a medical doctor or a biologist. During my high school years, up to about two weeks before I registered at university, my choice was to do architecture. I still don’t know why I changed my mind so abruptly. I can only guess that the decision was made in a moment of my adolescence when one searches for new things and tends to make quick decisions almost intuitively.

Once I decided to go into medicine I developed an interest in learning about the brain and how it influences our thoughts and behavior. In my home country, I had been through a public high school that stimulated my interest in science but in those days there was much political unrest in Argentina and by the time I got to university it was rather difficult to stay focused on one’s studies. The authorities closed the university a couple of times and there were all sorts of disruptions and protests going on. Fortunately, there were also a good number of people struggling to protect and strengthen the institutions of learning and research under such difficult circumstances. Several of these individuals were role models who influenced my choices in terms of doing science and which field to choose.

In 1954, during my second year in medicine, I had a professor of chemistry who inspired and helped me a great deal. In those days it wasn’t very easy to get hands-on experience in a lab but he talked with me a few times about biomedical research and eventually asked if I was interested in spending time working in his laboratory. That’s where for the first time I used a pipette, a balance, a Bunsen burner and other basic tools of research. The following year I had to do my military service and by the time I returned to civilian life the political situation had changed and I could study and work with greater freedom than before. I graduated from medical school on the 10th of August of 1959. I can hardly remember the convocation ceremony but have never forgotten one of the sentences from our Rector’s speech: “Life is good to those who take it seriously.” I have repeated this sentence many times since in lectures and in talks.

A few hours after my graduation, I took an overnight bus and traveled to the capital, Buenos Aires, about 800 kilometers from where I lived and studied, to attend the 7th International Congress of the International Union of Physiological Societies (IUPS). This was my first scientific meeting! There I had the good fortune of listening to some of the top neuroscientists of the time: Eccles, Granit, Von Euler, Huxley and others, many of whom were Nobel Laureates. At that Congress I also heard a young Torsten Wiesel talk. I believe that was the first time he had spoken at an international meeting about his findings with David Hubel [visual system neurobiology, for which the pair won the Nobel Prize in 1981]. I was so excited by what I heard at the IUPS Congress that by the time I went back home I knew what I wanted to do for the rest of my life.

I chose Canada to train in neurology and neurosciences, in part because I was encouraged to do so by friends who had been living in this country to do medicine and research, and also because fresh in my mind were stories that my chemistry professor had told us about the work done in Toronto by Banting and Best [Frederick Banting and Charles Best, who co-discovered insulin in 1921]. I also had a friend who had been at the Montreal Neurologic Institute who insisted I should choose Canada to train. I paid $192 to fly to Toronto and had only about 10 dollars left in my pocket when I arrived there!

In Toronto I trained in clinical neurology and also spent time learning to do research, mainly at the Banting Institute, under an inspiring mentor, Professor Jerzy Olszewski. Dr. O.,
as many of us affectionately called him, was born in Poland and
had trained in Germany in brain cytoarchitectonics, an ana-
tomical discipline that focused on the distribution and relation-
ships between nerve cells in the central nervous system (CNS).
He had immigrated to Canada soon after World War II. At
the time I met him he was working on several research projects
including one on the nerve cell’s reactions to axonal damage.
Subsequently, in 1964, I moved to McGill University in Mon-
treal and also spent time doing research in England where I
learned electrophysiological techniques applicable to peripheral
nerve and muscle, and also electron microscopy.

Q: Well Zhigang, you wound up in Toronto also...

Zhigang: First, it’s really a great privilege to talk to Albert in
such a special way – he has been my hero for a long time.
I also went to the graduate school at University of Toronto
and also in the Banting and Best Institute. I got into science for
a much simpler reason, I grew up in China and got into college
when I was 14 years old. Actually my teachers and family
enrolled me to medical school because I didn’t yet have enough
knowledge for making such important choices. As an intern
in medical school, I was really struck by the lack of treatments
for many types of diseases. Even more, we didn’t know what
were the cause and mechanism of these diseases. So I felt it was
important to do medical research to understand these better.
Luckily, I was admitted to the Medical Genetics Graduate Pro-
gram at University of Toronto. Over there, I got more system-
atric training in genetics and molecular biology. Jim Ingles, my
advisor, was truly inspiring. Even though my English was barely
enough to communicate, Jim was very patient with me. His lab
was very small with a few students and a couple of technicians.
We had daily communication about scientific ideas, checking
the data, and that was a really great experience for me.

Although I did pretty well in Jim’s lab, most of the work
was in vitro biochemical studies. Towards the end of graduate
school, I contacted a number of professors in U.S. for a possible
post-doctoral position. One of them was Marc Tessier-Lavigne,
another great scientist from Canada. By then, he was a junior
faculty member at UCSF, the University of California, San
Francisco. His lab had just discovered a key molecule, netrin,
that functions in brain wiring. This was a landmark finding
in developmental neurobiology. I was really fascinated by this
amazing science. Luckily, I joined his lab, and that was really
the first time I got into the neuroscience. That was in 1996.

Q: Zhigang, I wonder if you could talk a little bit about how you
started to work in the specific area you did. You said Albert was
your hero. Certainly he laid a revolutionary groundwork for under-
standing that regeneration is not a hopeless study.

Zhigang: As a postdoc at UCSF, within weeks, I heard about
the great work of Albert and how he showed that grafting a
piece of peripheral sciatic nerve to the injured brain or spinal
cord could allow axon regeneration, pointing to the importance
of the hostile environment around the lesion site. My project
in Marc’s lab involved identifying the receptor of semaphorin,
an axon growth inhibitory molecule. As a result, we found that
semaphorin is a receptor. A natural direction was to follow that
with ligand/receptor studies and to continue studying signaling
mechanisms. Maybe because of my background in medicine,
I was always interested in more translational directions, and
wanted to make progress toward treating clinical disease. For
me, it was a natural progression from axon growth during de-
velopment to axon regeneration after injury in the adult. When

I started my lab at Boston Children’s Hospital in 2000, I started
working only on axon regeneration. Back then we often talked
about Albert and his work; he had already optimized all of the
good techniques and made a lot of very important discoveries.

Albert: You’re being too generous....

Zhigang: No, no, that is true. At the first, our goal was to find
the environmental molecules that inhibit axon regeneration.
By then many people had made very important contributions,
including Martin Schwab, James Fawcett, Jerry Silver, Steven
Strittmatter, and Marie Filbin. Our initial push was very similar
to what they had been doing; we were also looking for addi-
tional molecules. Indeed, we found a new inhibitory molecule,
oligodendrocyte myelin protein. However, when people made
generically mutant mice to knock out its expression in vivo,
there was not too much regeneration after injury.

So at that time we were a little bit concerned – the question
was, which and how many specific molecules might be really
be important for regeneration? I remember a conversation with
Tessier-Lavigne and a few others at a meeting at Baltimore,
perhaps nine years ago. We were discussing how many factors
might be important for axon regeneration. Marc cited a few
examples in the history of biology research and argued that no
matter how complicated a biological process is, there always is a
key mechanism. To me, that was very inspiring.

We reasoned if removal of extracellular inhibitors is not
enough, we might want to think hard about the intracellu-
ar mechanisms. At that time, we decided to turn our search
toward the inside of neurons. Every one knows that immature neurons can grow axons, but most mature neurons cannot. We took quite a few different approaches to find out why. At first, we collected many transcription factor genes [molecules that control the activity of genes] and induced them into cultured neurons individually or as a combination, to see which factors could increase axon growth. This was similar to what Yamanaka [Shinya Yamanaka, MD, PhD, who won the Nobel Prize for his stem cell work] did to make iPSC cells, [induced pluripotent stem cells – made by reverting a mature cell to its embryonic state] and we did this before his group published the paper on iPSC cell technology. Unfortunately we ended up with a long list of molecules but we still hadn’t figured out which were most important, partly because of some technical limitations. We were using *in vitro* systems and we didn’t have a reliable way to measure axon growth. So that’s one approach.

Another approach we took was to ask why mature neurons stop growing axons. Thanks to all graduate school courses I took at Toronto, I learned quite a bit about general cell biology. All cell types have a set of growth suppressors to prevent individual cells from overgrowth in an adult animal – not only neurons, but for almost any cell type to stop growing. That is why all cells, tissues, and even organisms have certain size limits. Therefore, a possibility might be that within a mature neuron certain molecules block growth. If so, genetically switching off these molecules may allow these axons to regrow.

Just as Albert described, the right techniques are crucial to answer scientific questions. To test our hypothesis, we used genetically engineered mice developed by other labs. Moreover, the optic nerve injury techniques had already been worked out by Albert and other people. My postdoc fellow, Kevin Park, learned optic injury skills when he was a student with Alan Harvey in Australia. Also my neighbor [at Harvard] Larry Benowitz is an expert in this area. With these tools and skills, it was a rather straightforward task to assess which mutant mice showed axon regeneration after optic nerve injury. After testing about 15 different mouse lines, we found that PTEN deletion could increase very robust axon regeneration.

Later on, Kai Liu, another postdoctoral fellow who trained with Wise Young [at Rutgers], demonstrated that PTEN deletion could promote the regeneration of corticospinal tract axons after experimental spinal cord injury. Because of the complicated nature of spinal cord injury models, Kai and I were very careful interpreting our results. Even before publication, we sent our data to other experts, including Oswald Steward, Binhai Zheng and Mark Tuszyński, for analysis. Jae Lee in Zheng’s lab even performed experiments to replicate our data. Over the course of these studies, we learned a lot about spinal cord injury models from these experts. Of course, this is the only first step and we still have a lot to do in the future.

**Q:** Science is built upon layers of knowledge, built upon the shoulders of the people who came before you. And I know that you, Dr. Aguayo, have spoken about the great Spanish neuroscientist Santiago Ramón y Cajal many times and that his work, well over 100 years old, is still resonant in research today. Could you comment on this great scientist and his influence?

**Albert:** Role models, such as Cajal, and interactions with teachers, peers and students play an important role in science, where knowledge is based mostly on observations and the experiences of others before you. Hence the value of a good training environment, openness and collaboration. There is also serendipity, the pleasant surprise generated by an idea or finding that some times, out of sheer luck, stimulates your imagination and incites you to tackle a new problem or use a new approach to investigate something that is already of interest to you. I guess that a good dose of confidence and conviction as well as patience are also important in research.

Once I organized my lab in Montreal on my return from England I began to study interactions between peripheral nerve fibers (axons) and their ensheathing cells, the cells of Schwann. Some of these studies were done in mutant mice and involved the grafting of nerve segments. In the late 1970s this work was extended to the spinal cord in a collaboration with Richard Bunge and Patrick Wood, then at Washington University in St. Louis. The aim of this particular project was to find out if Schwann cells grown *in vitro* could remyelinate previously demyelinated axons in the spinal cords of rodents. At that time in Montreal we had also begun to consider the possibility that, as Cajal had suggested many years before, Schwann cells could provide conditions that facilitated axonal regrowth from the injured spinal cord. The idea was further stimulated by discussions then held in the field on ways to avoid the “barriers” imposed on axonal growth by the altered glial environment of the injured CNS. These discussions took place at a meeting at the Smithsonian Institute in Washington in the late 1970s, to which I was invited by Bernice Grafstein, one of the leaders of regeneration research who pioneered early studies on the intrinsic mechanisms involved in axonal growth.

This was also the time when the HRP [horseradish peroxidase] tracer had became available as a research tool. With my colleagues Peter Richardson and Sam David, we wondered if we could use HRP to investigate the origin of the axons that penetrated peripheral nerve (PN) grafts to determine if they came...
from the CNS or were only peripheral “contaminants” from nerve roots, as LeGross Clarke in Oxford and others elsewhere had previously suggested to explain Cajal’s intriguing findings. Peter initiated the studies in the spinal cord and a paper was published in Nature in 1980 that provided HRP evidence of regeneration of spinal axons into PN segments grafted between the stumps of the fully transected spinal cord of adult rats.

Shortly after, in 1981, Sam David and I published a second paper in Science reporting similar observations in a different set of grafting experiments that we called “the handles.” They involved using a fairly long nerve graft of approximately 3.5 cm placed outside of the spine, in parallel with the spinal cord. One end of the graft was inserted into the brainstem and the other end went into the mid-thoracic portion of the spinal cord. This kind of a “bridge” gave us a long segment of nerve that facilitated the labeling and electrical recording techniques we wanted to use to study regenerating spinal axons anatomically and functionally. It also caused our laboratory animals considerably less disability than that which follows a complete spinal transection. With some of the students and postdocs we subsequently used variations of this new experimental approach to investigate regeneration from other CNS regions, such as the cortex of the brain, subcortical nuclei, brain stem, cerebellum, etc.

In October of 1983, at the end of a lecture I gave at the Institute of Neurology, Queen Square, London, I had the good fortune to meet Kwok Fai So, from Hong Kong University. He was the person who first suggested we use the optic nerve as a paradigm to further investigate CNS regeneration. He spent a year with us in Montreal developing the technique and the results of those studies were published in 1984; most of the work done subsequently by the Montreal group focused on the growth and function of regenerated axons in the visual system. Perhaps the approach that Zhigang and others have taken in regeneration research may provide a greater growth strength research showed that in adult rodents different kinds of CNS neurons from the eye, brain, spinal cord, etc., had the capacity to regrow for very long distances after injury and, at least in the visual system, to eventually form functional synapses that could transsynaptically activate targeted neurons in the part of the brain where retinal axons terminate. These studies also demonstrated that this “latent” capacity to regrow could be enhanced by changes in the environment of the damaged axons, thus raising interesting questions about the extrinsic conditions that facilitate or inhibit such regenerative capacities.

Q: The process of science bridges the work in both of your labs.

Albert: Yes. Zhigang, I think you should be given a lot of credit because you succeeded in an amazing way at the right time, taking advantage of tools that can influence important intracellular mechanisms involved in the growth of damaged axons. One of the advantages of the approach you have taken is that it provides clues on possible ways to further enhance what appears to be a relatively weak regenerative capacity in many of the nerve cells of the adult mammalian CNS. Indeed, neither the provision of a growth-permissive environment such as that harbored in the PN grafts that we used in our experiments nor those approaches that derive from the important studies done by Schwab, Strittmatter, Filbin, Fawcett, Silver, and several others on the identification and blocking of growth-inhibitory molecules expressed in the CNS, has resulted in the regrowth of a majority of the axons that are damaged in the CNS. Thus far, we remain unable to get CNS axons to regenerate as successfully as PNS axons do spontaneously, without much help from us.

One possibility, strongly supported by Zhigang’s experiments, is that a greater “push” arising from the injured nerve cells is required to overcome the mentioned molecular barriers created by injury to the CNS. Your most recent experiments on the rodent’s injured optic nerve where you interfered with the expression of the gene-transcription factors Socs3 and PTEN strongly suggest that such “push” can be given. This is quite exciting because it suggests that it may be possible to increase neural growth and hopefully restore connectivity without having to resort to surgical interventions or the use of transplants that circumvent injury sites, as we did. You’re using new knowledge and powerful new molecular tools to enhance the innate capacity of the nervous system to repair itself.

These neural growth processes are known to be active during fetal and early post-natal development and seem to persist post-natally at a slower pace. For instance, axonal growth rates are greater during the first year but peak again through adolescence when body and limb extension accelerate and neuronal remodeling is enhanced. The magnitude of the post-natal growth of certain spinal fiber tracts is exemplified by the approximately 10-fold increase in the length of the human spinal cord that can take place between birth and age 20. It is therefore intriguing that spinal cord injuries in children and young individuals are not followed by even a limited replication of what nerve cells are clearly capable of accomplishing in the undamaged spinal cord. Perhaps the approach that Zhigang and others have taken in regeneration research may provide a greater growth strength
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mental connecting interneurons.” How so? There could be some circuit remodeling happening. It may also involve a sort of relay system moving down the cord. Propriospinal axons from the cervical cord activate interneurons in the thoracic segments that, in turn, activate neurons in the lumbar segments.

The next question may be, should modern rehabilitation techniques involve arm training in concert with leg training to enhance locomotor recovery? Too soon to say yes – more studies are needed – but it wouldn’t be hard to integrate arm exercises with leg activity.

While at UCLA, Shah collaborated with fellow Associate Guillermo Garcia-Alias; he is also an author on the recent Brain paper. Garcia-Alias came to the Edgerton lab having been an Associate at James Fawcett’s lab in London – Fawcett is also a member of the Reeve Consortium. There, Garcia-Alias studied spinal nerves, and why they don’t grow very well after injury. It’s largely because of tough scar tissue that forms in the lesion area. Using a bacteria-derived enzyme called chondroitinase, or Chase, the lab was able to degrade the scar and thus promote axon growth, and recovery. The Chase story continues as Fawcett and others try to find the best ways to deliver the enzyme in a clinically relevant manner.

Meanwhile, Garcia-Alias became fascinated by the activity and recovery work being done in the Edgerton lab. “When I saw the work at UCLA I wanted to be part of it,” said Garcia-Alias, who is originally from Spain. “We have made great progress and for us Associates in the Consortium, this has broadened our horizons and deepened our thinking. We are all more than ever committed to bringing our research toward helping patients.”
that enhances these capacities and overcomes the barriers created by CNS injury. Time and hard work will tell.

Zhigang: Thank you so much, Albert. I agree, eight or nine years ago, most of those tools were available. Perhaps an advantage for me is my background in basic biology, which allowed the generation of relevant hypotheses. With all available tools, it was not too difficult to test such hypotheses. In this aspect, it is extremely important for the field to recruit talented young scientists with different backgrounds. In fact, none of these experiments were done by me alone. Over the years I have been extremely lucky in recruiting outstanding people to the lab.

Q: So Albert you mentioned a couple of words, conviction and confidence. As we look at where we are now, answering the question why axons cannot regenerate, do we have confidence and conviction that there may be a clinical answer for this?

Albert: People may at times lose perspective of how much the field of spinal cord injury treatment has advanced in only a few decades. Until less than a hundred years ago serious spinal cord injuries irremediably resulted in paralysis, great suffering and an early death. Now there are thought to be several million survivors of spinal cord injury. Not only have they survived but many of them live an active life and are well integrated in society, some being recognized leaders and role models, like the late Christopher Reeve in the U.S., and Rick Hansen in Canada.

What made this extraordinary change possible in only a few decades? The answer is the new knowledge that emerged from a medical science that has evolved so impressively and so rapidly in recent times. It was the discovery and use of anesthesia, X-rays, antibiotics, novel surgical techniques, appropriate nursing care and rehabilitation, etc., as well as the many social changes that have taken place concerning public awareness of the needs and possibilities of spinal cord injury patients. It is clear that the main engine behind this success story has been the explosion in knowledge generated by the application of the scientific method and new research technologies to the solution of problems in medical biology and related disciplines.

It is very exciting that now we are considering ways in which to heal and mend the spinal cord itself. Axonal regeneration is only a part of it, as Zhigang has already mentioned. Restoring useful functions is the objective of this entire research field and this requires the solution of other major problems such as axonal guidance to the right targets, appropriate connectivity, etc. It may be surprising to many readers that we still do not know how much has to be restored anatomically to recover a satisfactory level of function.

The work of Reggie Edgerton and his Associates in the Reeve Consortium provides an example of the need to overcome our still limited understanding of issues such as those of what is required for the recovery of human stance and ambulation. Their studies and those of others in the field, such as Sten Grillner in Sweden and Serge Rossignol in Montreal, have shown that spinal cord training protocols, which include robotic and manual tools as well as techniques that influence neuronal excitability (epidural stimulation, etc.), can lead to a significant functional recovery in the absence of any other intervention aimed at regrowing and reconnecting damaged nerve fibers.

Zhigang: I agree completely. These amazing successes by using electrical stimulation suggest that even small numbers of spared axons can be recruited with impressive functional outcomes. This provides a nice example for powerful homeostatic effects on neural modulations as proposed by Eve Marder, Cori Bargmann, and others. Now, with more regenerating axons we and others have achieved, it would be exciting to test whether such modulatory means as stimulation could enhance functional recovery after spinal cord injury. On the other hand, it would be interesting to better understand how this works, how electrical stimulation promotes functional recovery.

Q: Zhigang, I wondered if you could address the sense of confidence and faith that you're doing will continue to grow.

Zhigang: I also feel optimistic. Axon growth is a first step – just chapter one of the neuroscience textbook. If you think about it, axon growth, synapse formation, or synapse reorganization, there are many different steps there. I think the field is getting much more mature. Now we understand each of these individual steps better than before, and we have much better tools. For example, with regenerating axons, we are able to analyze whether or not they can conduct electrical signals from one neuron to another neuron – an in the case of what Albert described, the retinal signal to the superior colliculus and other targets. We might find some steps to be wrong, and this could allow us to find a relevant solution, an accessory treatment. In the end, we might need a combinatorial strategy to achieve functional recovery. In light of recent medical advances in areas such as AIDS and cancer, such combinatorial strategy, instead of a single magic bullet treatment, might be more realistic solution.

Albert: I remember from my student days what Bernardo Houssay, a Nobel Laureate from Argentina, said: “Science is not expensive. What is expensive is ignorance.” We need to invest in good science and in programs that support multidisciplinary collaborations in spinal cord research. What lies ahead is not easy, it is likely to be very difficult at times, but I continue to be optimistic about the outcome.

Zhigang: I completely agree. I feel even with the limitations of the current situation, we can still do good science.

Q: And is it fun?

Albert: Well, I can tell you and, especially those readers who are young and perhaps interested in doing research, that doing science is great fun. I am sure that Zhigang will agree.

Zhigang: I do. It is always a great feeling to find something new. If such a finding is somehow helpful for treating human patients, that would be even better. Not all professionals have such privilege.
The Big Idea aims to propel the paralysis community toward a new era of groundbreaking treatment. It’s a movement to transform what it means for individuals to live with a spinal cord injury.

Our goal is to raise funds to expand the remarkable functional recoveries shown by four participants in epidural stimulation experiments to 36 more individuals.

Ultimately, The Big Idea’s mission is to make this therapy available to men and women living with paralysis worldwide. Join the movement now by donating to help fund this research and support the paralysis community. See www.ReeveBigIdea.org