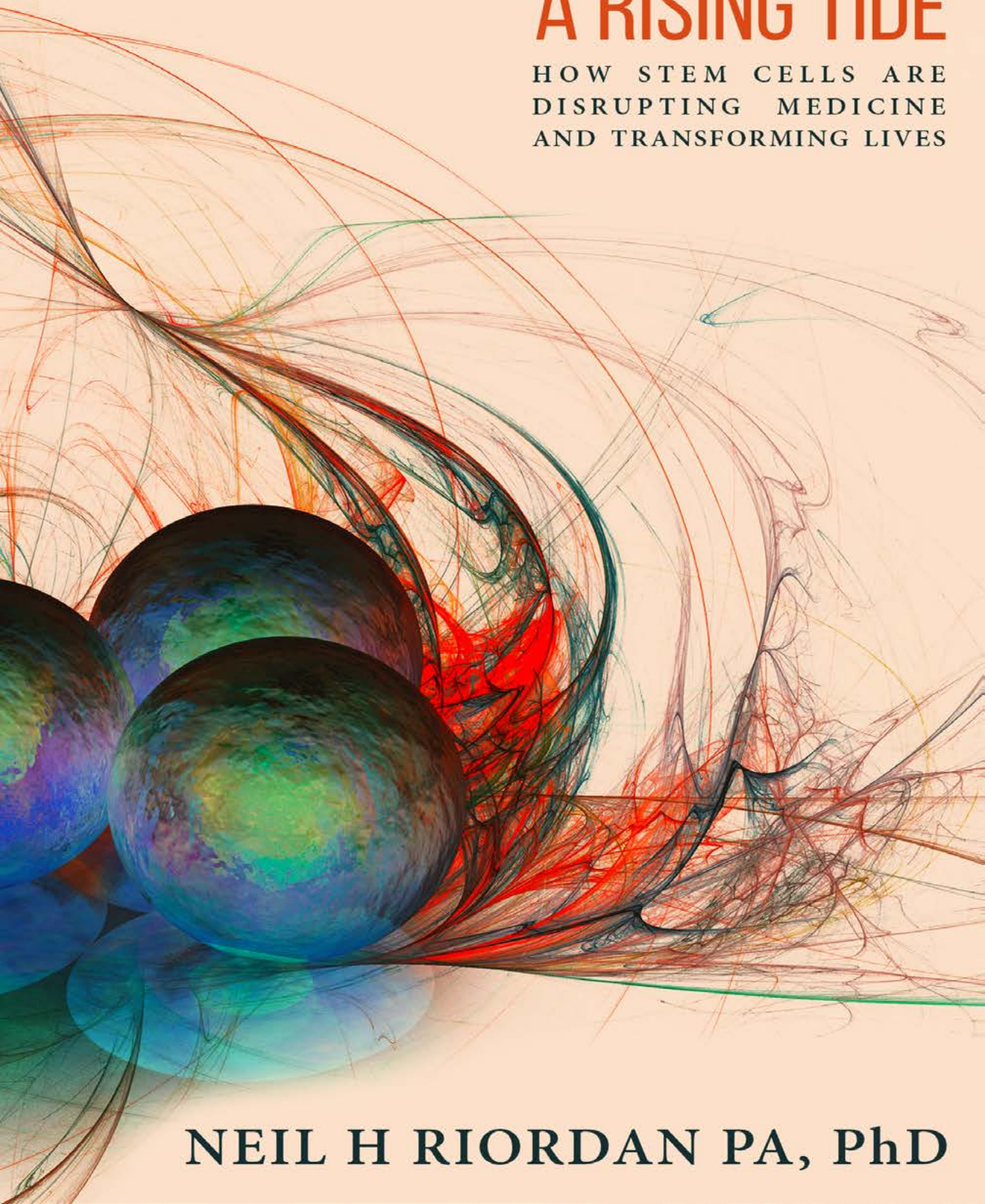
STEM CELL THERAPY

A RISING TIDE

HOW STEM CELLS ARE DISRUPTING MEDICINE AND TRANSFORMING LIVES



NEIL H RIORDAN PA, PhD

"Neil takes readers on a riveting journey through the past, present and future of stem cell therapy. His well-researched, educational and entertaining book could change your life. I highly recommend it."

Tony Robbins, NY Times #1 Bestselling Author

"100 years old will soon become the new 60. Stem cells are a key therapeutic to enable this future. Dr. Riordan's book is your guide to why this is true and how you will benefit. A must read for anyone who cares about extending their healthy lifespan."

Peter H. Diamandis, MD; Founder, XPRIZE & Singularity University; Co-Founder, Human Longevity, Inc.; Author of NY Times Best Sellers *Abundance* and *Bold*

Stem cells are the repair cells of your body. When there aren't enough of them, or they aren't working properly, chronic diseases can manifest and persist.

From industry leaders, sport stars, and Hollywood icons to thousands of everyday, ordinary people, stem cell therapy has helped when standard medicine failed. Many of them had lost hope. These are their stories.

Neil H Riordan, author of *MSC: Clinical Evidence Leading Medicine's Next Frontier*, the definitive textbook on clinical stem cell therapy, brings you an easy-to-read book about how and why stem cells work, and why they're the wave of the future.

"I'm the luckiest guy in the world. Stem cells have given me my life back."

Sam Harrell – Football coach and Multiple Sclerosis patient

"I never want to go back to autism before stem cells."

Marty Kelly – Parent of a child with autism

NEIL H RIORDAN, PA, PhD

Neil H Riordan is an accomplished scientist and developer of regenerative medicine therapeutics, with more than 70 peer reviewed publications and more than 40 patents and patent applications to his credit. He is the author of MSC: Clinical Evidence Leading Medicine's Next Frontier, a groundbreaking compilation of stem cell studies for more than 30 medical conditions, with over 800 references to peer-reviewed articles. Dr. Riordan founded Medistem Panama, a leading stem cell laboratory and research facility that is ISO 9001 certified and fully licensed by the Panamanian Ministry of Health. He also founded the Stem Cell Institute in Panama, where his mesenchymal stem cell technologies continue to be implemented in patients, now numbering in the thousands, with autoimmune and degenerative diseases and injuries.

Stem Cell Therapy
A Rising Tide

How Stem Cells are Disrupting Medicine and Transforming Lives

Neil H. Riordan

Stem Cell Therapy: A Rising Tide
How Stem Cells are Disrupting Medicine and Transforming Lives

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This book is not intended as a substitute for the medical advice of physicians. The information provided in this book is designed solely to provide helpful information on the subjects discussed. The reader should regularly consult a physician in matters relating to their health and particularly with respect to any symptoms that may require diagnosis or medical attention. While all the stories in this book are true, some names and identifying details have been changed to protect the privacy of the people involved.

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Foreword

As I read this book, I became very emotional. I had to go back about 28 years ago when my wife and I sat in a doctor's office and listened to a neurologist list in grim detail how our beautiful three-year-old son Ryan would spend his next 20 years. The doctor told us there was nothing that they could do at that time. He suggested that we do everything we could to keep Ryan active in order to maintain the strength he had as long as possible. And hopefully in the next 20 years they might find a cure for muscular dystrophy. The prognosis changed our lives forever. It was a very painful time for all of us.

As I continued to read about all of the patients who have been treated by Dr. Riordan, I realized that we all had one thing in common: traditional medicine had given up on us. There was nothing that could be done. Our own government, founded on the premise of life, liberty, and the pursuit of happiness, had evolved into overreaching bureaucracy that would attempt to prevent us from seeking lifesaving alternative treatments.

But once again, we all had something else in common. We found a man who was willing to do everything in his power to offer us options and give us hope for the future of our loved ones. Dr. Riordan has truly dedicated himself to his profession as a medical pioneer. He has sacrificed everything he has to give those who have been told there are no options a fighting chance and real hope for the future.

Dr. Riordan has never wavered in the face of scrutiny. It takes true courage to stand up to the often judgmental "traditional" medical community—those who act offended when you suggest that there might be a different way.

Fortunately for all of us, Dr. Riordan had the foresight to look beyond the walls of traditional medicine and fight the fight for us. I encourage you to read this book, and not just the chapters related to your condition. As a whole, the book lays out Dr. Riordan's courageous and successful journey through his stories and the stories of his patients.

Thank you, Dr. Riordan, for all that you have done for us and our families. You truly are a hero!

George Benton, Ryan's father

Introduction

BY ARNOLD CAPLAN, PHD

Neil Riordan, PhD, PA is a pioneer of the highest order, in some ways like John Glenn or Neil Armstrong. Neil has ventured where the routes were uncharted and the dangers huge. His rocket of cell therapy was launched on a rickety platform filled with hopes and dreams, and powered by an engine of money. This pioneer has hacked his way through the jungle of naysayers and has produced miracles of enormous proportions. He has taken our scientific dreams and translated them into a high-caliber medical facility that does good by offering exposure to cell therapy treatments that we working scientists only dream about.

Although there are those in my professional realm who would say that Neil is a medical "cowboy" who "experiments" with human subjects, I would say that he is providing access to therapies that are no more experimental than one sees every single day in the surgical suites of major medical centers. In such situations, the surgeon is "forced" to improvise because of the complexity of the wound field. Such improvisation sometimes involves using materials that are not approved but that the surgeon "feels" will work well in the situation he faces. For example, human decellularized skin from dead people was approved for topical applications for ulcerated wounds in diabetic patients. But these "membranes" are fabulous for closing abdominal surgical wounds in hernia repair operations and have changed the way such closures are done. This surgical improvision, originally performed by a "cowboy" surgeon, is now the standard of care. We move forward in medicine by the skill and insightful work of pioneers—some with IRB approval and some not. Riordan's procedures with MSCs currently have IRB approvals.

In a sense of transparency, let me say that I have accepted honoraria from Neil Riordan and gifts of hotel rooms, meals, and, indeed, infusions of MSCs. These all have monetary value, but none influences my opinion. The monetary success of Neil's enterprises evoke jealousy in some entrepreneurs, but Neil's continual reinvestment of money into his next medically successful enterprise displays his true motives—the advancement of a medically necessary science despite great obstacles. The key to his success is in the enormously high quality of his facilities; the people, doctors, nurses, receptionist, PR team, etc. are *all* highly principled and care about the patients they serve. These people care about what they do because Neil recruits them for their skills and attitude. He does not discuss this in this book, but they are present on every page. He talks about Dr. Paz, but he does not tell you of his long medical experience and his reputation in the United States and in Panama for caring and experienced medical judgements. In all of Neil's clinics, quality control labs, hotels for patients, and restaurants where they eat, the staff behind the scenes are dedicated to providing the highest quality medical care possible. Some clinics and hospitals in the United States could take lessons from the Riordan gang. That said, the cell-based therapies Neil's clinics provide have not all been approved and tested by double-blind, placebo control and rigorously monitored clinical trials, although such trials are currently underway. But, like innovative surgeons, these open-label uses have proven effective, as hopefully we will see in published peer-reviewed reports of his studies.

Each chapter of this book recounts the personal stories of how Neil's unwavering confidence that cell-based therapies with MSC preparations from fat, marrow, or umbilical cords can make a medical difference. Neil made medical tourism work, and what he has done is highly laudable, not only because of the patients he has helped, but because of the laws that have been written to support cell-based therapies in Panama. This book is not what I pleaded with Neil to write, however. I have, for many years, begged him to give us outcome reports of his many patients: what they have as clinical problems, what they walk in with, and the longitudinal outcomes after the cell infusions. Hopefully these will be forthcoming, but they are not in this book. What is here in these pages is, none-the-less, amazing.

I first learned about Neil's clinic in Costa Rica and thought his procedures and therapies were brilliant. And these were crude compared to those currently underway in Panama. The Panama GMP-production facilities, his offices and treatment rooms, and the products including MSCs from umbilical tissue are of the highest quality. These are the vehicles and the platform that allow him to write this treatise of the therapies they provide. It is a shame that we have to fly to Panama to have access to these therapies instead of having them available in the United States. How long will it take for such therapies to be available to the patients covered by Medicaid or Medicare instead of those from Beverly Hills or Long Island who can afford to travel to Panama?

Almost daily I receive emails from people who want access to "stem cell" treatments. I tell them that I am just a PhD researcher and cannot suggest an avenue of treatment for medical issues. If you have this book in hand, read the chapters. They are honest, open, and spellbinding. While Neil is not a medical doctor, his clinical experience as a physician assistant along with his research background have prepared him for the serious medical issues for which Neil has organized cell therapy treatments, often with quite significant outcomes. Neil is certainly a student of the medical arts and an expert using innovative treatments. I have talked to patients of Neil's clinics and their family members about their treatments; the stories told in this book are just the tip of the iceberg. This is an interesting book and an interesting and gutsy journey of Neil Riordan. His physician father would be proud to recognize Neil's passion and medical achievements.

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January 15, 2017

Chapter Seven

MULTIPLE SCLEROSIS— CALMING THE IMMUNE SYSTEM

Of all the diseases and chronic conditions we treat with stem cells, the one that I have the best personal understanding of is multiple sclerosis (MS) because I had something very similar to it that time I got the bends.

They told me when I was being treated in the UK that the lesions that form in the brain after a severe case of the bends are the same as the lesions that form when someone suffers from multiple sclerosis. The thick, foggy feeling I experienced, the numbness in my extremities that made walking or any kind of movement a discouraging chore, and the way my days became dim and my mood sunk low were the same effects that MS patients struggle with every day. For me, though, there was hope that the treatments we undertook could reverse the worst of it. Not so with most of the people who suffer with MS.

Shortly before we set up our clinic in Costa Rica, articles started to appear in scientific journals that described experiments working with stem cells to alleviate MS symptoms in mice,[1] and one limited-success case study with a human patient who was treated by Iranian doctors.

The science behind using stem cells to treat MS made sense to me. Multiple sclerosis is an autoimmune system disorder in which the body's immune cells attack the central nervous system—the brain, the optic nerve, and the spinal cord—destroying the myelin sheath, the fatty substance that protects the nerve cells. Once that protective barrier is damaged, the nerve impulses that travel between the brain and the spinal cord are blocked or distorted, affecting walking, balance, coordination, and vision. As the disease progresses, those severely affected may lose control of their bowels and sexual function and can become confused and forgetful.

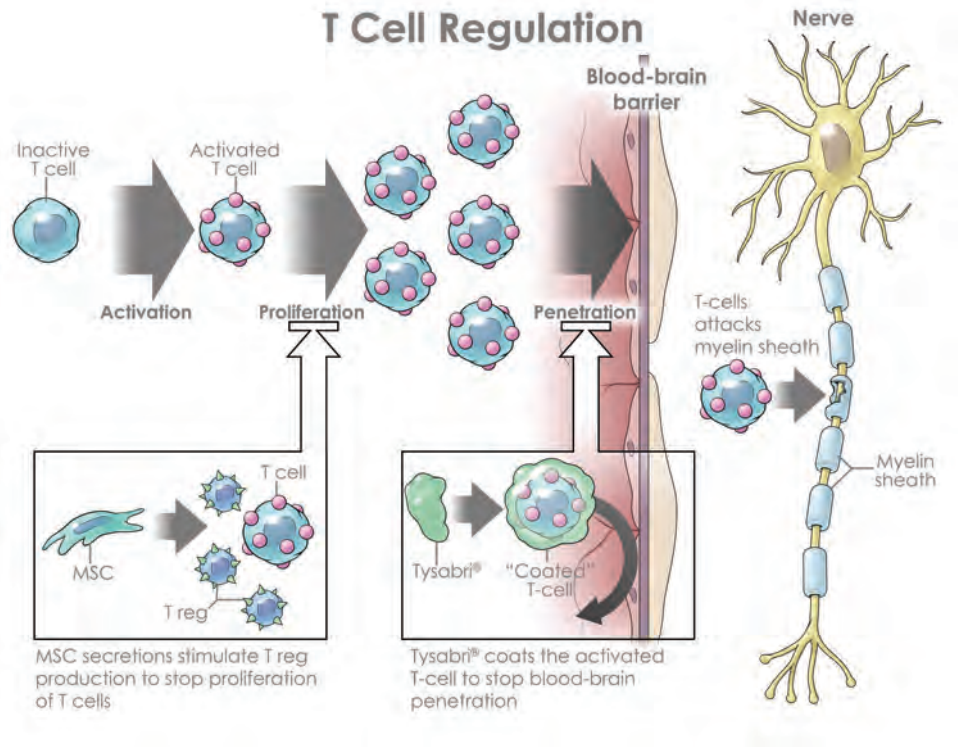
We'd had success working on other autoimmune disorders using stem cells to block the inappropriate immune response and to create the right conditions for tissue regeneration. I was eager to try our techniques on MS partially because I believed we could be very effective where conventional pharmaceutical treatments with steroids, immune modulators, and immune suppressants had not, and partially because I knew how these patients felt.

The goal of our umbilical cord MSC treatments for patients with multiple sclerosis really has nothing to do with repairing the damaged or destroyed myelin in the lesions found in the brain and spinal cord. Because multiple sclerosis is first and foremost an autoimmune disease, and not neurological, one goal is to address the immune dysfunction. At the root of the disease is a pool of immune cells called T cells, which actively proliferate, cross the blood-brain barrier (BBB), and attack myelin. These cells are not typically found in great numbers in the brain and spinal cord—they are found throughout the rest of the body. These T cells, for reasons unknown, clone themselves until they become an army of T cells. Our primary goal, then, is to interfere with myelin-specific T cell reproduction (also called *clonal expansion*). Mesenchymal stem cells have been shown in multiple studies to have the capacity to block this so-called clonal expansion of activated T cells. In a way, MSCs immunosuppress, but unlike some drugs that suppress the immune system, this specific blocking of activated T cells does not quash the entire immune system—the cells and their secretions only block the clonal expansion. Other drugs that suppress the immune system—for example, the steroid hydrocortisone—have an effect on the entire immune system, which can increase the risk to the recipient of infectious diseases and even some cancers. Steroids are catabolic, meaning they break down tissue. MSCs have

the opposite effect—they are anabolic. They stimulate regeneration. They are the body's way of naturally keeping the immune system in check.

Multiple sclerosis is essentially the same condition as rheumatoid arthritis and type 1 diabetes. All three involve this proliferation of T cells—in multiple sclerosis they attack the myelin that protects nerves; in rheumatoid arthritis they attack the lining of the joints; and in type 1 diabetes they attack the beta cells in the pancreas. T-regulatory cells usually keep T cells under control but are unable to keep up with T cell proliferation in these autoimmune diseases. MSCs produce T-regulatory cells, which decreases activated T cells, addressing autoimmune dysfunction.

A new drug prescribed for relapsing-remitting MS called Tysabri® acts as a coating for T cells, preventing them from penetrating the blood-brain barrier or spinal cord. Preventing T cells from entering the brain may seem like a good idea, since activated T cells are responsible for destroying the myelin that leads to MS, but the drug also prevents inactive T cells from reaching



the brain to protect it from infection. Tysabri essentially compromises the brain's immune system. One of the worst side effects of this drug is a condition known as progressive multifocal leukoencephalopathy (PML), a potentially fatal viral disease that triggers inflammation throughout the brain. Because MSCs target the original clonal expansion of activated T cells, MSC treatment for MS obviates the need for a drug like Tysabri because it addresses the root cause of the problem.

If it were the goal of the treatment to induce remyelination, then certainly the route of delivery would be of greatest importance. You would want for the cells (or whatever proposed remyelination agent) to be as close as possible to the lesions requiring the repair. In my opinion, it will be difficult to successfully treat multiple sclerosis by remyelination alone because if you do not address the immune problem you will continue to lose myelin. Therefore, getting the cells to the lesions for myelin repair is not particularly important. Further support for this opinion is that there is very good evidence that the body has the innate ability to regenerate myelin without intervention. There are three good examples of this.

The first example comes from a condition called Guillain–Barré syndrome, an autoimmune disease that results from an immune attack on the myelin of peripheral nerves. It involves an ascending paralysis and can be life threatening if the paralysis gets high enough to affect breathing. Guillain–Barré syndrome is treatable and generally temporary. In 80 percent of patients the underlying nerves are not irreparably damaged, and there are no long-term neurologic symptoms, while 20 percent experience permanent nerve damage[2] because the axons of the nerves are damaged. The good news is that the disease is temporary. The better news is that in mild cases in which the axons were not destroyed, complete remyelination occurs—the body has the capacity to restore myelin.

The second example comes from a phenomenon seen with serial MRI images of the brains in people with MS. Fifty percent of these low-intensity lesions known as "black holes" revert within one month of appearance, indicating that remyelination has occurred spontaneously.[3]

Further evidence for supporting the immune system and not the central nervous system in MS comes from the work of several groups, including

Northwestern University, that are using chemotherapeutic conditioning whereby the immune system is wiped out (along with the bystanding hematopoietic stem cells), followed by bone marrow reconstitution using previously harvested bone marrow stem cells.[4]

Our turning point patient was Richard Humphries, a gregarious and affable Texan whose life spiraled downhill dramatically when he first suffered symptoms of MS in 2005 at age 50. At that time, Richard was a high-powered hospital executive, the administrator for a chain of nursing homes in Texas who supervised a staff of 140 people.

At first, Richard dismissed his symptoms as aberrations. At 6 feet, 5 inches tall, he's a big guy. He'd always been very active, playing a lot of golf, running three miles a day and biking six miles or more several times a week. One spring day he was cycling with his wife and noticed that his thighs were going numb, but he dismissed it. Then his wife started to notice that he was less coherent. One Saturday afternoon he came home from a golf tournament at his church and she told him he was acting like he was drunk, although there hadn't been any alcohol at the tournament. Still, he brushed this off as a one-time oddity. Until the seizures started.

Imagine this big guy, head of a big organization, dropping to the floor and curling up in a fetal position as his body rocked, his left arm contracting first, then his left ankle curling. Very quickly the number of seizures escalated from a few a day to so many that he lost count. Richard remembers one weekend when he had 132 seizures. Some hours he'd have one every six minutes.

He went to see a few neurosurgeons in his area, all of whom ran tests on him but couldn't diagnose his illness. One of the doctors prescribed anti-seizure medication, which slowed the number of seizures for a while, but they soon returned. When they came back, the seizures presented differently. After the seizure was over, Richard was out of it for quite some time. He wasn't conscious of what anyone was saying to him. He could repeat someone's words back to them, but he had no sense of what they meant. It was as if he were in a totally different world. Finally, in October 2005, he and his wife journeyed to the Mayo Clinic in Minnesota where the neurosurgeon quickly diagnosed his MS.

Richard was getting worse and so was his family's situation. He was fired from his job at the hospital because his bosses said he was unreliable and had become a workplace hazard. Richard entered a world of darkness. He had been the major breadwinner for his family of four children, two in college, and now no one would hire him. He had a tough time even being useful around the house. One day he went to the big box hardware store a few miles from home and couldn't figure out how to get back. "I didn't even have enough function in my brain to dial my wife," he said. "Everything kind of went gray, and I sat in the parking lot for a couple of hours until I figured out that if I got to that street right there, it would get me pretty close to my house. The street took me close to my house, but then I realized I missed the turn to my street. After a couple more mistakes, I finally find found my way home, but it took three and a half hours."

As he sat in his bed, struggling to make it to the bathroom on his own, he decided he was a terrible burden to his family. The most honorable thing to do, he thought, was to set them free of him. When his wife came home, he told her he knew she didn't sign up for this kind of life. If she wanted to divorce him, he was granting her permission. His wife, a surgical nurse, looked at him astounded. She had been at his side during the worst of seizures, massaging him and speaking softly to him until they subsided. She told him she took her vows to him seriously, and if he wanted a divorce he would have to be the one to initiate it. She wasn't going anywhere.

At first, Richard had responded well to the medicines that treat MS. His seizures decreased in 2006, but by 2007 they were back. The drugs he was prescribed had started to lose their effectiveness. The doctors changed his meds, with some improvement in his condition, but by the end of 2007 he was having 30 to 40 seizures a month.

In 2008, Richard's brother, a retired attorney, started looking into stem cell treatments for MS, and found our clinic in Costa Rica. He offered to finance Richard's treatment with us. Richard later told me he was pretty scared when he arrived, but it didn't affect his sense of humor. He was in a treatment room being assessed by one of our staff the first time he saw me. "Either you're the janitor, or you're the guy who owns this place," he said, not very impressed with my wardrobe.

After he got more comfortable with the clinic and saw with a professional's eye the quality of the service we provide and the high scientific standards for our treatments, he made a very unusual offer. He took me aside, placed his hand on my arm, and said, "If you've got anything you've wanted to try, something new you've been thinking of experimenting with, you can try it on me." Richard was willing to try something new because everything he had tried so far hadn't worked. He was hoping for a breakthrough treatment.

"I could see the wheels turning in your head," Richard later told me. "I could see the smoke coming out of your ears."

In fact, there was something we'd been talking about for a year, but we hadn't had a patient like Richard who was willing to be our subject.

We'd been having good luck with stem cells from umbilical cords, but we knew there was another repository of cells that remained untapped: fat. As we age and begin the middle-age spread, we have fewer and fewer stem cells, many of them stored in our fat. Some researchers had had success liposuctioning fat from mice and then culturing the stem cells for treatments, but no one had yet tried it on humans.

By that time I had had many conversations with Bob Harman, DVM, MPVM, the founder and CEO of VetStem Biopharma, the first company in the United States to provide fat-derived stem cells to veterinarians for use. He told me about a dog with the equivalent of rheumatoid arthritis they had treated successfully. Rheumatoid arthritis, as I discussed at the beginning of the chapter, is essentially the same disease as multiple sclerosis—the body mounts a Th1 immune response against the joints. In multiple sclerosis, the target is the myelin sheath that surrounds the nerves.

Richard said he was willing to let us try it with him. We were the first to use these stem cells from fat tissue in humans.

We were the first to use these stem cells from fat tissue in humans.

Interview with Bob Harman, DVM, MPVM, Founder and CEO of VetStem

I met veterinarian Bob Harman in the Bahamas back in 2003. He was checking out our clinic for a friend with liver cancer. He was familiar with stem cell therapies because the year before he had founded his own company, VetStem, the first United States-based commercial veterinary stem cell company. For 15 years prior to that, he was the CEO of HTI BioServices, a preclinical research company for veterinary and human pharmaceutical development. Bob and I catch up with each other on a regular basis.

Neil Riordan: What is VetStem and how has it evolved over time?

Bob Harman: When we first looked at the technology, I thought that using these kinds of cells therapeutically would change everything about the dogma surrounding treatment of chronic and acute disease. Adipose-fresh cells could be something that was affordable

We consulted with a plastic surgeon who was willing to work with us on the experiment. Since plastic surgeons normally treat the fat from liposuction as a waste product, we had to sterilize his equipment and be extremely careful about the way the extracted tissue was handled after the liposuction was complete. A single bacterium in the mix would ruin the material. After a thorough sterilization of the plastic surgeon's room and his equipment, Richard went in for liposuction.

We took the fat into our laboratory and digested it with enzymes, isolating the stem cells so that we could culture them for Richard's treatment. I have to admit, I wasn't that familiar with the after effects of liposuction. I told him, "You will experience some bruising," because that was the way the plastic surgeon had phrased it. I was pretty shocked when Richard raised his shirt the next day and showed me a dark purple expanse of skin three quarters of the way around his midsection from just below his chest down to his hips.

For Richard's first treatment, it took nine days to administer the mesenchymal stem cells that we had isolated from his own fat. It took that long for two reasons. First, the gold standard for testing for sterility was culturing

and doable in the short term in veterinary medicine. From day one, we determined that we eventually needed an off-the-shelf product in order for the treatment to be affordable. That meant that using autologous (self-derived) fat cells would be an interim solution that allowed us to get data, intellectual property, clinical experience, market exposure, and to build credibility. But eventually, the FDA's CVM (Center for Veterinary Medicine) would have to approve the allogeneic (donor-derived) treatments just like on the human side. That was the idea from the beginning, but it has taken longer than I originally thought. We're going on 14 years now. And we have only been working on development of allogeneic cells for three years.

NR: VetStem heretofore has been providing a service to veterinarians whereby they can do a biopsy of adipose tissue from their animals, right?

BH: In all these years, we have not sold one stem cell. All we do is provide a contract service for vets. It's a service. We operate under what's called "regulatory discretion," which means that the service is low regularity priority. We met with the FDA in 2003 before providing

the cells for 10 days to ensure there was no bacterial contamination. Second, MSCs like to migrate to inflamed areas, so we wanted the inflammation from the liposuction to dissipate. His own MSCs were augmented with umbilical cord stem cells. Richard reported no side effects but little improvement early on. In retrospect, I believe that the slow pace of improvement in that first session was due to some of the cells homing to the liposuction sites. The ideal treatment would be to harvest the stem cells from the fat, send the patient home to heal completely, and then have him or her return for treatment. That's one of the problems with operating outside the United States. Most patients don't want to make two trips for what is essentially one treatment.

The cells started to work a few months later, though. The pain Richard had been having in his neck and shoulders subsided, and two months after the treatment he had to lower the volume on his hearing aid because his hearing had improved. The big progress came three months after that first treatment when suddenly his brain started to work again. He wasn't confused anymore, and his seizures subsided. Plus, he was able to have sex again. I don't think we've ever had a patient who expressed such gratitude.

treatments for any veterinarians. We meet with the FDA regularly and they have continued to say this for over ten years because the service is provided legitimately, following FDA good tissue practices (GTP) guidelines and with no problems. They have inspected us and we talk with them every year.

NR: So the veterinarian does the biopsy, takes fat tissue from the animal, and ships the sample to you for processing. You then process the tissue into digested stromal vascular fraction (SVF), or the cellular part that includes stem cells, T-regulatory cells, and endothelial precursor cells (EPCs), and then you overnight the SVF back to the vet for injection into the animal.

BH: Yes. So we don't diagnose, prescribe, or treat. We are a processing lab. We provide data and continuing education to the veterinarians so that they have informed consent and knowledge about the possibilities for these SVF cells.

NR: How many animals have been treated?

In February 2009, Richard returned to Costa Rica for a second treatment. He thought if it worked as well as the first one, he might be able to ditch the hearing aid altogether. We treated him with essentially the same protocol, and his hearing did improve. The side benefit we didn't expect was that he also started to tolerate heat better. Richard lived in Texas, which is a very hot part of the world. And he loves golf. When the MS came on, he couldn't endure being out on the golf course. After the second treatment, Richard not only went out onto the course, he started teaching golf. For the first time in four years, he was bringing money home to his family.

Although we were the first to use autologous (self-donated) fat-derived MSCs, and we had a lot of success using these cells for many years, we discovered that the robustness of these cells varies, which we found correlates (inversely) with the benefits of the treatment. In those patients with less-than-robust cells, we augmented their cells with umbilical cord MSCs. Eventually, we replaced the use of fat cells altogether in favor of umbilical cord MSCs because we could better control the quality, select for cells with the best ability to control inflammation, and, maybe most importantly,

BH: Over 12,000. Mostly horses and dogs, split about evenly, plus a couple hundred cats. We also got the opportunity to be funded by the Office of Naval Research to study adipose stem cells in therapy of wound healing primarily in the dolphin, but also have done work in the sea lion. We have published one study and are preparing a manuscript for a second paper in which we took adipose cells by liposuction from the dolphin, did a full characterization[1]—flow cytometry, all the things you do to characterize the cells—and did a blinded controlled study of those stem cells in treating skin wounds.[2] After that we became known as the "exotic animal guys." So we have now done work for multiple zoos and private collections. We're probably at 30-plus species now, including giraffes, rhinos, elands, antelopes, pilot whales, beluga whales, orcas, and penguins. There will be a segment on an education channel on the treatment of an eye problem in an injured wild caught seal. So it really is helping this wild population, in particular endangered species like the northern white rhino, when they don't respond to typical pharmaceutical therapy. This isn't something we do for profit.

reduce the time of treatment and eliminate the waiting period between harvest and treatment.

Richard and I became friends partially because we share a strong spirit of adventure, and also because we have a very similar sense of humor. He and I communicated by phone or by email several times a week. At his last treatment in May 2010, he made another unusual request.

By then, I'd decided to concentrate our research and our clinic facilities in Panama. Richard said that when he came for his fourth treatment, he wanted to swim in both the Atlantic and the Pacific Oceans in the same day. I realized that despite all my years as a competitive swimmer and a professional diver, I'd never thought of doing something like this. I told Richard yes. It was a great way to celebrate his return to health.

We started at a resort next to the Pacific that had a beautiful golf course. Richard, the guy who couldn't even find his way home from the hardware store a few years back, shot a 68, four under par. I did less well. But I made up for it that night at blackjack.

NR: You have a registry of the stem cell treatments. Have there been any serious adverse events?

BH: I think there have been none that are "likely or probably" related to the therapy [this is an FDA classification]. As you know, from the beginning we decided to be data driven, trying to get peer reviewed trials before we make recommendations. We've created our own internal library here, always trying to comply with FDA guidelines on tissue processing and handling. We operate as a tissue bank and processing bank, fully under good tissue practices. I don't think anyone else in the vet industry does that.

NR: You're about to issue a press release about your new GMP facility right? And you are in the process of being approved by the FDA for a product that would be off-the-shelf (donor-derived) and not autologous (self-derived).

BH: That's correct. We have three FDA veterinary investigational animal new drug applications. It's very similar to your investigational new drug (IND) approval on the human side. We filed for use in horses, dogs, and cats. When approved, the use will be under review

The next morning, we jumped in the Pacific for a pretty good swim, nothing too athletic for two middle-aged warriors. We changed our clothes and got on the road for the three-hour drive to the Atlantic.

When we got to the Atlantic, I think both of us were a bit underwhelmed. There was no easy way to get into the ocean from the place where we parked. We had to clamber over rocks trying to figure out the best way to enter the Atlantic. We were standing on the edge of a dock with Richard trying to estimate the depth of the water, hemming and hawing, and I thought we should just go for it. I jumped in and told him the water was beautiful, even though it was not exactly crystal clear like the water we'd splashed in a few hours before.

"Come on, coach!" I yelled.

He hesitated for a few moments more and took the plunge.

We only stayed in the Atlantic a few minutes, but we were grinning the whole time. This was a victory for both of us—for me and my research, and for Richard, his family, and the rest of his life. The next time he visited his

of the FDA. We created what we believe is the only veterinary-specific, GMP-compliant cell production facility in the world. After approval, we will have cells available "out of a bottle" in the freezer at the clinic. The advantage to allogeneic (donor-derived), is that the animals will not have to undergo anesthesia and fat biopsy, and then wait a day or so for treatment. The cells will be available at lower cost, with no surgery, and available for same day injection.

NR: What conditions are vets using the cells for now, and for what indications will the allogeneic cells be used?

BH: In both the dog and horse, by far the primary use is in orthopedics—osteoarthritis; tendon, ligament injury, and joint therapy; sometimes bone repair—for acute and chronic orthopedic diseases. The first allogeneic dog product will be for osteoarthritis in the dog—intraarticular (into the joint spaces) injections for the treatment of chronic degenerative joint disease.[3] We are expecting approval in 2018 for that. Our commercial marketing partner, Aratana Therapeutics, will deliver the product to market for us.

neurologist, the doctor was amazed. Although the MRI showed Richard still had the lesions on his brain, he'd moved from primary progressive MS to relapsing-remitting MS, the version of the disease that has the fewest episodes of pain, seizures, and confusion.

Speaking of coaches, Sam Harrell was a Texas High School Football Hall of Fame coach who was diagnosed with multiple sclerosis in 2005 at age 50. He first noticed something was wrong when his vision changed. About two years later his lower legs were affected and walking became difficult. He soon needed to use a golf cart to get out on the field and became extremely sensitive to the heat. By age 55 he had to retire from the career he loved due to his loss of mobility and coordination.

At that time Sam was only able to take small steps, shuffling his feet—even turning around was a big effort. He would focus his attention on the movement of each leg as he walked and had to concentrate on how he was going to get from point A to point B. His days were filled with routine. He'd

NR: You have had some cases of dogs with a rheumatoid arthritis-like disease that recovered with SVF treatment.

BH: Most dogs that are treated have osteoarthritis, but dogs can also get immune-mediated polyarthritis. They don't have RA factors like humans, but the disease is very similar. It's systemic. There is an attack of the inside of the joint by the immune system. And we treat it systemically as well (by IV injection). We have seen multiple dogs with this condition. We get reports back from the owner or the veterinarian. They see improvements clinically. When we see something like that, it has real potential to cross over into the human field. You have treated RA cases with a substantial degree of success since our early discussions about our applications in dogs.

NR: Yes, our first RA patient had a fantastic response to SVF injections of her own fat. That was the beginning of our use of SVF in patients with autoimmune disease. You and I have coauthored papers on this.[4,5,6,7]

wake up, eat breakfast, read his bible, watch television, and answer email. Then he'd look up at the clock and it would read 10:30 a.m. "Well, in another hour and a half I can make myself a sandwich. That will take about 30 minutes. Then in five more hours Cindy will be home and at least there will be someone else in the house," he told himself. They would go to bed around nine or ten o'clock and wake up the next day and do it all over again. The monotony of his routine wore on him. He felt an immense lack of purpose in life and became depressed.

Around that time, a friend of Sam's told him about Richard Humphries' recovery after stem cell treatment. Sam knew he had to meet Richard, so he tracked him down and invited him to lunch. After hearing his story and seeing Richard's results in person, he decided to contact our clinic.

Sam came down for two treatments but did not gain impressive benefits. And yet, he knew something was happening inside and was drawn back for another treatment. After his third treatment, everything changed. His transformation didn't happen overnight, but he slowly gained movement, balance, and coordination. He could lift his leg again, then walk, and

BH: Yes. Interesting aside, we started out by injecting the therapeutic cells into the injured tendon or joint. But in our CE course, we educate about how cells work. Based on Arnold Caplan's work, we taught about the migratory nature of these cells. So I was telling small animal vets to inject the cells into the joint, but they began asking about intravenous injections. The literature supported the safety of such injections. Those veterinarians—every one of them—would tell us that the dogs did better, faster, and it appeared to have more longevity of effect when given both intravenously and intra-articularly. Nearly 100 percent of treating veterinarians do both now. I think we help the dogs feel better right away by reducing global inflammation by the IV therapy.

NR: What do you think are the potential applications for MSCs, from what you've seen, in the animal world as well as human?

BH: Clearly from the observation that an autoimmune disease—the polyarthritis—can be transferred to use for multiple sclerosis, lupus, rheumatoid arthritis, and other autoimmune diseases. We have seen immune-mediated skin diseases in dogs as well as

eventually even ride his bike. Before long, he was back to coaching. "I'm the luckiest guy in the world," Sam said. "It's given me my life back. I'm coaching again, standing out in 100 degree heat every day and not riding the golf cart." He no longer needs to wear a brace to walk or use a walker—he can run, jump, and turn on a dime. He doesn't have to think about moving from one place to another—he just moves. He went from taking a maximum of 200 steps a day to clocking 10,000 steps a day on his Fitbit®. "I tell people I'm 60, but I feel 40."

"I'm the luckiest guy in the world," Sam said. "It's given me my life back."

Sam's experience with stem cells is a sharp contrast to his experience with conventional medical treatment of multiple sclerosis. "I had never heard about the possibility of improving when I went to doctors in the United States," he said. Doctors told him, "Let's keep taking this medication so that you might get worse at a slower rate." The difference stem cells have made in Sam's life is remarkable. He has since been back for two more treatments,

lupus and conjunctivitis. UC Davis recently published a study on the use of lacrimal-gland injection of stem cells for conjunctivitis in dogs[8]. I personally think they could have given the cells IV, and it probably would have done the same thing.

UC Davis also treats gingivostomatitis, a horrible dental disease in cats marked by severe and chronic inflammation of the gingiva (gums) and mucosa. Standard treatment is to remove all of the teeth. A few IV stem cell treatments have been shown[9] to turn off the autoimmune disease.[10]

IV therapy can turn off gut inflammation in dogs with inflammatory bowel disease , which is very similar to inflammatory bowel disease in humans. Atopic dermatitis in dogs is another area of stem cell therapy.

In cats, kidney disease is a big one. I don't suspect that this disease is too different across species. We have treated close to 200 cats with this disease and are working on a manuscript.

which have continued to improve his condition. "I think it's the next huge wave of medicine, myself," Sam says.

Holly Huber had big dreams and aspirations. She was well, active, and didn't have health concerns because she was living a health-conscious life in San Diego. But when she was diagnosed with multiple sclerosis in 2004, an explanation for the years of clumsiness, forgetfulness, dizziness, and weight loss that had gone unnoticed or had been explained away by doctors finally came to light. Prior to her diagnosis, Holly had noticed a loss of sensation when urinating, along with difficulty viewing her computer screen, and she knew something was wrong. She had told herself that she'd get it checked out "when this big work project is finished." And so, more time passed. She had seen a few doctors but was never quite sure what to ask. She was misdiagnosed for quite some time.

When Holly finally had an MRI done with contrast in 2004, a neurologist was able to diagnose her with progressive MS. "He rattled off a list of drug

You know, if I speculate too much it sounds like snake oil. It's not easy to figure out which of these diseases are worth putting the effort on. There is a lot of discussion about ocular diseases, corneal injuries, retinal disease. I know a vet group in Israel that is treating retinal degeneration—similar to macular degeneration—with sub-retinal stem cell injections in the dog. There is clearly evidence for treating or preventing sepsis. I think the emergency room is a place you can envision using a migratory repair cell in patients with multiple organ and tissue trauma, just like they do today by hanging a bag of fluids with steroids as the standard of care.

NR: Drowning in opportunity, right? You've got to pick your battles and run down one track or another.

BH: True, and you've done the same, Neil, with clinical trials. We have tried to do the same. We just published a blinded, placebo-controlled, 93-dog, nine-site randomized clinical trial.[11] It's the first and largest one done in veterinary regenerative medicine. And we just initiated a 240-dog, 17-site trial. So that kind of data, and trials you are doing in Panama,

names during a very short appointment, saying, 'Go read about them. There's one medication I can give a patient on Friday, and she has flu-like symptoms over the weekend, but she's okay to take care of her kids on Monday.'" That was the extent of the visit. Holly was so distraught that she cancelled her upcoming vacation to Australia.

From there her MS progressed rapidly, and within a few months Holly collapsed on her floor, unable to walk. She went through all the standard MS medications, none of which worked to halt her disease progression and most of which left her with side effects. She spent $400,000 on medications over the course of four years.

When she came to our clinic in 2008, she was in constant pain from the numbness in her limbs. She could no longer have intelligent conversations and was often at a loss for words. She fell more times than she could count and stayed barricaded in her home. She felt as though she had wax paper over her eyes due to the optic neuritis caused by one of her brain lesions.

After her first stem cell treatment Holly began to feel her arms and legs again. Her balance improved. She could gargle again—a benefit only

is the only way to escape the stigma of being snake oil. Papers are so hugely important because the industry gets accused of treating patients unnecessarily and without data. It's the way it is with new technology. But as we get better data, pharmaceutical companies gain interest, and vet schools add programs in regenerative medicine. Ten years ago they said I was crazy, inappropriate, and didn't have data.

NR: In Panama we just finished our multiple sclerosis trial, with 1800 data points per patient. It's a safety trial with efficacy signal. The next one is a 33-patient autism trial with one-year follow-up. After that is our rheumatoid arthritis trial.

BH: Obviously, you are from the United States and you have a perception of quality standards. I have visited about a dozen offshore clinics in the past decade, but there is no place I would go to or send family to except your facility. As you know, I brought my own daughter down to be treated because I had the comfort level in your SOPs (standards operating procedures), clean rooms, hoods, and staff. I have a problem with many kit manufacturers and in-clinic systems. Literally hundreds of doctors' offices that do SVF

MS patients would appreciate. Since her first visit, she has been back thirteen times. She now walks, thinks clearly, and is able to maintain a normal lifestyle driving, cooking, climbing stairs, and flying on her own. "You changed my life and gave me a future," she told me. "Everything was so fogged when I was diagnosed and on all those medications. There was a moment when everything became clear again—all of my hopes and dreams."

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therapies do not even have an SOP written down. People are trained over the phone or in a few hours. As you know, it takes months to years to train qualified people to handle tissue. You took that standard with you to the Bahamas, Costa Rica, and Panama. We do the same thing here. There are dozens of vet clinics across the country that do in-clinic without a hood, no sterility tracks, no cell counts. You followed that same pattern of having really good release criteria, data, cell counts, and sterility checks. It's not that I'm worried about the cell therapies, it's that the clinicians are dangerous if they do not follow high quality standards.

NR: There are about five cases that keep getting rehashed. I could say that all of them are due to bad medical practice.

BH: We have 400+ SOPs here. It's cumbersome, but it's the right way to do medicine. We don't even let a small animal clinician use our products in the field unless they take our continuing education course and pass the exam.

NR: What is your overall take on the stem cell world?

BH: When I started in 2002 and I saw a beating heart in a dish at a stem cell meeting in San Diego, I thought, "Oh, this is really easy. All you have to do is make this tissue and put it anywhere." Back then that's how we thought these cells worked. But over the next five years, the Arnold Caplans of the world went from talking about creating tissue to talking about the trophic effects. I just followed what the animals were telling us. When you see that the cells aren't working like you think, but they are giving you a really positive outcome, you follow the clinical evidence, collect data, and do good studies. All of that tells you how it appears to be working, and shows you how to change your approach to use those mechanisms better. Follow the patients, go look at the science, and then come back to the patients. To reverse the old cliché, I think it goes from bedside to bench.

Jason Upshaw was diagnosed with MS over twenty years ago. He first came to our clinic in Costa Rica in 2008 with relapsing-remitting MS. He boarded the plane to Costa Rica on a wheelchair, unable to walk even a few feet without exhaustion. "I still had a lot of numbness and tingling," he said. After his first stem cell treatment he was able to walk off the plane, collect his luggage, and walk out to the parking lot. "It improved my life in one treatment," he recalled. His numbness and tingling gradually faded, his fatigue improved.

Two years later his fatigue began to increase. "I wanted to get a head start on it, so I came back," he said. "Before I got to rock bottom, where I was before I went to Costa Rica, I wanted to get back down to try to stay ahead of the curve." By then our clinic had moved to Panama, so he flew down to our new clinic there. "I have been coming back ever since," he said. For Jason, periodic treatments and not pushing his known limits of exertion keep his symptoms at bay. "If I'm smart and listen to my body, I really don't have any problems," he said.

Mesenchymal Stem Cell Treatment for Multiple Sclerosis

Multiple sclerosis (MS) is a chronic and progressively debilitating disease in which the immune system wears down the protective myelin sheath that insulates the nerves. Nerve damage may be observed by magnetic resonance imaging (MRI) as plaques in the nerves of the brain, spinal cord, or the optical system. Symptoms include visual, motor, sensory, balance, and cognitive problems.

Certain medications that have some efficacy in modulating the immune system have been incorporated as the standard of care for MS.[5] However, the benefits are lost as the disease progresses, and they do not help with regeneration of the nervous tissues that have already been damaged.[6]

Mesenchymal stem cells (MSCs) secrete anti-inflammatory, antifibrotic, immunomodulatory, and regenerative molecules that stimulate the repair and regeneration of inflamed or damaged tissues, and as such are being tested as an option for the treatment of various conditions.[7,8] In the case of multiple sclerosis, MSC secretions stimulate the body to produce more T-regulatory cells (key for keeping the immune system in check), further modulate the immune system by decreasing the activity of dendritic cells (immune system activators), and exert a direct protective effect on the central nervous system.[9]

Treating MS patients with MSCs has been shown to be a feasible alternative in animal and human studies. MS mouse models have reported improvements in neurological functions and on repair rates, which illustrates the potential for MSCs to modulate an overactive immune system[10] and to reduce inflammation.[11] An early study that caught my eye was published in 2003 by researchers from Northwestern University's Feinberg School of Medicine.[12] The 21 patients in the trial, ages 20 to 53, had relapsing-remitting MS that

Jason's wife Michelle has been with Jason through every step. She is impressed by our facilities.

When it comes to MS, people often ask, "How many treatments does it take to get me over my disease?" We are trying to push a rock up a hill. People have different sized rocks and different sized hills. When the activated T cells are diminished, they can no longer attack the myelin in the brain. When the myelin is not being attacked, the body has an amazing ability to remyelinate nerves that have not been denuded. The smaller the rock and the smaller the hill, the fewer treatments are necessary to remyelinate the nerves.

had not responded to at least six months of standard treatment. The study showed reversal of neurological dysfunction in early-stage MS patients by killing off their own immune stem cells with chemotherapy (while also killing off the bone marrow), and reinfusing previously harvested bone marrow stem cells to restore the bone marrow. This treatment in effect "reset" the subject's immune system—depleting it of the activated T cell population that could penetrate the blood-brain barrier. The disease stabilized in all patients, and 81 percent of patients improved by at least one point on a disability scale. This validated the fact that immune modulation can shut down MS, without affecting CNS myelin/neuronal damage directly—most importantly it demonstrated that remyelination occurs naturally and that remyelination should *not* be the focus of MS therapy. In 2011, researchers from the University of Cambridge completed a phase I/II clinical trial with 10 patients and showed that treatment with autologous MSCs was safe.[13]

A recent systematic review of 83 studies reported 24 applications of MSC treatment for MS.[14] The progression of MS has been shown to slow or stabilize for most patients in the first year after MSC treatment, with no serious adverse events.[15] Improvements in vision[16] and in disability scores[17] have also been reported. Several MS clinical trials are currently approved and recruiting for MSC treatment in many countries, including the United States,[18,19,20] France,[21] Spain,[22] as well as at the Karolinska Institute in Sweden.[23]

Patients with MS have been safely treated at the Stem Cell Institute since 2010 with no adverse effects, and the group has consistently published case studies and proposed the use of MSCs to treat MS.[24] Preliminary results of our completed clinical trials, to be published shortly, as of this writing suggest significant differences between pre- and post-treatment responses to the Multiple Sclerosis Impact Scale questionnaire.[25]

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Chapter Seven

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