There is a natural and rather ego-gratifying tendency among most of us doctors to believe that “real” medicine began with our practice of it. Of course, the problem with this is that someone failed to inform historians and fix the history books, which tell a decidedly different story!

I can illustrate this by taking a page from my own life and career – which is also the topic of this article, namely adult stem cells and their clinical application to turning the tables on various chronic diseases and medical conditions.

I first learned about the use of bone marrow stem cells as a young physician extern in the Department of Hematology and Oncology at the University of Washington in 1969. At the time I thought that stem cells were something hitherto hidden from most other doctors and that my associates and I were going to launch a new age of regenerative medicine with them. There was actually some good reason to think this. The particular program that I was part of was directed by physician Edward Donnall (“Don”) Thomas, whose illustrious career culminated in his being awarded the Nobel Prize in Physiology or Medicine with another physician, Joseph E. Murray, in 1990, for the development of cell and organ transplantation. It was Thomas who actually developed bone marrow transplantation as a treatment for leukemia. He and his team ultimately did over 4000 human marrow transplants. However, as I discovered later on, stem cells were not exactly unknown to medicine ... and the new age of regenerative medicine would dawn a little later than I originally anticipated.

It was actually in the year 1908 that the Russian histologist Alexander Maksimov (1874–1928) proposed the use of the term stem cell at a hematologic society congress held in Berlin, Germany. He crafted this term to help describe something that he had observed about blood; namely, that all blood cells develop from a common precursor cell. This theory of common descent, or the “unitarian theory of hematopoiesis,” was based on years of extensive research by Maksimov. Other experimental work that he did supported his contention that lymphocytes of the blood and lymph nodes are undifferentiated cells. But, like many developments in medicine, there was a great lag time between the discovery of stem cells and sufficient acceptance to spur on additional exploration of their nature and possible medical uses. All told, things didn’t get really going until the 1950s into the 1960s. At that time almost 200 allogenic (unrelated donor) marrow transplants had been performed in humans but with no long-term successes. Then, in 1958, Edward Donnall Thomas made history when he injected bone–marrow containing stem cells into a 3-year-old leukemia patient, which had been harvested from her identical (healthy) twin. The young child did well for 6 months, but then had a recurrence of her cancer.

During February 1961, Canadians James E. Till, a biophysicist, and Ernest A. McCulloch, a hematologist, published findings in the journal Radiation Research which proved that the existence of cells that can self-renew repeatedly, also known as “stem cells.” Both worked for the Ontario Cancer Institute (OCI) at the time. In 1968, University of Minnesota doctors performed the first ever hematopoietic stem cell transplantation (HSCT) for patients with inherited cellular immunodeficiency conditions: one was a child with severe combined immune deficiency (SCID) and the other a child with Wiskott-Aldrich syndrome (WAS). The donors in both cases were matched siblings.

Then, in 1969, after years of work on histocompatibility and the development of antibiotics that inhibit transplant rejection, Thomas performed the first successful allogenic bone marrow transplants. Bone marrow transplantation, of course, proved a powerful way to turn the tables on leukemia, and was also eventually employed to successfully combat a multitude of other diseases including aplastic anemia, Hurler’s syndrome and other inherited metabolic disorders, severe combined immunodeficiency (SCID), sickle cell disease, and Wiskott-Aldrich syndrome.
Stem Cells

Discoveries in stem cell science happened at a fairly rapid clip beginning in the 1970s. I will quickly touch on some of the highlights plus my work with umbilical cord stem cells abroad before focusing attention back on the biological and clinical treasure trove which is bone marrow.

• In 1978 stem cells were discovered in human umbilical cord blood.
• In 1981 the very first in vitro stem cell line was developed from mice.
• In 1988 embryonic stem cell lines were derived from a hamster, and in 1995 the very first embryonic stem cell line was created from a primate.
• In 1997, a lamb was cloned from stem cells and dubbed “Dolly.”
• In 1997 the origins of leukemia were traced to defects in hematopoietic stem cells or cancer stem cells.
• In 1998, James A. Thompson at the University of Wisconsin isolated cells from the inner cell mass of early human embryos and developed the first embryonic stem cell lines. During the same year, John D. Gearhart at Johns Hopkins University, derived germ cells from cells in fetal gonad tissue.
• And in 2006, researchers successfully “reprogrammed,” or transformed, somatic cells into a stem-cell-like state. This new type of stem cell was subsequently called induced pluripotent stem cells (iPSCs).


By the late 1990s I, like many physicians, had become keenly aware of the work being done with embryonic stem cells and their purported promise to usher in a new age of regenerative medicine. However, as ethical objections over using embryonic stem cells gained traction and studies appeared showing that these stem cells produce teratomas in lab animals, many researchers and doctors began focusing on adult stem cells.

In order to appreciate the appeal of adult stem cells to doctors like me who were looking for ways to remediate or cure a wide swath of diseases and medical conditions, it helps to understand the type and nature of stem cells that reside in embryos versus those typically found in nonembryonic, somatic tissues:

Embryonic stem cells are pluripotent; that is, they possess the potential to differentiate into any of the three germ layers that give rise to all the organs and such in all of us: endoderm, mesoderm, or ectoderm. This means that they can become any fetal or adult cell type. In their native embryonic environment, they get a carefully orchestrated series of signals from surrounding tissue that guides them to follow specific developmental pathways in precise ways (i.e., a baby results). When these signals are missing, out of their normal order, conflicted, or present in the wrong quantities as happens when these embryonic stem cells are implanted in the tissues or organs in animals, they can remain undifferentiated, differentiate into a cell type at odds with the tissue they are engrained in, or even form a teratoma.

Adult stem cells, which arise after early stage or embryonic development and are found in our organs, plus adipose, dental pulp, and many other tissues, are more restricted in terms of the bodily cell types that they can become. This makes sense, as most of these stem cells never leave the tissue or organ that they are part of and basically serve to replenish cells that die off as well as promote the repair and regeneration of local tissues that incur damage due to aging, disease, or injury. In addition, stem cells exist in umbilical cord blood and the gelatinous Wharton’s jelly that surrounds umbilical cord blood vessels, as well as the amnion and amniotic fluid, and placenta. These stem cells are more biologically plastic or versatile than adult stem cells taken from fully developed tissues and organs yet, unlike embryonic stem cells, do not form teratomas.

The adult stem cells in most of the body’s organs and tissues tend to be a mix of multipotent, oligopotent, and unipotent stem cells. These terms refer to the developmental plasticity or versatility of these stem cells. In a word: multipotent stem cells can differentiate into a number of somatic cell types, but only into those of a closely related family of cells. Oligopotent stem cells, on the other hand, can differentiate into only a few cell types such as lymphoid or myeloid cells, while unipotent cells can generate only one somatic cell type, their own, though they possess the property of self-renewal (which sets them apart from non-stem cells).

General Classification of Stem Cell Plasticity (Developmental Versatility)

Totipotent
All bodily cell types (e.g., somatic cell types, germ cells, etc.)
Fertilized egg, zygote, morula cells
Adult totipotent stem cells

Pluripotent
All somatic cell types; e.g., heart cells, kidney cells, neurons, etc.
Inner cell mass (ICM) of blastocysts
Embryonic stem cells
Adult pluripotent stem cells; e.g., from body tissues such as bone marrow, umbilical cord, umbilical cord blood, etc.

Lineage-committed
Germ layer lineage stem cells
Ectoderm-associated stem cells
Mesoderm-associated stem cells
Endoderm-associated stem cells

Multipotent: Cell specific
Neural stem cells
Cord blood stem cells
Hematopoietic stem cells
Most bone marrow stem cells

Unipotent:
Committed to becoming a single cell type
Dopamine-expressing neurons
Muscle cells
Cartilage
Insulin-producing cells

Interestingly, bone marrow tissue and umbilical cord blood contain a wealth of multipotent stem cells, including mesenchymal stem cells, but also some pluripotent stem cells such as a small number of very small embryonic-like stem cells (VSELs). So why don’t
these pluripotent stem cells form teratomas when implanted or infused in animals or people? Apparently, they have been exposed to growth factors or other bioactive molecules in the more developmentally advanced tissues which they come from that are absent in embryos, and which leave them far less prone to form teratomas.

Like many doctors in countries outside the US, I learned of the pioneering work of Paul Niehans et al. and their transplantation of live fetal tissue transplantations (usually sheep) and was impressed by their reported clinical successes and safety of this treatment approach. These safe and apparently effective treatments preceded and paved the way for clinical work in people using human (nonembryonic) stem cells. Between 1991 and 2001, I worked with a Mexican orthopedic surgeon who used shark embryonic tissues to successfully treat spinal cord injuries.

Armed with this background, and having done an exhaustive review of the published research available at the time plus foreign stem cell patient case histories, I could plainly see that adult stem cells were not only safe but largely effective in terms of producing clinical benefits in a number of diseases and medical conditions in both adults and children. With an eye out for opportunities to wade into the world of stem cell medicine, my orthopedic surgeon colleague in Mexico signaled that he was interested in and had the legal clearance to begin working with pure umbilical cord stem cells in his country. We forged a collaborative agreement and, once he was ready to begin treating patients with cord stem cells, I proceeded to set up a nonprofit research institute bearing my name (Steenblock Research Institute [SRI]) in southern California for the purpose, in part, of helping educate and track patient coming from the US and elsewhere for umbilical cord stem cell treatments in Mexico. This was March 2003.

In the years that followed, the staff at SRI accumulated response and outcome data on over 1000 patients treated in Mexico. With my participation, we also carried out an open-label pilot study in Mexico during 2004 in which 8 children with cerebral palsy were treated with a subcutaneous injection of 1.5 million CD34+/AC133 umbilical cord stem cells. Through this study not only did we reveal statistically significant improvements in a number of bodily functions in the majority of those treated, but we also documented a partial resolution of cortical blindness in a 5-year-old boy with optic nerve hypoplasia.10

Some of the clinical successes we were seeing in Mexico were laid out in a book that I coauthored, titled Umbilical Cord Stem Cell Therapy: The Gift of Healing from Newborns12 (Basic Health Publishing; 2006).

But as wonderful as umbilical cord stem cell therapy had proved to be, I could not help but wonder what stem cells from a patient’s own fat and bone marrow (autologous stem cells) might do. They should, I reasoned, do as well or better than cord because they are autologous and would not be cleared by the patient’s immune system, something that was likely occurring with respect to a large percentage of the allogenic cord blood stem cells being infused in patients in Mexico.

Given my past involvement with bone marrow transplant work at the University of Washington, I naturally gravitated to working with bone marrow stem cells. The big question was a regulatory one: I knew that purifying or processing bone marrow stem cells beyond a certain point with the aim of using the end product in patients would require filing an IND (investigational new drug) application with the FDA and going through the formidable and costly new drug approval process. But what if I merely took bone marrow, spun it down in a centrifuge, removed the top layer (buffy coat), and then administered it to patients?

To get an answer to this, I asked my FDA–regulations savvy lawyer, Rick Jaffe (JD, Columbia University School of Law), to query the FDA. Within a few weeks, the answer came back: the use of “minimally manipulated” bone marrow was not regulated by the FDA and fell under the practice of medicine.

With this answer in hand, I began working with bone marrow aspirate concentrate (BMAC). This was spring 2005, and since then I have performed over 2000 BMAC treatments.

As the focus of my clinical work in 2005 was turning the tables on neurological conditions such as chronic stroke, I naturally began using BMAC on these sorts of cases.

I knew from my work with umbilical cord stem cells in Mexico that in neurological insults or conditions in which ischemia, hypoxia, or neuroinflammation was present, biochemical compounds, especially the chemokine (cell signaling protein) stromal-derived factor (SDF)-1, are released, acting like a homing beacon to cord blood stem cells.11

Interestingly, various studies done since I began using BMAC in 2005 have shown that when inflammation occurs in the brain, the sufferer’s bone marrow will mobilize stem cells, some of which make their way through the blood–brain barrier to the inflammation site.12,13 Given the existence of this natural mechanism for dealing with inflammation spawned by injury or disease, my use of BMAC amounts to augmentation of a natural process.

By 2010 I had enough patient response information and test results to tell me that my use of BMAC in patients under age 40 uniformly produced good-to-impressive clinical improvements, while virtually the opposite was true in those over 40. The fact that these older patients were typically juggling more chronic medical issues than the younger ones accounts for part but not all of their less-pronounced clinical responses. Another, far greater contributor was the age-related shift in the proportion of stem–cell rich red marrow content to yellow, fat-rich, and stem–cell poor marrow tissue. This might have tempted me to conclude that biology is destiny if it were not for the fact that I had found a reversal in this pattern in older patients who exercised daily by running or walking,
spent a great deal of time hiking in the high mountains, or regularly donated blood. They tended to have healthier, more abundant red bone marrow than their less active peers. Not surprisingly, I found that older sedentary people had significantly poorer clinical results when treated with a simple BMAC. I also observed that the bone marrow in people with emphysema, Parkinson’s disease, or dementia (as well as many other chronic diseases and medical conditions) had diminished in quantity and quality to the point that most of the cells were senescent!

One way to get old, yellow–fat dominated marrow to produce red marrow would, I reasoned, be to use intermittent hypoxia therapy (IHT), which simulates mountain climbing. I had numerous older sedentary patients do IHT (in my clinic) and saw the bone marrow do the expected “color shift.” The presence of more red than yellow bone marrow naturally gave these oldsters a greater complement of healthier “younger” stem cells as well an increase in the numbers of circulating healthy stem cells.

As I thought about ways to turn the tables on this biological reality, I recalled a line of evidence pointing to the fact that if large numbers of stem cells were mobilized from the marrow, it would respond by producing fresh, new stem cells that would likely be more vigorous than those had been “purged.” I then did PubMed and other database searches to check on this and turned up many papers by David T. Scadden and his associates at Harvard (dating from roughly 2008 on) that pointed out this very thing and included lab animal evidence supporting it. However, there were no studies which I could locate indicating that bone marrow stem cell mobilization had been used in people for the purpose of gauging whether the vacated stem cell niches would be filled with more pristine, vigorous stem cells. This prompted me to see what would happen if I gave injections of FDA-approved colony-stimulating factors such as Neupogen to mobilize bone marrow stem cells, especially in older, sedentary people. And, sure enough, the marrow responded by generating abundant new, more vibrant stem cells.

With experimentation, I found that large numbers of new stem cells were produced when Neupogen was given for 5 consecutive days by injection followed by a 2-week wait. This was verified by the stem cell biologist at SRI, who examined bone marrow samples taken from patients prior to the “Neupogen purge” and then again 2 weeks later following the 5-day series of Neupogen injections. He found greater than 10 times more healthy stem cells in the postpurge samples.

Not unexpectedly, older patients who did the Neupogen purge and then had bone marrow harvested and given back to them as a BMAC treatment did far better than those their age with similar medical problems who had not undergone the purge. Most had neurological diseases or conditions such as chronic stroke, ALS (Lou Gehrig’s disease), multiple sclerosis, Alzheimer’s and other dementias, or traumatic brain injury.

As the clinical successes mounted, I began treating young people with neurological problems such as cerebral palsy, Huntington’s disease, and autism. I also found myself increasingly doing BMAC treatments on people with nonneurological issues, including those with joint, ocular, cardiac, kidney, respiratory and gastrointestinal diseases, and conditions.

Of course, while I labored away at the clinical level with BMAC and found it safe and effective, especially with respect to joint and certain neurologic diseases and conditions, the research world was not sitting idle. Well, not exactly, anyway. There were a handful of studies designed and carried out that pointed to the fact BMAC is safe and produced significant clinical benefits for specific medical challenges. I’ll summarize two of them:

In 2011 Tufts Medical Center carried out a pilot, multicenter, prospective, randomized, double-blind, placebo-controlled study for “no option” critical limb ischemia (CLI) patients. Thirty-four patients wound up treated with BMAC and 14 received sham injections. There were no adverse events attributed to the injections. Bottom line: the BMAC treated group demonstrated trends toward improvement in amputation, pain, quality of life, Rutherford classification, and ABI (ankle brachial index) compared with controls.

And in May 2011 Arthroscopy: The Journal of Arthroscopic and Related Surgery published results of a prospective study in which 25 patients (mean age, 46 years) with grade IV cartilage lesions of the knee underwent a miniarthotomy and concomitant transplantation with BMAC covered with a collagen I/II matrix (Chondro-Gide; Geistlich, Wolhusen, Switzerland), and were then followed for 2 years. Patients showed significant improvement in all scores on seven evaluative tests at final follow-up ($p < .005$). In addition, MRI scans revealed good coverage of the lesion and tissue quality in all patients. No adverse reactions or postoperative complications occurred.

Interestingly, on October 21, 2015, I searched the US government clinical studies database Clinicaltrials.Gov for bone marrow aspire concentrate and turned up seven studies that are actively recruiting patients. Most of these involve BMAC use for various orthopedic and musculoskeletal issues. None of these concern neurologic diseases or conditions.

The clinical successes that I and others have seen with use of autologous BMAC naturally raises the question, how do the stem cells in BMAC work to effect healing and restoration? That is, do the various adult stem cell types present differentiate into the cell types of the tissue that they engraft in or in one way or another become cell types that encourage healing and restoration, or do they secrete substances that have a paracrine (cell–cell signaling) effect that mediates or heals, or both?

The quick and short answer is “both,” which I will now illustrate with information gleaned from a handful of telltale studies:

In 2002 University of Minnesota researchers induced stroke in rats and 1 week later grafted purified human
mesenchymal stem cells (MSCs) into the cortex surrounding the area of infarction. Following sacrifice of the animals, histological analyses revealed that the transplanted human MSCs were expressing biomarkers for astrocytes, oligodendroglia, and neurons. The grafted cells’ morphological features, or appearance, however, was spherical, with few of the structures associated with astrocytes and such. In 2007 Japanese scientists induced skin wounds in mice and then IV injected them with MSCs (derived from mice bred to produce green fluorescent protein [GFP] in their tissues). They detected GFP-positive cells at the wound sites associated with specific markers for various skin cell types such as keratinocytes, endothelial cells, and pericytes. The treatment resulted in accelerated wound repair. And in another 2007 study, New York Medical College researchers explored the fate of bone marrow stem cells injected into infarcted (transgenic) mice. The researchers found that the bone marrow stem cells engrafted, survived, and grew within the myocardium by forming connections with resident myocytes (heart muscle cells). This and a confluence of other evidence showed that the bone marrow stem cells had transdifferentiated; that is, converted from one cell type to another, and acquired cardiomyogenic and vascular characteristics and traits (phenotypes) that culminated in restoration of the animal’s infarcted hearts.

Other studies have revealed the transdifferentiation of bone marrow derived stem cells into insulin-producing cells in animal models of diabetes (streptozotocin-induced diabetic mice), differentiation of engrafted bone marrow-derived mesenchymal stem cells into specific and distinct lung cell phenotypes in animals with bleomycin-induced pulmonary damage, and much more. Many skeptics have pointed out that no matter how many millions of adult stem cells are infused into patients, the numbers that actually engraft and differentiate or transdifferentiate in target tissues or organs are too low to have a major impact on whatever damage or disease is present. This might be true if healing and restoration depended on the differentiated or transdifferentiated cells alone. However, both I and many others working in stem cell medicine contend that the infused cells, both those that engraft and those that do not and are eventually cleared or die off, facilitate healing by other means. This brings me to the paracrine and other effects of substances secreted by these cells, a mechanism that in my opinion probably accounts in large part for the remediative, healing, and restorative impact seen in the clinic.

During the past decade or so, researchers have identified numerous growth factors (plus a chemokine) that are expressed by bone marrow stem cells, typically upon engraftment. These are the principle ones:

**Platelet-derived growth factor:** PDGF promotes tissue remodeling and cellular differentiation, participates in inductive events involved in patterning and morphogenesis, and promotes angiogenesis.

**Vascular endothelial growth factor alpha and vascular endothelial growth factor beta:** VEGF-alpha and VEGF-beta both stimulate vasculogenesis and angiogenesis. VEGF also stimulates neurogenesis in vitro and in vivo.

**Transforming growth factors (TGFs)** TGFA, TGFβ1, TGFβ2 and TGFβ3: TGFs are a family of structurally related proteins that control proliferation, differentiation and other functions in many cell types

**Bone morphogenetic proteins (BMPs) 1, 2, 3, 4, 6, 7, 8B, R1A, and PR2:** These growth factors have various effects, most being integral to cartilage and bone development plus fracture repair. One, BMP7, is involved in renal development and repair.

**Nerve Growth Factor (bone marrow mesenchymal stem cells):** NGF is a small protein that is important for the differentiation, growth, maintenance, and survival of sensory and sympathetic neurons. It also functions as a signaling molecule.

Source for growth factors listed above: “Growth factors and gene expression of stem cells: bone marrow compared with peripheral blood.”

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**Stem Cells**

**Hepatocyte growth factor (Bone marrow mesenchymal stem cells):** HGF is a paracrine cellular growth, motility and morphogenic factor that targets and acts primarily upon epithelial cells, endothelial cells and also hematopoietic progenitor cells. It has been shown to have a major role in wound healing and adult organ regeneration.

**Insulin-like growth factor-1:** IGF-1 binds to the insulin-like growth factor 1 receptor present on many cell types in many tissues. It is one of the most potent natural activators of the AKT signaling pathway, a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death. In addition, IGF-1 is a primary mediator of the effects of growth hormone (GH).

**Stromal-derived factor-1:** SDF-1 promotes hematopoietic cell mobilization and migration, among other things.

In addition, adult stem cells have also been found to express various chemokines, bioactive lipids (such as sphingosine-1-phosphate and ceramide-1-phosphate), as well as microRNA, also written as miRNA (i.e., small noncoding RNA molecules that act to downregulate gene expression in a variety of ways), and RNA that many researchers think are primary drivers of tissue and organ regeneration by virtue of paracrine signaling.

Especially exciting are findings showing that activated stem cells secrete microvesicles (MV’s) or exosomes, which are small, spherical membrane fragments shed from cell surfaces or that are secreted from the endosomal compartment within cells that inhibit programmed die-off (apoptosis) of cells residing in damaged tissues, as well as stimulate their proliferation and promote vascularization. One research group found that these stem cell-generated MV’s “contained ribonucleoproteins involved in the intracellular traffic of RNA and selected pattern of microRNAs, suggesting a dynamic regulation of...”
A paper concerning this has been prepared for submission to a top-tier peer-reviewed journal.

Dr. David A. Steenblock earned his BS degree from Iowa State University, then an MS in biochemistry and doctor of osteopathy (DO) degree from the College of Osteopathic Medicine and Surgery in Des Moines, Iowa. His postdoctoral training included three years at Case Western Reserve University, one year at the Oregon Health & Sciences University, and a clinical rotating internship at Providence Hospital in Seattle, Washington. During the late 1970s, he founded the first integrative medicine clinic west of the Mississippi River. In the years since he has done pioneering clinical work including the use of hyperbaric oxygen therapy to treat stroke (starting in 1989), umbilical cord stem cell therapy (Mexico from 2003), and, since 2005, stem cell rich bone marrow aspirate concentrate (BMAC). In October 2015 he was awarded the Academy of Comprehensive Integrative Medicine’s (ACIM) “Lifetime Achievement Award” at its NeuroRegeneration Conference (Orlando, Florida) in recognition of his more than 40 years of contributions “to the betterment of mankind and the advancement of integrative medicine.”

While at the ACIM conference, Dr. Steenblock gave a presentation on amyotrophic lateral sclerosis (ALS), or “Lou Gehrig’s disease,” that included data and insights gleaned from an observational study he did of 54 spinal cord ALS patients whom he treated over a 4-year period (2011–2015). He shared evidence he found in the majority (52 of 54 SALS patients) that links spinal injury and subsequent reinnervation to injuries in the brain–cerebrospinal barrier, breaches which then admit specific neurotoxic compounds, activated and damaged immune cells that secrete misfolded SOD1, as well as other cell and nerve cell toxic players (some of which are selectively lethal to motor neurons). He also discussed his use of bone marrow stem cells and other means to repair these breaches, offset and reverse the damage, and counter the ALS disease process. The spinal injuries/reinjuries and the symptoms and pathological damage that Dr. Steenblock discovered provide both a unique risk factor and biomarker for SALS. If validated by subsequent research, this is something that physicians and researchers can use to better diagnose SALS.

A paper concerning this has been prepared for submission to a top-tier peer-reviewed journal.