

contents

SPRING 2018

features

11 Pole Sport & Sex

Meet Erin Clark, a wheelchair user from Canada who is making people pay attention to pole sport—and her.

12 Risky Business

When the widely-respected Cochrane Collaboration published its review suggesting there was no benefit to single-use catheters, Dr. Andrei Krassioukov had doubts.

14 Cover Story

Aging with SCI: minimizing the potential physical and mental health pitfalls, and a closer look at some of your SCI BC Peers who are meeting the challenges of getting older.

24 Rare Air

How basic incremental science uncovered the fact that acute intermittent hypoxia can help improve breathing function for people with high level quadriplegia.

28 Vantastic

Need wheels? Delta Wheelchair Vans, owned and operated by SCI BC Peer Barb Schober, can help.

30 Hidden Assets

Recent research reveals the spinal cord may have the ability to control breathing all by itself, without brain input.

departments

4 editor's message

An update on TNCs such as Uber and Lyft, and why we think they're potentially good for people with SCI.

6 gear & gadgets

New products, devices and aids to daily living that might make a difference in your life.

8 events

Important dates for your calendar.

10 peers

A pictorial look back at SCI BC's recent Women of SCI (Strength – Confidence – Independence) event.

13 ask the SPIN DOCTOR

Recent warnings about fluoroquinolone antibiotics provide more incentive to avoid UTIs.

33 Participate in Research

ICORD research projects that need your participation.

34 last word

On the eve of cannabis legalization in Canada, research from Spain confirms weed's ability to calm spasticity.

Cover illustration by Maya Pankalla



11



14



24



28



Rare Air

Acute intermittent hypoxia, or AIH, has emerged as a promising treatment to strengthen the respiratory ability of people with high level incomplete quadriplegia. AIH therapy, which involves breathing air containing lower-than-normal levels of oxygen, also has potential to improve walking and grasping for people with any level of incomplete SCI. One of the pioneers of this research is the University of Florida's Dr. Gordon Mitchell, who agreed to share what we think is a remarkable detective story of how basic, incremental science resulted in such a promising treatment.

Hypoxia. It's a word that many readers know well—and dread. After all, hypoxia is one of the most serious consequences of sleep apnea. And sleep apnea is a big problem for a lot of people with SCI—particularly those with quadriplegia.

Hypoxia occurs when body tissues are deprived of adequate oxygen. In extreme cases, death is the ultimate outcome. Even mild to moderate cases of sleep apnea, which limits the amount of oxygen entering the bloodstream, results in hypoxia that can, over time, lead to serious health problems.

But it turns out that hypoxia has an upside—one that is so significant that it may become a game changer in the search for ways to restore function after SCI. In simple terms, the central nervous system, when subjected to hypoxia, attempts to “fight back” in order to minimize the impact. It does this by producing growth factors that encourage neuroplasticity—the incredible ability of neurons to change, rewire, and regrow.

The best example of this to date is that, in the presence of carefully-prescribed, intermittent, low doses of hypoxia, the nerves that control breathing are “encouraged” to grow and make better connections. This increases the strength of the breathing signal that's being sent to the muscles that control the lungs, and therefore the ability of the lungs to take in more oxygen.

Evidence also suggests that this same benefit of AIH can be used to strengthen the connections of other motor neurons, such as those involved in leg and hand function.

Obviously, any treatment that is able to strengthen the remaining nerve connections after an incomplete SCI could make a big difference in people's lives. Better breathing ability and a stronger grasp are possible outcomes for people with higher level incomplete injuries. Improved walking ability for people with lower level incomplete SCI is another promising possibility.

In order to fully understand



AIH and its possible implications for people with incomplete SCI, let's flip the calendar back a few decades to the 1970s, as Dr. Gordon Mitchell was just beginning his career as a neuroscientist.

Today, Mitchell is Preeminence Professor of Neuroscience and Professor of Physical Therapy at the University of Florida, and Director of the university's Center for Respiratory Research and Rehabilitation and McKnight Brain Institute. But back in the 70s, he was a grad student who became fascinated with the concept of neuroplasticity—the idea that neurons might have the ability to regrow and rewire themselves in the brain and nervous system.

"My interest in the beginning wasn't focused on SCI at all; I barely thought about that," says Mitchell. "The truth is that I was simply interested in the idea that plasticity is an important feature of the respiratory control system. At the time, there was a very strong sense among respiratory physiologists and neuroscientists that neuroplasticity was not an important feature of motor neurons, nor that it was relevant to the neural system controlling breathing. When I would ask questions about it, most thought the issue had already been solved. Consequently, I focused on other topics for the next ten years of my career."

Then, in the mid-1980s, as Mitchell and his colleagues were studying breathing during exercise, they accidentally observed responses that, in Mitchell's mind, could only be explained by the presence of plasticity in the neural system controlling breathing. Intrigued by the idea that the central nervous system was not just static wiring (think of a house's copper wiring) and the possible implications of this, he made the decision to focus the next phase of his research career on identifying forms of neuroplasticity in respiratory motor control.

Fast forward to the late 1990s. Mitchell, who had completed his PhD at the University of California Irvine, had been a professor since 1992 at the University of Wisconsin's Department of Comparative Biosciences. By this point, research



Graduate student Shakeel Ahmed supervises an AIH treatment in Dr. Mitchell's laboratory at the University of Florida.

had confirmed that, in animal models, intermittent periods of low oxygen consumption could indeed trigger plasticity in the phrenic nerve, the conduit by which signals to breathe are sent from the brain through the spinal cord to the respiratory muscles. And it was also becoming clear that serotonin, an important growth factor or neurochemical, was involved in the process—the hypoxia triggered release of serotonin near spinal motor neurons, initiating plasticity.

But what no one had recognized was that all of this could be highly relevant in the SCI world.

"That realization first emerged when Tracy Baker (a graduate student at the time) and I discovered that the actions of serotonin were in the spinal cord, and not in the brainstem as originally thought," says Mitchell. "This finding was made in the late 1990s, but wasn't published until 2002 in the *Journal of Neuroscience*."

The implications were enormous. Since the plasticity was occurring in the spinal cord, it immediately raised the question: could AIH-induced plasticity be harnessed to strengthen spared neural pathways at the site of an incomplete SCI—and restore function in the process?

"Some thought it was a naïve idea, but we had to try, using a rat SCI model," says Mitchell.

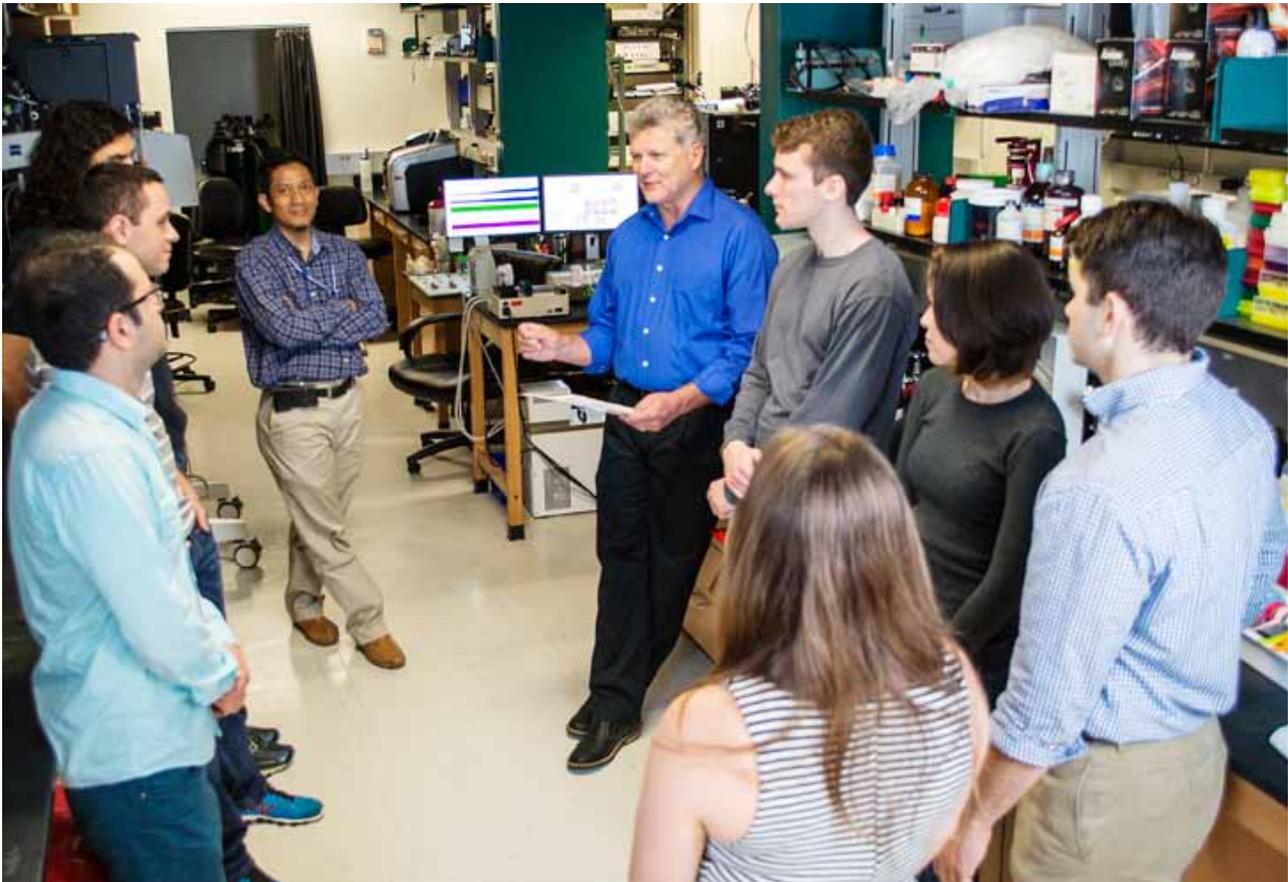
The resulting study, led by postdoc student David Fuller (now a professor at the University of Florida) saw the

rats receive six five-minute episodes of low oxygen per hour for 12 hours each night—the time of the day when rats are most active. The result was a breakthrough: after one week, these daily exposures greatly increased the ability of the rats to generate phrenic nerve activity (and presumably breathing) below the injury. This study was published in the *Journal of Neuroscience* in 2003.

"In the end, we look back and realize that we were lucky in our initial study," says Mitchell. "The key to this treatment is the dose, and it turns out that a low dose is better. High doses of intermittent hypoxia trigger brain and spinal inflammation, leading to pathology and undermining the ability of AIH to trigger beneficial plasticity. With 20/20 hindsight, if we had used a frequency of hypoxic episodes of 10 or greater, we would have been disappointed, and we likely would have moved on to other things."

Over the next decade, Mitchell and other scientists incrementally added to their knowledge and the body of evidence that suggested that AIH had significant potential as a therapy to restore function.

First came the discovery that the release of serotonin after AIH therapy in turn stimulated the production of Brain Derived Neurotrophic Factor or BDNF, and confirmed that it's BDNF that is ultimately responsible for triggering the plasticity in the phrenic nerve.



Dr. Gordon Mitchell leads a discussion about AIH with his laboratory team at the University of Florida.

“This paper gave substance to our mechanistic understanding and led to a 15-year series of papers giving us a fairly comprehensive understanding of just how this works,” explains Mitchell. “Understanding mechanisms is really important, since it reassures us that we are studying something real, and improves our ability to refine the best treatment strategies to restore function after SCI.”

Meanwhile, complementary work demonstrated that the AIH not only worked in restoring phrenic nerve capacity in breathing, but also in walking ability in incomplete SCI—first in animals, and then in humans.

But Mitchell says the real leap came in 2014, when the Trumbower laboratory (then at Emory University) and the Rymer laboratory in Chicago completed a randomized, double-blind cross-over design study of walking ability in humans with chronic incomplete SCI.

“In this study, AIH was applied for five successive days, either alone, or followed by 30 minutes of walking practice,” says Mitchell. “With combined training, the improvement in walking ability was substantial—greater than 35 percent—even days after the training had ended. I think this study raised awareness among a broader community of rehabilitation scientists.”

Today, there are six published studies confirming the efficacy of AIH in humans with chronic SCI, including studies of walking ability, breathing ability and hand function. Buoyed by the results, Mitchell and other scientists working in the field now have many additional studies underway, and were recently inspired to create the Therapeutic Intermittent Hypoxia Consortium to share information and stimulate further progress.

Members of the newly-formed consortium, which is led by Mitchell, have their work cut out for them.

“My personal priority is to continue basic research into mechanisms, and to push new knowledge into consideration for clinical application as soon as is practical,” says Mitchell, who moved from the University of Wisconsin to his current positions in Florida in 2014. “We have a great team focused on this approach, and we need to test it adequately before we lose that momentum.”

Mitchell and his team are seeking answers to several specific questions. For example, are the mechanisms behind improvements in breathing ability the same as those responsible for AIH’s ability to improve function in other motor neurons, such as those controlling the legs and hands? Does gender and age make any difference in outcomes in humans, as has shown to be the case in animal studies? Can a combination of AIH and various compounds enhance outcomes, as has been demonstrated with caffeine?

He also wants to know if the therapy has applications beyond SCI.

“Another gratifying outcome would be translation to other clinical disorders that compromise movement,” he says. “If this is a generalizable strategy to restore movement, will it work in those suffering from ALS? MS? Stroke? Peripheral neuropathies? Post-polio syndrome? There are so many other clinical disorders that may benefit from this approach.”

Meanwhile, priorities that other consortium members will work on include development of a standardized device, with safety monitoring and the ability to log data, to deliver the doses of low-oxygen. Identification of biomarkers to help pinpoint which individuals are likely to benefit most from the therapy is another area of research being undertaken by consortium members.

Finally, there’s the burning question of whether or not AIH treatment results in permanent or temporary results.

“What we know is that a single presentation of AIH will trigger plasticity for a day,” he says. “If we expose rats or humans to five to seven days, then the plasticity and functional benefits last nearly a week or more. We don’t yet know if daily use for months will have longer or even permanent effects. That is one of our knowledge gaps.”

If effects don’t prove to be permanent, what are the implications?

“Will a treatment that can help function for a week be useful?” asks Mitchell. “In many respects, AIH is a bit like exercise, but without the need to move. However, it’s clear that traditional rehabilitation in combination is beneficial. Meanwhile, the therapy on its own is easy to administer. It’s not stressful. Would it be worth 45 minutes of time taking therapy, while surfing the web or reading a book or listening to music, in order to enhance walking or hand function for the day? If it’s not possible to elicit permanent effects, it would be really helpful to receive community input on whether or not limited duration benefits will be useful.”

Clearly, while the entire AIH research field is promising, there remains a lot of

Don’t try this at home, kids.

Perhaps you’ve read this and are scheming about ways to try AIH on your own. After all, a form of intermittent hypoxia is already being used by endurance athletes seeking to enhance training by mimicking a high-altitude setting. But Mitchell advises against it—there are just too many unknowns, and exact dosages are critical for safety, in terms of oxygen content of the air and the duration and frequency of treatment.

Meanwhile, you might be wondering who makes a good candidate for AIH. Generally, anyone with an incomplete injury could potentially benefit. But Mitchell points out that, for the moment, some people have to be excluded.

“For example, we currently rule out individuals with a history of seizures in our studies, yet we have no real knowledge that this is a problem,” he says. “It is possible that repetitive acute intermittent hypoxia could even suppress seizures. Experience may eventually tell us that these concerns were unfounded, but a cautious approach is prudent for now. For those with sleep apnea, we also run into a dilemma. Almost 80 percent of individuals with cervical SCI have sleep apnea. Can we rule them out from studies, particularly since daytime intermittent hypoxia is in fact more effective at improving breathing in otherwise healthy people with sleep apnea? These types of dilemmas are the reason we need to keep pressing to obtain real evidence concerning the limits. Clearly, this is a process. I expect that, even if this treatment makes it to clinical practice, we will continue to learn and evolve and refine our therapeutic use—just as with any other treatment.”

work to be done. And that’s where the elephant in the room becomes really obvious: who funds this research?

“It is very hard to raise adequate funds for this type of research, as much as we wish to know the answers,” concedes Mitchell. “Efforts are underway to secure adequate funding in each of these areas, but we are far from our goals.”

The reason is clear. How do pharmaceutical companies, who are by far the largest funders of all medical research, make money from low-oxygen air?

Mitchell concedes this is a concern. But based on existing interest, he is optimistic that a medical device manufacturing company may step up to the plate. And he also believes the work is so important that other funding sources that aren’t motivated solely by profit will eventually see the value and come to the table—for example, private foundations and forward-looking government agencies that recognize the work may actually result in cost savings down the road.

Meanwhile, the promise of this research makes it easy for Mitchell to get into his lab every morning and help lead

the charge—even after four-plus decades as a scientist working in the field.

“For me, there is a lot of gratification in understanding basic biology—such as the fact that there is plasticity in the neural system controlling breathing, and that we are gaining understanding of how it works. When I was a grad student, we thought of motor neurons as ‘copper wire’ relays between the brain and muscles. Now we know that phrenic motor neurons have exceptional capacity for plasticity. I also find gratification in seeing ideas developed through studies of respiratory physiology translate into an understanding that similar plasticity occurs in other motor systems, including those governing leg, arm, tongue and laryngeal functions.

“And of course, the usual use of the word translation is to see benefits in healthcare. This is an enormously gratifying part of our investigations. After so many years of basic research, we are seeing clear potential that the ideas may impact clinical practice. For me, the ultimate hope is for progress to continue as we explore basic biology, and translate that knowledge to SCI and many other disorders that compromise movement.” ■