

STEM CELL THERAPY

An abstract graphic featuring several overlapping spheres in shades of blue, green, and purple. These spheres are surrounded by a dense, swirling mass of thin, multi-colored lines (red, orange, green, blue) that create a sense of dynamic movement and complexity, resembling a network or a biological process.

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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info@neilriordanbooks.com

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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 improvisation, 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.

Arnold I. Caplan, PhD
Skeletal Research Center
Department of Biology
Case Western Reserve University
10600 Euclid Avenue
Cleveland, Ohio 44106
January 15, 2017

Chapter Eight

HEART FAILURE TURNAROUNDS— A NEW APPROACH

Daniel Wills, like most people, didn't think much about his heart. There was no history of heart disease in his family. At the age of 45, Daniel was still an athlete, running daily as he had when he was a cross country star in high school. He had no trouble keeping up with the younger jet mechanics at the hangar where he worked at O'Hare International Airport outside Chicago.

One crisp fall day in 2005 Daniel went on a short jog, but when he got home it seemed as though he couldn't recover. He felt nauseous and "kind of blah" instead of experiencing the usual endorphin high. "I didn't suspect anything," Daniel remembered. "I thought, 'Oh, it's one of those days when it's just not there.' I didn't tell anyone." That night he went to bed sweating and feeling queasy, but the next morning when he woke up refreshed, Daniel brushed the whole episode aside.

Three weeks later when the same symptoms recurred, Daniel could not deny that his body was sending him some powerful signals. He called his doctor who told him to get checked out by a cardiologist. He was diagnosed with congestive heart failure, a fatal condition in which the heart pumps less

blood than the body needs to survive. The failing heart still pumps, but as the heart's blood flow slows down, the blood returning through the veins backs up, causing congestion in the tissues. People with congestive heart failure get short of breath and tire rapidly when they exert themselves.

"If you don't get this valve repaired, you could die within six months," Daniel's cardiologist said.

He sat there for a few minutes trying to absorb this new reality. A diagnosis of congestive heart failure would be a shock to anyone, but it's a rare diagnosis for someone so young and healthy. The long-term prognosis for him was shocking too—his doctor told him that people diagnosed with this form of heart failure have a life expectancy of only seven to eight years. "I could feel my face flushing. I was overwhelmed like I'd never felt before."

When he left the cardiologist's office to start back to work, Daniel had to pull over and rest a minute in the Walmart parking lot. "It was likely that I wouldn't die tomorrow, but I knew I wouldn't live to see eighty," Daniel said. "I had a thirteen-year-old daughter and an eighteen-year-old son." His new reality weighed heavy on him.

Daniel scheduled the surgery for three weeks from the date of his diagnosis. The heart valve repair was successful, but his recovery was very slow. A neighbor friend came over every day to take Daniel out for a walk, but the walks were labored. "This thing changed my life." He altered his diet to mostly vegetables and very lean meats and stopped drinking beer, but despite all these changes he couldn't build his abilities back up to where he was before.

"I couldn't sustain exercise at first," Daniel said. "But some months after the operation I found I could bike, although not as far as I wanted to go."

Despite his rigorous discipline, the repair of his heart valve hadn't made much of a change in Daniel's condition. Doctors gauge the health of the heart by watching the readings of the heart's left ventricle ejection fraction, a measurement of the volume of blood pumped out of the left ventricle, or heart chamber, during a heartbeat. In a normal, healthy heart, the ejection fraction ranges between 50 and 70. At the time of Daniel's diagnosis, his ejection fraction was 30, half the healthy amount. Three years after the

operation, his ejection fraction numbers continued to decline. He dropped from 28 to 26. Sleep was increasingly difficult for him, as it is for many congestive heart failure patients, because when they lie down fluid collects in the lungs and causes shortness of breath.

The fact that he'd been so healthy all his life before the heart condition actually worked against him getting a heart transplant, the next step in his treatment. Heart patients qualify for a heart transplant when their ejection fraction hits 30, but Daniel was still active when his fell to 20, so the doctors hadn't yet put him on the transplant list.

"I asked my doctor where we were at. How could we change this? He said, 'All we can do is manage your condition until you qualify for a heart transplant,'" Daniel recalled. Many people die waiting for a heart transplant.

Daniel's marriage collapsed, and he became depressed and started seeing a psychiatrist. In fact, the whole Wills family was in despair about Daniel, who they thought might die at any time. In 2008, Daniel's mom went online searching for something—anything—that might offer Daniel another chance. What she found was that prestigious medical institutions such as the MD Anderson Center in Texas and Cedars-Sinai in Los Angeles were having success treating congestive heart failure—a disease that stubbornly defied all pharmaceutical and surgical attempts at a cure—with stem cells.



My staff and I started treating congestive heart failure shortly after I opened my clinic in Costa Rica in 2006. Our first patient was a physician from Texas whom I'll call Dr. Bill. He was a man like Daniel—in his early 50s and slowly dying of congestive heart failure—one for whom doctors held little hope of long-term survival. Congestive heart failure has many causes, but in Dr. Bill's case, his genes were the root of his trouble. His mother had died of heart failure at the age of 24, and other family members had also succumbed.

When he first contacted our clinic, Dr. Bill hadn't been able to practice medicine for some time. His ejection fraction was 30, and he was on the heart transplant list, but it was a procedure he wanted to avoid because he

knew it was no guarantee of a cure. A heart transplant is extremely painful, invasive, and dangerous, and would have cost him at minimum a quarter of a million dollars—that is, if a suitable heart could be found. Hearts are transplanted from people who are brain dead but still on life support, and they have to match the tissue type of the recipient to reduce the potential of the body rejecting the new heart. It's a highly selective process. After the transplant, he would endure a lifetime of immunosuppressant medications to prevent him from rejecting the foreign heart. Taking drugs to suppress the immune system increases the risk of opportunistic infections that, because of the medication, the body would be too weak to fight off.

He called our clinic a number of times asking to be treated with stem cells. We hadn't treated a heart failure patient up until that time, so we declined his request a few times. He believed, however, that stem cells could heal his heart. He was persistent. When he finally got through to me, he told me, "I am going to die waiting for a heart. I will never get a new heart due to my age. Please treat me. I don't care if I die trying—I am going to die anyway."

At first we were skeptical about using stem cells to repair the heart. There was some research on this. In 2003, scientists published papers that described how adult stem cells circulating in blood can be used to repair hearts, and that it is not necessary to take the stem cells from bone marrow.¹ In 2004, they found that stem cells use different methods to morph into the two kinds of cells needed to restore heart function. In animal studies, research showed that to make new heart muscle cells, the human stem cells fuse onto cardiac cells to produce new muscle cells called myocytes.² But to form new blood vessel cells the stem cells differentiate, or mature, by themselves to provide new endothelial cells that patch vessel damage. There was a study in Germany that showed that, when injected into mice that had had heart attacks, umbilical cord blood stem cells were drawn to the damaged areas where they stimulated the growth of new blood vessels.³ Other studies conducted in Germany and the Netherlands showed how stem cells could transform into cardiomyocytes (heart muscle cells), but there hadn't been a reported case of a human patient being treated for heart failure with stem cells. Still, Dr. Bill's situation was desperate and, based on our experience treating other diseases with stem cells, we knew with a high degree of certainty that our treatment would do him no harm.

We decided to use umbilical cord blood CD34+ and mesenchymal stem cells from the umbilical cord matrix. We knew, from experience and research, that CD34+ cells would home to damaged tissue and to hypoxic (low-oxygen) tissue. We had seen the way these cells arrived at the tissue damaged by low oxygen and then released factors that stimulated new blood vessel growth (angiogenesis).

Many studies have shown that new blood vessels, called collateral vessels, can help out a failing heart. To encourage the cells to do this work, we also added intravenous vitamin C after the umbilical cord MSC injections. This was based on the results of another study that had been conducted at Harvard Medical School that showed vitamin C could promote differentiation of stem cells into heart muscle cells.⁴

Mesenchymal Stem Cells for Congestive Heart Failure

Congestive heart failure (CHF) is a disabling and potentially deadly condition in which the heart weakens and cannot pump blood at a fast enough rate to meet the needs of the body. As a consequence, the flow of oxygen and nutrients to organs and tissue is reduced. Common symptoms of CHF are fatigue, shortness of breath, chest pain, and a limited capacity for physical exercise. CHF usually develops following an injury to cardiac tissue, for example after an infarction, or heart attack. The resulting acute inflammation may become chronic—elevated levels of inflammation markers^{5,6} and cytokines⁷ have been reported in CHF patients. For many heart failure patients, heart transplantation becomes the only treatment option after medications fail to increase ejection fraction.

Mesenchymal stem cells (MSCs) have properties that make them a viable option for CHF treatment. MSCs exert potent anti-inflammatory activities, regardless of tissue of origin.^{8,9} Mechanistically, MSCs suppress inflammation and modulate immune reaction through the secretion of cytokines.^{10,11,12} MSCs can also differentiate into cardiac-like cells¹³ and promote angiogenesis, delivering nutrients to the affected area and allowing regeneration.¹⁴ MSCs have been shown to stimulate myocardial regeneration, to inhibit pathological remodeling, and to stimulate angiogenesis in cases of ischemic heart failure.^{15,16} The administration of

MSCs post infarct (after heart attack) has been demonstrated to decrease the production of the inflammatory molecule tumor necrosis factor alpha (TNF- α) and to regulate inflammatory and anti-inflammatory cytokines, correlating with therapeutic benefits.¹⁷

Over 73 CHF animal studies have used MSC treatment,¹⁸ showing that they are effective in models of CHF.^{19,20,21} Treatment with MSCs for heart failure has also been shown to be safe in clinical settings,^{22,23} with significant reduction in reversible defects and improvement in ventricular function.²⁴ The results of several randomized clinical trials have been published in the last decade; a recent review of 23 trials (1,255 participants) concludes that there is evidence that bone marrow MSCs have a beneficial clinical effect in the long term.²⁵ Another review of 31 clinical trials (1,521 participants) reports a significant reduction in mortality and hospitalization, as well as an improvement in quality of life.²⁶ In 2010, our group reported positive results in quality of life questionnaires as well as chemical and physical improvements in a three-year follow-up of a patient treated for heart failure.²⁷ In a very recent study led by my colleague Amit Patel, MD at the University of Utah, 18 patients receiving umbilical cord MSC infusion showed improvements in heart failure, as demonstrated by an increase in the ejection fraction of the left ventricle.²⁸ Studies are still ongoing to establish the therapeutic effects of MSC treatment for CHF, to understand the mechanisms at the molecular level, and to find which type of stem cell is ideal for cardiac diseases.^{29,30,31,32}

Before he finished the series of injections, Dr. Bill reported that he had more energy and less shortness of breath. When the treatment was complete, he said that he felt so good he wanted to visit a doctor friend in Panama before going home. I had heard great things about Panama and asked him if he minded if I tagged along. He agreed.

We flew to Panama and met his old friend Jorge Paz-Rodriguez, MD. We also met Lic. Rodolfo Fernandez, owner of the largest clinical laboratory company in Panama. The three of us hit it off instantly. Dr Paz, called Georgie by his friends, and Rodolfo were very interested in what we were doing in Costa Rica. They said they wanted to come up and see our operation. Sure enough, six weeks later they jumped on a plane and came to visit me in Costa Rica. I recall them saying in unison, "We need to get this in Panama." They went back to Panama and hired an attorney to look into the legal situation regarding stem cells in Panama. What they found was a law that had been

passed in Panama a few years earlier. The law, which was passed in 2004, simply banned the use of embryonic stem cells, and allowed physicians to treat patients with adult stem cells, including umbilical cord stem cells, as long as the patient gave informed consent. Shortly thereafter, I took another trip to Panama and we started planning to set up operations there. We met with the Director of the City of Knowledge. Ultimately, we set up a small lab there and began operations in 2007. Georgie and Rodolfo are partners in our operation there. Georgie is the medical director of the clinic and Rodolfo is the laboratory director.

While visiting Panama, Dr. Bill and I made the obligatory visit to the Panama Canal, just a short drive from downtown Panama City. The Miraflores Visitor Center and museum stands at the side of one of the locks on the Pacific side of the canal and is a good place to observe the ships as they make the passage between two oceans. The observation deck is on the top of the building on the third floor. Excited to see the ships, we climbed the flights of stairs to the observation deck. As soon as we got to the top, Dr. Bill paused and put his hand on my shoulder as we gazed at the huge containership in the lock.

“This is incredible,” he said.

“Yes, this canal is an amazing feat of engineering, and this is a great view of the ships,” I replied.

“No, not that—I’m not short of breath!”

That was twelve days after his first treatment.

Dr. Bill went back to Texas and had an echocardiogram four months after his treatment. His ejection fraction had gone from 30 to 52. His cardiologist didn’t quite believe it. An improvement like that never happens in heart failure patients. A month later, his doctor repeated the test and found his ejection fraction had gone up to 55. Dr. Bill has since returned to work and enjoys a relatively normal life as of this writing.

As far as we can tell, when we treated Dr. Bill it was the first time congestive heart failure had been dramatically improved using umbilical cord cells in a human. By the time Daniel’s mother was searching the Internet for a

solution three years later, she found information on the clinical trials and experiments on animals. At MD Anderson, Dr. Edward Yeh's experiments on heart attack-induced mice showed again that the CD34+ cells survived in the left chamber of the heart for twelve months.³³ While they lingered there promoting new blood vessel formation, ejection fraction increased from 37 to 50 after the treatment. In another MD Anderson research project led by Dr. Yeh, he and his team discovered a "sticky" protein that helped adult stem cells fuse with heart muscle cells to grow new cells that would repair the damaged organ.³⁴

But while these researchers are still conducting their investigations, we have since treated 26 more people with congestive heart failure. All but two of them have had positive responses. One of those successes is Daniel.



Daniel's mom had found many clinical trials underway researching the efficacy of this exciting new treatment, but Daniel wasn't interested in participating in a clinical trial, even if he qualified. In a clinical trial, half the patients are treated and half get a placebo, or false treatment, so that scientists can compare the difference between treated patients and those who are not treated. Without any kind of treatment, Daniel was sure he wouldn't last many more years. He didn't want to risk being in the placebo group. Instead, he and his mom found our clinic.

After we accepted Daniel as a patient, he took money out of his retirement fund to finance his trip to the clinic. Then he called his family to tell them what he was going to do. Although his brother was skeptical, ten days after Daniel's announcement, Bryan and his wife decided that they would accompany Daniel when he came to get his treatment. His parents decided to come along too.

At the clinic, our understanding of stem cells and how they help the heart repair had grown dramatically since our first case with Dr. Bill. Research performed on hamsters in the United States by Dr. Te-Chung Lee changed the way we looked at treating heart disease. Dr. Lee did an interesting study on hamsters that had heart failure.³⁵ He had noticed that although

a very small percentage (one to two percent) of cells injected into the vein of animals were actually found in the heart, CHF symptoms improved. He designed what I consider a groundbreaking experiment to discover what was happening. For the experiment he used a hamster model of heart failure, which is considered by many to be clinically identical to human heart failure. His team injected one set of animals with MSCs into the hamstring muscle; they had previously demonstrated that cells injected there would stay there and not travel to other parts of the body, including the heart.

Additionally, they collected the growth medium that the cells were grown in (typically called the supernatant) and injected it into the hamsters' hamstrings. The liquid in which they were culturing the cells was rich in trophic factors—the chemicals in the bloodstream that encourage healthy cell growth. When either the cells or the culture medium was injected into the hamstrings, the hearts of the hamsters got better. So it wasn't that the cells necessarily needed to become heart cells, or that they even had to be injected intravenously—the cell-secreted trophic factors, whether from implanted cells or from the injections of only the trophic factors, would migrate to where they were needed and stimulate repair of the heart. The treated animals had improved heart function, decreased heart cell death, decreased damaged tissue, and an increased number of repairs in the heart.

Daniel received stem cell treatment over the course of five days. His treatment was the same, morning and afternoon. "And between times, we got to tour Costa Rica!" Daniel said, noting that it was one of the best vacations his family ever had.

As he headed home we told him, as we tell all our heart patients, don't expect big changes right away. Sometimes it takes up to six months to feel a difference. Yet we were very optimistic about Daniel because he was relatively young and, besides his heart, very healthy. We told him he might begin to experience some positive changes in as little as eight weeks.

Sure enough, eight weeks later Daniel started to notice he had more energy during the day and that he wasn't having breathing issues anymore. The big test, however, was the day that Daniel went to see his cardiologist for his regularly scheduled check-up.

Daniel had been apprehensive about telling his doctor about being treated with stem cells. A month before he was scheduled to fly down for treatment at our clinic, he had an appointment with his doctor. He was going to tell him what he was about to do, but he feared that the doctor might be so alarmed that he'd fire Daniel as a patient. Would the doctor forbid him from doing it? Just as Daniel was girding up for the battle, he got a call from the doctor's office informing him that his doctor had slipped in the bathtub and had to cancel his appointments for some time to come. When Daniel next saw his doctor, he'd already received his stem cell treatment.

Daniel's previous echocardiogram in January had been pretty grim—it was the one that showed his ejection fraction to be 26. Daniel looked on with concern, trying to read his doctor's face as he listened to Daniel's heart. He feared that the doctor sensed Daniel's condition was worsening. He ordered an echocardiogram and told Daniel he wanted him to take it right away, that day.

“Now I'm really nervous,” Daniel recalled thinking. “What did he hear?”

Normally it took the doctor a few weeks to get back to him after he received the results of an echocardiogram. Daniel was so nervous about the outcome that he didn't pick up when he saw his doctor's number on his cell phone.

“Dan, we got your echo results,” his cardiologist said. “I think you're going to be really pleased. Your echo came back with a 40 percent ejection fraction.”

“Holy crap!” Daniel said out loud. “That's really good!”

He was scheduled for a follow-up call with our clinic, and shortly before the appointment he faxed a copy of his echocardiogram, which showed him having some ejection fraction numbers as high as 45. When I saw it, I knew I wanted to speak with him. His first question was a bit of a surprise.

“How do you know that the stem cells are causing this improvement?” Daniel asked.

“There are some cases of spontaneous remission in people with your condition, but the vast majority of those are chronic alcoholics who quit drinking. Most people do not get better in a six-month time frame for no reason,” I told him. “You could ask any cardiologist in the world. You typically do not go from an ejection fraction of 26 to 45 on your own.”

As Dr. Lee’s work had helped to clarify, the heart was repairing itself by being “kickstarted” by the secreted trophic factors that encouraged the growth of new, healthy tissue in an ailing heart.



Morris Gray was diagnosed with heart failure over twenty years ago. He had 11 stents put in his heart, of which the last three blocked an artery and triggered a heart attack. Four years later he had an EKG and a nuclear scan, and his doctor told him there was nothing more he could do for Morris. A friend of his from Corpus Christi, Texas told him about our stem cell facilities in Panama. He looked into it and decided to come down for treatment in October 2011. “I didn’t feel anything for 30 days,” Morris said. “Then I started feeling better. I really felt good.”

Morris went back for another EKG in January 2012, and his doctor asked him, “What have you done? You have a normal EKG. You’ve never had one of those before.”

Morris hadn’t told his doctor about the stem cell treatment. “Do you think I ought to tell him?” he asked his wife. She said yes. When Morris told his doctor about the treatment, the doctor looked shocked. “How did they do it?” he asked. Morris explained the procedure to him.

Morris’s next three EKGs were normal. He received another stem cell treatment that repaired his kidneys, unexpectedly. “My kidneys have been bad my whole life, but now they’re fine,” Morris said.

“Morris’s doctor asked him, “What have you done? You have a normal EKG. You’ve never had one of those before.”

The turnarounds these heart patients like Daniel, Dr. Bill, and Morris experienced seem nothing short of miraculous. Rigorous studies like those being performed by my friend and colleague Dr. Amit Patel at the University of Miami hopefully one day will lead to effective cell/trophic factor therapy being broadly available in the United States and around the world.


References

Chapter Eight

1. Yeh ET, Zhang S, Wu HD, Körbling M, Willerson JT, Estrov Z. Transdifferentiation of human peripheral blood CD34+-enriched cell population into cardiomyocytes, endothelial cells, and smooth muscle cells in vivo. *Circulation*. 2003;108(17):2070-3.
2. Zhang S, Wang D, Estrov Z, Raj S, Willerson JT, Yeh ET. Both cell fusion and transdifferentiation account for the transformation of human peripheral blood CD34-positive cells into cardiomyocytes in vivo. *Circulation*. 2004;110(25):3803-7.
3. Ma N, Stamm C, Kaminski A, et al. Human cord blood cells induce angiogenesis following myocardial infarction in NOD/scid-mice. *Cardiovasc Res*. 2005;66(1):45-54.
4. Takahashi T, Lord B, Schulze PC, et al. Ascorbic acid enhances differentiation of embryonic stem cells into cardiac myocytes. *Circulation*. 2003;107(14):1912-6.
5. Sánchez-Lázaro IJ, Almenar L, Reganon E, et al. Inflammatory markers in stable heart failure and their relationship with functional class. *Int J Cardiol*. 2008;129(3):388-393.
6. Alonso-Martínez JL, Llorente-Diez B, Echegaray-Agara M, Olaz-Preciado F, Urbieto-Echezarreta M, Gonzalez-Arencibia C. C-reactive protein as a predictor of improvement and readmission in heart failure. *Eur J Heart Failure*. 2002;4(3):331-336.
7. Satoh M, Minami Y, Takahashi Y, Nakamura M. Immune modulation: Role of the inflammatory cytokine cascade in the failing human heart. *Curr Heart Fail Rep*. 2008;5(2):69-74.
8. Le Blanc K, Ringdén O. Immunomodulation by mesenchymal stem cells and clinical experience. *J Intern Med*. 2007;262(5):509-525.
9. Keyser KA, Beagles KE, Kiem HP. Comparison of Mesenchymal stem cells from different tissues to suppress t-cell activation. *Cell Transplant*. 2007;16(5):555-562.
10. Ortiz LA, DuTreil M, Fattman C, et al. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. *Proc Natl Acad Sci U S A*. 2007;104(26):11002-11007.
11. Madrigal M, Rao KS, Riordan NH. A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods. *J Transl Med*. 2014;12(1):260. doi: 10.1186/s12967-014-0260-8.

12. Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon- γ does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. *Clin Exp Immunol.* 2007;149(2):353–363.
13. Nishiyama N, Miyoshi S, Hida N, et al. The significant Cardiomyogenic potential of human Umbilical cord blood-derived Mesenchymal stem cells in vitro. *Stem Cells.* 2007;25(8):2017–2024.
14. Itescu S, Kocher AA, Schuster MD. Adult bone marrow-derived angioblasts for improvement of cardiomyocyte function after myocardial ischemia. *Gene Ther Reg.* 2001;1(4):375–386. doi: 10.1163/156855801760107037.
15. Hare JM, Fishman JE, Gerstenblith G, et al. Comparison of allogeneic vs autologous bone marrow-derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. *JAMA.* 2012;308(22):2369.
16. Chin SP, Poey AC, Wong CY, et al. Intramyocardial and intracoronary autologous bone marrow-derived mesenchymal stromal cell treatment in chronic severe dilated cardiomyopathy. *Cytotherapy.* 2011;13(7):814–821. doi: 10.3109/14653249.2011.574118.
17. Du YY, Zhou SH, Zhou T, et al. Immuno-inflammatory regulation effect of mesenchymal stem cell transplantation in a rat model of myocardial infarction. *Cytotherapy.* 2008;10(5):469–478. doi: 10.1080/14653240802129893.
18. Narita T, Suzuki K. Bone marrow-derived mesenchymal stem cells for the treatment of heart failure. *Heart Fail Rev.* 2014;20(1):53–68. doi: 10.1007/s10741-014-9435-x.
19. Yannarelli G, Dayan V, Pacienza N, Lee CJ, Medin J, Keating A. human umbilical cord perivascular cells exhibit enhanced cardiomyocyte reprogramming and cardiac function after experimental acute myocardial infarction. *Cell Transplant.* 2013;22(9):1651–1666. doi: 10.3727/096368912X657675. Epub 2012 Oct 4.
20. López Y, Lutjemeier B, Seshareddy K, et al. Wharton's jelly or bone marrow Mesenchymal Stromal cells improve cardiac function following myocardial infarction for more than 32 weeks in a rat model: a preliminary report. *Curr Stem Cell Res Ther.* 2013;8(1):46–59.
21. Liao W, Xie J, Zhong J, et al. Therapeutic effect of human Umbilical cord Multipotent Mesenchymal Stromal cells in a rat model of stroke. *Transplantation.* 2009;87(3):350–359. doi: 10.1097/TP.0b013e318195742e.
22. Mathiasen AB, Qayyum AA, Jørgensen E, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with severe ischaemic heart failure: A randomized placebo-controlled trial (MSC-HF trial). *Eur Heart J.* 2015;36(27):1744–1753. doi: 10.1093/eurheartj/ehv136.
23. Perin EC, Borow KM, Silva GV, et al. A phase II dose-escalation study of allogeneic mesenchymal precursor cells in patients with ischemic or nonischemic heart failure. *Circ Res.* 2015;117(6):576–584. doi: 10.1161/CIRCRESAHA.115.306332.

24. Perin EC, Dohmann HF, Borojevic, et al. Transendocardial, autologous bone marrow cell transplantation for severe, chronic Ischemic heart failure. *Circulation*. 2003;107(18):2294–2302.
25. Fisher SA, Brunskill SJ, Doree C, Mathur A, Taggart DP, Martin-Rendon E. Stem cell therapy for chronic ischaemic heart disease and congestive heart failure. *Cochrane Database Syst Rev*. 2014;(4):CD007888. doi: 10.1002/14651858.CD007888.pub2.
26. Fisher SA, Doree C, Mathur A, Martin-Rendon E. Meta-Analysis of cell therapy trials for patients with heart failure. *Circ Res*. 2015;116(8):1361–1377. doi: 10.1161/CIRCRESAHA.116.304386.
27. Ichim TE, Solano F, Lara F, et al. Combination stem cell therapy for heart failure. *Int Arch Med*. 2010;3(1):5. doi: 10.1186/1755-7682-3-5.
28. Tuma J, Carrasco A, Castillo J, et al. RESCUE-HF trial: Retrograde delivery of Allogeneic Umbilical cord lining Sub-Epithelial cells in patients with heart failure. *Cell Transplant*. 2016; January. [Epub ahead of print]
29. Silvestre JS, Menasché P. The evolution of the stem cell theory for heart failure. *EBioMedicine*. 2015;2(12):1871–1879. doi: 10.1016/j.ebiom.2015.11.010.
30. Menasché P. Stem cells for the treatment of heart failure. *Philos Trans R Soc Lond B Biol Sci*. 2015;370(1680):20140373. doi: 10.1098/rstb.2014.0373.
31. Poglajen G, Vrtovec B. Stem cell therapy for chronic heart failure. *Curr Opin Cardiol*. 2015;30(3):301–310. doi: 10.1097/HCO.000000000000167.
32. Winters AA, Bou-Ghannam S, Thorp H, et al. Evaluation of multiple biological therapies for ischemic cardiac disease. *Cell Transplant*. 2016;25(9):1591-1607.
33. Wang J, Zhang S, Rabinovich B, et al. Human CD34+ cells in experimental myocardial infarction: long-term survival, sustained functional improvement, and mechanism of action. *Circ Res*. 2010;106(12):1904-11. doi: 10.1161/CIRCRESAHA.110.221762.
34. Zhang S, Shpall E, Willerson JT, Yeh ET. Fusion of human hematopoietic progenitor cells and murine cardiomyocytes is mediated by alpha 4 beta 1 integrin/vascular cell adhesion molecule-1 interaction. *Circ Res*. 2007;100(5):693-702.
35. Shabbir A, Zisa D, Suzuki G, Lee T. Heart failure therapy mediated by the trophic activities of bone marrow mesenchymal stem cells: a noninvasive therapeutic regimen. *Am J Physiol Heart Circ Physiol*. 2009;296(6):H1888-97. doi: 10.1152/ajpheart.00186.2009.



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