Using Stem Cells to Treat Injury and Disease

William A Argus MD

Fort Wayne Quest Club

November 9, 2018

Introduction

As you know, my day job is in ophthalmology, but outside the office I have a strong interest in adult developmental psychology and the power of the human imagination. As such, I can spot development almost anywhere, even in writing Quest papers.

My first paper was about personal debt and would it bury the baby boomers. It led me to discover the abstract nature of money and how our ideas about money have developed over time. My second paper was about women in medicine. Sex roles have changed over time and I examined the difference between masculinity and femininity, and I asked which might make for a better doctor. My third paper was about economic morality. Do we need more or less government spending? But even the idea that government could affect the economy was a new idea. 100 years ago, before economics was even considered a science, economic booms and busts were considered part of a natural cycle. It had not yet occurred to people that government could regulate the economy, let alone ask whether it should or not.

Today, my fourth paper is about an even newer concept—stem cells. Pluripotent stem cells can develop into different cell types depending upon their local environment. Stem cells are about potential, and they call into question many of our preconceived notions about nature and nurture. Scientists who study stem cells ultimately study the mechanisms of development and how cells transform themselves into more specialized tissues. As you will see, stem cells are another product of the human imagination. Finally, while researching the biology of stem cells, I reconnected with the beauty of life itself. This paper provided the

opportunity to revisit Mother Nature's wonder, to witness again some of her mysteries and magic, and to be reminded that life is both a miracle and a gift.

Using Stem Cells to Treat Injury and Disease

Doug Melton was a research scientist, tucked away in the corner of a biology lab, discreetly studying frogs when his life would change forever. His infant son Sam was diagnosed with type I diabetes. He promised himself that he would switch gears and dedicate his life's work to finding a cure for diabetes. He started working with a mouse model and tried to find a method to convert fetal stem cells into insulin producing beta cells. His resolve intensified when his daughter Emma was diagnosed with the same autoimmune disease at age 14. After 20 years of hard work, he succeeded and he published his work in the prestigious journal *Cell.*[1] Stories like this peak our interest in the curative potential of stem cells.

When I was assigned this topic, my first thought was of Indianapolis Colts quarterback Peyton Manning. A local hero with strong ties to Riley Hospital, his career was extended by 4 years after he reportedly went to Europe and had stem cell surgery on his neck. But when I went searching for scientific reports about his surgery and those of other famous athletes, the cupboard was bare. Although Peyton's successful surgery was reportedly done in Europe with stem cells, he never confirmed this. Why? Why is all this stem cell research so secretive? Would some of his fans have been offended by the use of fetal stem cells? Would his marketing value have gone down? Perhaps some banned substance, such as growth hormone, was temporarily used as part of the protocol? Was the surgery

[1] (Pagliuca, 2014)

proprietary and thus a trade secret? Or perhaps nothing was done at all? Indeed, finding good research about stem cells is very difficult. There is surprisingly little reliable information to share with you about stem cell therapy for injury and disease.

I found a few trials with some interesting results. Some surgeons thought that stem cells might improve the repair of surgical fistulas, and in a Phase II clinical trial of 71 patients, that appeared to be the case. So with much optimism, a more definitive phase III clinical trial was performed. The beauty of these trials is that the patients and the observers are masked as to who received stem cells and who did not. When the observers were masked, the surprising the result was that stem cells did not help at all. There was a 40% success rate with or without stem cells.[2] Similar results were found with most controlled studies.

In spite of this rather dismal report card, stem cell clinics have recently popped up all over the United States. A brief review of their claims reveals that they can treat "Common neurological conditions include Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, spinal cord injuries, stroke, and traumatic brain injury." They can also treat autoimmune diseases including: "Multiple Sclerosis (MS), rheumatoid arthritis, and scleroderma." And of course they can treat "Common degenerative conditions include congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes, kidney disease and liver disease. Clinical research has shown that transplanted stem cells *could* migrate to damaged areas and help promote structural and functional repair as well as working to stimulate

[2] (Stem Cell Therapy for perianal fistula in Crohn's desease, 2016)

various *restorative* processes."[3]

This is pure nonsense. One clinic in Georgia was a recently shut down by the FDA after it blinded two patients. Adipose stem cells were injected into the vitreous and within three weeks both patients had bilateral retinal detachments.[4] And in 2011, Europe's largest stem cell clinic was shut down after an undercover investigation. Two children suffered brain hemorrhages, with one fatality, if after injections with stem cells.[5] Experts in stem cell research accused the clinic of preying on vulnerable patients.

How did stem cells become the latest version of Laetrile? Why are so many patients willing to try this new version of snake oil? I am reminded of one of my favorite works, *Extraordinary Popular Delusions and the Madness of Crowds*[6], originally published in 1840. Charles MacKay suggested that all charlatans exploit one of the three universal vulnerabilities. These vulnerabilities are part and parcel of human nature. They are 1) the promise of getting rich, 2) of being able to predict the future, and 3) the fountain of youth. Depicted here is the Greek goddess Hebe. All stem cell clinics, legitimate and otherwise, borrow the buzz phrase "regenerative medicine." Where did the idea of stem cells come from and how did it get so corrupted?

If you look into the science of stem cells, you will quickly discover some of the

[3] (US Stem Cell Clinic, LLC)

[4] (Wan, 2018)

[5] (Mendick, 2011)

[6] (MacKay, 1980)

marvels and intricacies of life itself. Science seeks to understand some of nature's mysteries. In my own career, I have had the great privilege of working on the most beautiful organ in the body – the eyeball. After all these years, I am still in awe of nature's work. Even on a bad day, I can turn up the magnification on my microscope and watch the pupil dance to the examination light, or watch individual red blood cells meander through the capillaries. Look at this pristine cornea, this perfectly clear window to the soul. When I first started my career, we did not think the cornea was dynamic. Then one day the new entity was discovered (corneal verticillata). Now no one could ever have predicted that a new cardiac drug (amiodarone) would stain corneal epithelial cells. But now that these cells were stained, we could see that epithelial cells were being continuously generated and migrating across the cornea. The cornea was dynamic, and the concept of a corneal stem cell entered our imagination. Further work confirmed that corneal stem cells do exist, and that some chronic corneal diseases are due to damaged stem cells. These patients are now treated by transplanting stem cells from their other eye to restore corneal clarity.

Corneal stem cells are not a revolutionary idea; they are simply an extension of what we have known before. We have known that certain cells, such as red blood cells, have limited lifespans (approximately 120 days). It is obvious there must be something such as bone marrow that constantly generates new blood cells. These are mother cells that create an endless supply of daughter cells throughout one's lifetime. The mother cell remains unchanged. However, a true stem cell is something that is pluripotent; that is, it can become many different things. It does not just create daughter cells, it actually becomes something else, something more specialized. A stem cell might become a liver cell or a kidney cell or brain cell.

Where did the idea that a cell could have multiple different potentials come from?

There are many stories to tell in the evolution of cell biology, but I will just share one with you. Eric Wieschaus[7] was a biology student a few years ahead of me at Notre Dame, and we both had the privilege of studying under a famous geneticist, Harvey Bender. As Eric tells it, he was mesmerized by the development of the fruit fly. While I fell in love with the eyeball, he was enamored by larvae. After fertilization, the single celled zygote grows to an oblong mass about 100 x 40 cells, amorphous and without differentiation. All the cells look to be same. Then the embryo begins to fold and take structure (gastrulation). It is as if a symphony awaits the conductor's signal, and then the music begins. How is this development controlled? He postulated that there must be developmental genes yet to be discovered. He and his colleagues created several mutant strains. In the end, he discovered developmental and regulator genes that turned out to have widespread implications for throughout the animal kingdom. Some of the genes would later be known as oncogenes. His work was so revolutionary that he would win the Nobel Prize in 1995.

Trying to understand his work is a challenge, and it gets very complicated quickly. But what I want to emphasize is that it had long been assumed that there must exist genes for structures like eyes and ears, and fingers and toes. But it was not as obvious that there must be genes to *prepare* cells to become eyes and ears, and fingers and toes. Eric's work demonstrated that there were numerous stages to development and that each stage was being controlled by developmental and regulator genes. Many of these genes are found throughout the animal kingdom

[7] (Wieschaus, 1995)

and produce similar patterns of development.

So let's look at a human embryo. Just as with the fruit fly, the embryo becomes a non-descript mass of cells called a blastocyst, and then the symphony begins with gastrulation. This tissue will become the fetus. First it will differentiate into the three germ layers (ectoderm, mesoderm, and endoderm), and then each layer will further prepare to make the organs and tissues. The ectoderm will form skin and nervous system; mesoderm will form muscle and connective tissue, and endoderm the alimentary canal (digestive system). At each stage, numerous genes are turning off and on to regulate development. If any of these required genes are absent, development will be arrested. One of his many discoveries was 2 genes called *twist* and *snail*, two genes that are required for mesodermal development.

This is a 28 day old fetus. If thalidomide is present, this child will not develop any arms. The nerve buds for the arms form on day 28. Thalidomide is a neurotoxin and will stunt the growth of the nerve bud. The development of the arms and the subsequent development of all those intricate fingers, muscles, and bones is dependent upon each of the previous stages, including this neural bud formation. Thalidomide has no direct effect on muscles and bones, but they won't form without the healthy nerve bud. The nerve bud is a necessary step in the chain reaction to follow. *Everything* is dependent upon the successful completion of the previous stages.

So for this embryo to make it all the way to adulthood, it will need more than just good luck. In addition to the right genetic make-up, it will need a healthy prenatal environment. And if it avoids childhood diseases and countless other bumps in the

road, it just might make it to adulthood. What can we predict about this adult? It will probably look something like its parents. It may even share some personality characteristics with its parents. It may be lucky enough to have its grandfather's musical ear. It may have its mother's laugh. How does this miracle happen? How does this single cell contain so much information?

And that's not all we know about this adult. We also know that this human being will think about right and wrong, and good versus evil. He will have needs and desires. At times he will exhibit jealousy and envy. How is all of this encoded in this single cell? The surprising answer is that it is not. Do you think there is a gene for jealousy somewhere, maybe on chromosome 14, or a gene for selfishness on chromosome eight? These things are not specifically coded for, but if the symphony is allowed to progress through stage after stage after stage, these qualities will unfold and flower before your eyes. It is the miracle of life and human nature.

These ideas have evolved over time. If we go back to the single cell and ask what people would have said 500 years ago, they would have asked if this was the product of royalty or not. Birthright would determine whether this entity was either a prince or a pauper. Your station in life was deemed to be fixed. It was a fundamental property, and not subject to change. Paupers come from paupers, slaves beget slaves, and bastard children have no property rights whatsoever, even if they turn out to be Leonardo da Vinci. 500 years ago, people believed that things were fixed and pre-determined. We know otherwise today. It is not so much about what something *is* but rather what it can *become*. What is something's potential? Potential is a function of the age old controversy: nature versus nurture.

So if we return to the human fertilized egg, what can we say about this entity without projecting too much pre-determination? What we can say for sure is that it is the ultimate stem cell. It is not just a mother cell creating daughters, and it is not just a pluripotent cell able to transform into a specialized tissue cell. This fertilized cell can divide and become part of something more, something bigger and more complicated, something we call an organism. It can become a human being. And if it somehow makes it through the many stages from blastocyst and gastrulation, through all the germ layers and differentiation and birth and infancy and early childhood and makes it to adulthood, human nature will have unfolded in all its glory. There will be love and kindness; there will be jealousy and hate. There will be a search for meaning and purpose in life. And of course we know there are at least three more things. He will be susceptible to the three universal con games. He will worry about money, he will have anxiety about the future, and he will worry about his health. And when infirmity strikes, which it no doubt will, he will dream about a fountain of youth. He will come to fear his own mortality and hopefully come to grips with it.

So how did stem cell therapy become so corrupt and the latest version of snake oil? The answer is that it was in evitable. It could be no other way. Human beings are the only species capable of thinking abstractly including thinking about time. Every other animal lives in the moment, but only we can envision a tomorrow. Only we can use our imaginations to envision different possible scenarios. Only we can dream of different tomorrows. And that wonderful ability to plan ahead carries with it an anxiety about the future. Only our species has anxiety about the future. This anxiety about the future can distract us from the task at hand. That is why so

many sports psychologists emphasize staying in the moment. But when anxiety about the future is combined with our survival instinct, we envision our own mortality. The fundamental instinct for survival will lead us to the fountain of youth. We can imagine and dream of our own invincibility. And this fellow Questers is one of the most fundamental con games that we are all susceptible to.

Most of you came here today to learn something new and exciting. You thought that stem cells would be interesting, but in the back of your mind you also thought that one day this information about stem cells might come in handy, didn't you? Conscious or unconscious, you were falling prey to the powerful myth of the fountain of youth.

But you are not alone! Some of our most prominent citizens recently fell hook, line, and sinker for a scheme designed by this attractive young lady in her signature black turtleneck. She was able to convince investors that she could predict the future with a single drop of blood. She could detect a range of illnesses from cancer to diabetes with a single finger prick. She garnered over $700 million in venture capital and in 2013 partnered with Walgreens to market her product. Her star studded Board of Directors (Or Board of Suckers) included former secretaries of state George Shultz and Henry Kissinger, general Jim Mattis, former Wells Fargo CEO and Chairman, former CEO of the Bechtel Group, former secretary of defense Bill Perry, and two former US senators, Sam Nunn and Bill Frist, a heart transplant surgeon. Elizabeth Holmes completed a trifecta – predicting the future, making investors rich, and creating the promise of a fountain of youth.

This Quest paper has no doubt been other than what you expected. There are legitimate stem cell researchers, such as Doug Melton, who are working diligently to decipher some of the developmental mysteries of cell biology. However, not all of his work is altruistic. In addition to Melton's funded work at Harvard, he has formed a for profit company called Semma, named after his two children Sam and Emma. In two years he has acquired 50 million dollars in venture capital, hoping to tap into the $30 billion annual market for insulin. But if you are going to have an intelligent conversation about stem cells, you need to separate the scientific research from the treatment hype. I think it is also paramount to acknowledge how far we have come from the concept of predetermination. Our founding fathers fundamentally challenged the notion of a blue blood when they claimed that all men were created equal. Our founding fathers knew about the lesser angels of human nature and created a Constitution and the Bill of Rights to protect us from tyranny. However, our founding fathers knew nothing about biology. They knew nothing of stem cells, enzymes, disease, and development. But they knew what human nature could produce in its adults, including an occasional insatiable appetite for money and power.

Both stem cells and human beings have potential to develop into something more. We are all collections of stem cells, growing, evolving, and changing every day. We now can say that neither stem cells nor human beings are predetermined. There is a fundamental nature and there is nurture, and it is the interplay between nature and nurture that will determine the final result. Predestination is a fallacy. To paraphrase John McCain, greatness is not inevitable.

If greatness is not inevitable, how do we promote it? How do we create an

environment to maximize human potential? How do we help these babies, these small human becomings, reach their potential? The next time you attend a baptism, listen to the pleas for help from the minister. These human becomings will need guidance to develop the moral character so necessary for greatness. These stem cells will need help from parents, family, school, and church. Greatness is a team effort, not a solitary journey. You cannot wash away evil with baptismal water any more than you can wash away death in a fountain of youth. But the people who wrote those prayers centuries ago knew about the importance of nurture, because the path to greatness has many obstacles, and we all need help at times. And you will hear those pleas for help in other ceremonies, such as marriage, where another new entity, the union of two people, is another stem cell whose greatness is not inevitable.

Everyone in this room has been very lucky. We have all survived the many stages of development. We had the good fortune of some good genes and good parents and good mentors and a good environment. And we are still growing and learning. We know that our brains are growing new neurons and connections every day. We have lead charmed lives because we had the privilege of having mentors who helped us emphasize the positive aspects of human nature. These mentors helped us reach for the stars. They taught us, among other things, that money can't buy everything. They taught us that kindness and charity will supersede greed and selfishness in the long run. These concepts are not obvious and we still need help encouraging our better nature. We are bombarded daily by advertisers that appeal to our lesser angels. They imply that we *can* buy happiness with some product, or live longer with their snake oil. It is difficult to face mortality without dreaming of a fountain of youth.

Shakespeare suggested to us that life is a stage. May I suggest to you that life is actually a series of developmental stages, all dependent upon the successful completion of the previous stages? This is true whether you are describing cellular biology or human consciousness. There is a fundamental nature, but reaching one's potential is not inevitable. Biology is not destiny. The environment determines the expression of genes and overall success. Examining the concept of stem cells helps us to think about the potential of what might become and what might have been. Life is about development, and greatness is about moving forward into greater complexity, not regressing backwards.

Life is a gift, a precious gift that we do not always appreciate. Even over the hill Quest members need to be reminded of this at times. Our symphonies are still playing. They may not as loud as they used to be. The movements might be a little slower. Some of the tunes may be repeated a little too often. The beat goes on. Live your life. Reach for your better angels. Watch out for extraordinary popular delusions and the madness of crowds. Seek the things that money can't buy. Be grateful, for that encourages you to stay in the moment. And continue to develop and grow, reach for the stars, and encourage others to do the same. For the answer is never to go backwards. Greatness only comes with growth and development. Continue to do the hard work of personal growth and aspire to be part of something bigger. And if you are lucky, you just might attain access to some of the noblest virtues of the human imagination, like resilience, wisdom and compassion. These virtues are not inevitable, and society needs a lot more of them. Life is a miracle. Cherish the journey. And be a good stem cell.

Bibliography

A Closer Look at Stem Cell Facts. (n.d.). Retrieved from International Society for Stem Cell Research: www.isscr.org

A Closer Look at Stem Cells. (n.d.). Retrieved from http://www.closerlookatstemcells.org/

Abelson, K. T. (2018, March 14). *New York Times.* Retrieved 10 2018, from https://www.nytimes.com/2018/03/14/health/theranos-elizabeth-holmes-fraud.html

al, M. e. (2009). Small Molecules Efficiently Direct Endodermal Differentiation of Mouse and Human Embryionic Stem Cells. *Cell Stem Cell*, 348-358.

Bajak, A. (2016, August 12). *Will Embryonic Stem Cells Ever Cure Anything?* Retrieved from MIT Technology Review: technologyreview.com

Expanded adipose-derived stem cells for the treatment of complex perianal fistula. (January 2009). *Diseases of the colon and rectum*, Volume 52 pages 79-86.

MacKay, C. (1980). *Extraordinary Popular Delusions And the Madness of Crowds.* New York : Three Rivers Press.

Mendick, R. &. (2011, May 8). *Europe's Largest Stem Cell Clinic Shut down after death of baby*. Retrieved from The Telegraph: https://www.telegraph.co.uk/news/worldnews/europe/germany/8500233/Europes-largest-stem-cell-clinic-shut-down-after-death-of-baby.html

Pagliuca, F. .. (2014). Generation of Functional Human Pancreatic Beta Cells In Vitro. *Cell*, 428-439.

Sandel, M. J. (2009). *Justice: What's the Right Thing to Do?* New York: Farrar, Straus, and Giroux.

Stem Cell Therapy for perianal fistula in Crohn's desease. (2016). *Gastroenterology Hepatology*, 637-640.

US Stem Cell Clinic, LLC. (n.d.). Retrieved 2018, from http://usstemcellclinic.com/

Wan, W. &. (2018, May 9). *FDA seeks injunction to stop two stem cell companies after patients blinded.* Retrieved from The Washington Post: https://wapo.st/2IsGvys

Wieschaus, E. (1995, December 8). *From Molecular Patterns to Morphogenesis, the Lessons from Drosophila*. Retrieved from nobelprize.org: nobelprize.org