

## REPORT

### Adult Stem Cells

#### New Hope for Curing Degenerative Diseases

By Denis Rodgerson, PhD, Ron Rothenberg, MD, FACEP, and Wayne A. Marasco, MD, PhD



The potential to heal once incurable degenerative diseases such as cancer or heart disease by regenerating cells that have failed or are about to fail is now within our grasp, thanks to the emergence of an exciting new field of medicine: regenerative medicine using adult stem cells.

Indeed, tissues such as heart muscle that were long thought to be non-renewable have now been shown to be regenerated through this novel therapy. By using adult stem cells, scientists have avoided the controversy that has stymied advanced embryonic stem cell research in the past. Adult stem cell therapy offers an unprecedented step forward in the history of medicine and the applications of this new form of regenerative medicine are potentially unlimited.

#### EMBRYONIC VERSUS ADULT STEM CELLS

Considerable confusion surrounds the use of stem cells, not only with the general public, but indeed with scientists and physicians. This confusion has been compounded by the ethical, moral, and political issues that have arisen around the sources of stem cells. Broadly speaking, there are two classifications of stem cells: those that are derived from embryos (embryonic stem cells, ESCs) and those that come from other sources (adult stem cells [ASCs] or somatic stem cells). All stem cells, whatever their source, have three general properties: they are capable of dividing and renewing themselves for long periods; they are undifferentiated; and they have the ability to develop into specialized cell types.

Embryonic stem cells are derived from a clump of cells formed after fertilization, which is called the inner cell mass (ICM). The cells of the ICM rapidly differentiate to form all of the cell types in the human body, hence creating a fetus and then a human being. If the cells of the ICM are harvested and grown in appropriate culture conditions, however, they will replicate indefinitely and, when suitably stimulated, will differentiate into three germ layers: ectoderm, mesoderm, and endoderm—representing any cell lineage of the body. This potential to differentiate into any other cell type in the body is referred to as plasticity (or pluripotency).<sup>1</sup> Given their high degree of plasticity, however, embryonic stem cells not only have the capability of becoming beneficial tissue, they also can differentiate into cancerous (malignant) cells. While it has recently been reported that these cells can be derived from sources other than embryos, there is broad consensus that much more research is required before human therapies based on embryonic stem cells can be safely pursued.<sup>2</sup> Thus, while these cells have great importance in unraveling the processes by which cells proliferate and differentiate, there are currently no approved treatments or human trials using embryonic stem cells.

In contrast, adult stem cells are derived from non-embryonic origins, including bone marrow, peripheral blood and, paradoxically, cord blood, placental cells, and amniotic fluid (note that cord blood and placental cells must be collected and banked at the time of birth for future use, while amniotic fluid is drawn from the fluid surrounding a growing fetus). Adult stem cells are thought to be capable of facilitating all the body's natural repair processes. Since the production of adult stem cells does not require the destruction of an embryo, these cells are not associated with any ethical or political controversy. Readily obtainable, these cells have been used for many years for therapeutic purposes.

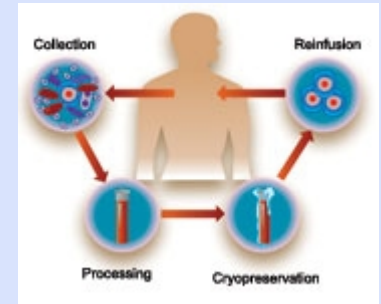
#### PRE-DISEASE HARVESTING AND LONG-TERM BANKING OF STEM CELLS

The prospect of effective regenerative therapies for cancer, heart disease, autoimmune diseases, chronic non-healing wounds, and a wide range of other diseases raises the issue of the availability of a patient's own stem cells. Preferably these cells would be harvested before the onset of disease and before risk factors for disease compounded by natural aging have diminished their potency and effectiveness. The concept of banking adult stem cells is now well established through cord blood banks.<sup>42</sup> It is estimated that approximately 5% of newborns (200,000 per year) in the United States now have their cord blood stem cells stored for future therapeutic applications.

Until a few years ago, the only source of stem cells outside the newborn period for an individual's own use was from the withdrawal of bone marrow fluid through a needle put into the pelvic bone (a technique called needle aspiration), usually done under general anesthesia. Recently, however, mobilization of a person's stem cells from the bone marrow into the bloodstream has been validated in healthy individuals.<sup>43,44</sup> This approach makes it possible to collect a large quantity of adult stem cells sufficient for multiple medical therapies, without the costs and uncertainties associated with micro-collection methods. Indeed, adult stem cells harvested from non-mobilized peripheral blood or adipose tissue often require ex vivo (outside the body) expansion to obtain sufficient numbers of adult stem cells for many autologous therapies.

### **A SIMPLIFIED REGIMEN FOR ADULT STEM CELL COLLECTION FROM HEALTHY ADULTS CAN BE SUMMARIZED AS FOLLOWS:**

Following clearance with a history and physical examination, the person receives a subcutaneous injection of granulocyte colony-stimulating factor, a growth factor that stimulates the bone marrow to release stem cells into the bloodstream. On the second day, the injection of granulocyte colony-stimulating factor is repeated. On the third day, the person is connected to a machine that will collect the stem cells, called an apheresis machine. The process involves placing a needle in the vein of one arm and connecting this needle to the apheresis machine, which separates the desired cells from all the other components of the blood (such as plasma and red cells). These residual components are then returned to the individual by way of a second needle placed in the vein of the other arm. The process typically takes about three hours, during which the person is seated in a comfortable chair watching a movie or listening to music.



The collected stem cells are then sent to a processing laboratory where they are treated so that they may be permanently stored. This process protects the structural and functional integrity of the cells prior to cryogenic storage. These agents, together with a very slow, computer-controlled and documented reduction in temperature, allow cells to be cooled to well below freezing with no loss of viability or functionality. Once this sub-frozen state is achieved, the cells are transferred to a storage tank containing liquid nitrogen at a temperature of approximately -196° C. Cells that have been properly processed can be maintained for many years without significant loss of post-thawing viability.<sup>45</sup> Cells that are removed from the cryogenic environment and thawed must be used within a short period and cannot be re-frozen. Stem cells are therefore stored in multiple aliquots so that any number of containers can be withdrawn and thawed to meet a required cell dose, without affecting the remainder.

## **ADULT STEM CELL THERAPIES**

It was initially believed that the ability of adult stem cells to regenerate tissue was limited to the type of tissue in which they resided. This is now known not to be the case. Numerous studies have confirmed that, although these cells do not have the universality of the embryonic type, they do have the capacity for self-renewal, are able to differentiate into other cell types and are capable of generating differentiated cell progenitors (similar to stem cells) of different (perhaps all) cell lineages. Their potential to differentiate into cell types found in other tissues means they can travel to a site of damage, penetrate the damaged tissue, and then regenerate this tissue by a process called transdifferentiation. It is these properties that have formed the basis for therapies in which adult stem cells have been used.

### **BONE MARROW TRANSPLANTS: ADJUVANT CANCER CARE**

One of the areas in which adult stem cells have become widely used is in the treatment of blood cancers including leukemia, lymphoma, and multiple myeloma. Since the 1990s, bone marrow transplants using blood-derived stem cells, which are capable of generating all cell types of the blood and immune system, have been used to regenerate bone marrow damaged by the effects of chemotherapy and/or radiation. Without healthy bone marrow, patients with these cancers cannot make the blood cells needed to carry oxygen, fight infection, and heal wounds. Healthy, transplanted bone marrow therefore restores these functions.

## **STEM CELL DONORS**

Often, because of the lack of an identical donor, adult stem cells obtained from a genetically well-matched healthy donor are infused into the affected recipient (known as "allogeneic" infusion, as opposed to using a recipient's own stem cells) to create a healthy immune system free of cancer. These donor stem cells are obtained by a technique called apheresis, in which a machine selectively separates stem cells from donor blood and returns the rest of the blood to the donor. During this process, the donor most often receives a medicine (or "mobilizing agent") called granulocyte colony-stimulating factor, which stimulates the bone marrow to release stem cells into the bloodstream where they can be easily collected after several days of treatment. Although this method has proved successful in providing sustained remission or cures of underlying diseases, donor stem cells do pose problems in that they can either be rejected by the recipient's immune system or they may attack the recipient's cells in a serious condition called graft-versus-host disease. In order to reduce the magnitude of rejection and graft-versus-host disease, tissue from both the donor and recipient must be matched to be as compatible as possible. Often, recipients must take

immunosuppressive drugs for the rest of their lives to prevent rejection, which is associated with morbidities such as increased risk of serious infections.<sup>3,4</sup>

An alternative to using closely matched donor stem cells (“allogeneic” infusion) is to use the recipient’s own stem cells, known as “autologous” infusion. The use of these “autologous” cells avoids all of the problems associated with donor stem cells and also confers significant clinical and economic benefits. Intuitively, collecting and banking blood-derived stem cells many years before the onset of disease, known as pre-disease harvesting, should minimize the presence of tumor cells or tumor stem cells. Furthermore, banking an individual’s own stem cells may one day be life-saving in the event—particularly in those with strong family or occupational related risk factors for cancer—that a diseased organ needs to be replaced with one grown from their own cells.

## ADULT STEM CELLS: WHAT YOU NEED TO KNOW

- Soon it may be possible to cure devastating diseases such as cancer, autoimmune illness, and heart disease through the use of adult stem cells. Derived from bone marrow, peripheral blood, cord blood, placental cells, or embryonic fluid, adult stem cells can perform all of the body’s natural repair processes.
- Unlike embryonic stem cells, adult stem cells can be gathered without the destruction of an embryo. The use of adult stem cells thus does not entail complex ethical, moral, or political issues.
- Adult stem cells are widely used in bone marrow transplants following treatment for blood cancers such as leukemia and lymphoma.
- Adult stem cells show promise in restoring heart structure and function following heart attack and in improving chronic heart failure.
- Scientists believe that adult stem cells hold promise in managing autoimmune and neurodegenerative diseases.
- Stem cell health can decline over time due to illness or poor lifestyle choices. Harvesting and storing your stem cells now could allow you to benefit from advanced curative stem cell therapies in the future.
- Nutrients such as green tea, vitamin D3, carnosine, blueberry, and DHA, along with bioidentical hormone replacement, may help stimulate optimal stem cell proliferation and function, thus promoting regeneration and healing.



Cryopreservation of stem cells

## RESTORING HEART FUNCTION

Heart disease shows some of the greatest potential for the application of stem cells. Ischemic heart disease accounts for approximately half of all cardiovascular deaths in the United States, with over one million people suffering a heart attack each year. A heart attack leads to the death of the heart tissue and causes the muscle cells of the heart to be depleted. It also progressively remodels the structure of the heart, further reducing its ability to pump blood. For a long time, it was believed that the heart was a “post-mitotic” (non-renewable) organ composed of muscle cells that had completed the differentiation process, and therefore had limited capability of regeneration following an injury such as a heart attack. This belief is now being effectively challenged by mounting evidence to show that not only do endogenous self-repairing mechanisms exist, but that these and other regenerative processes, such as the development of new blood vessels, can be activated, or facilitated, by adult stem cells. These findings, and other observations, have led to a number of clinical trials that have tested the ability of stem cells to restore heart function in patients with acute

heart disease. Early studies focused on establishing the safety and feasibility of using a patient’s own stem cells to improve heart function following a heart attack.<sup>5-7</sup> Although research is ongoing, many controlled studies have also compared similar groups of patients on standard medical therapy after a heart attack with those on therapy plus an intracoronary infusion of their own stem cells. The results have been encouraging, revealing a positive effect of stem cell therapy on improving cardiac function outcomes, such as blood flow within the heart, wall motion, left ventricular function, and reducing the size of damaged heart tissue.<sup>8-17</sup>

## NATURAL THERAPIES SUPPORT STEM CELL HEALTH

Stimulating the healthy growth of stem cells is a critical component of every anti-aging program. Studies have shown that specific nutrients and hormones can encourage the growth or proliferation of stem cells in one’s body, thus promoting regeneration and healing.

In a groundbreaking study, scientists took several nutrients known for their health and cognition-enhancing benefits and studied their effects, alone and in combination, on the proliferation of bone marrow and hematopoietic cells (which are capable of

generating all cell types of the blood and immune system).<sup>46</sup> The researchers found a dose-related effect of blueberry, green tea, catechin, carnosine, and vitamin D3 on the proliferation of human bone marrow. Furthermore, combinations of these nutrients stimulated bone marrow proliferation by as much as 83%, compared with only 48% in a control group, which received a growth factor medicine called granulocyte colony-stimulating factor.<sup>46</sup>

Another natural compound showing promise for boosting stem cell health is resveratrol. Derived from red wine, resveratrol has demonstrated significant health benefits ranging from cardiovascular protection to anticancer effects.<sup>47</sup> It is believed that resveratrol works by mimicking the effects of calorie restriction, the best anti-aging strategy to date, through mechanisms such as reducing oxidative stress, boosting energy production, and regulating gene expression.<sup>48</sup>

Recent studies have also linked the cardioprotective effects of resveratrol with the regeneration of endothelial progenitor cells, which are derived from stem cells and can be collected by the stem cell collection process described on page 42. These progenitor cells are a vital component in helping to repair blood vessel damage. Indeed, aging and compromised cardiac function are associated with low numbers of these cells.<sup>49</sup> One animal study found that low concentrations of resveratrol increased the number and function of endothelial progenitor cells in repairing the injured endothelium of the aorta.<sup>50</sup>

Adult stem cell repair is also influenced by supplementing with the omega-3 fatty acid, docosahexaenoic acid (DHA). This compound is essential for healthy brain growth and development. It also plays a crucial role in supporting normal brain function, including learning and memory. Results from a recent study revealed that DHA may exert its effects by triggering the differentiation of neuronal stem cells to produce new neurons in the brain.<sup>51</sup> This interplay among nutrients, stem cells, and growth factors offers promising hope for slowing down and preventing neurodegenerative diseases.<sup>52</sup>

Another method to support stem cell proliferation and function is through optimizing hormone levels. Using bioidentical hormones (which are identical to those naturally occurring in the body), it is possible to restore deficient adult hormones to youthful levels. Stem cell-enhancing effects have been noted with both growth hormone and estradiol replacement therapy.<sup>53,54</sup> In fact, animal studies have shown that estrogen and growth hormone enhanced the action of stem cells in cardiac repair.<sup>55,56</sup> Additionally, a study in men aged 60-75 years old found that testosterone replacement therapy increased muscle mass by stimulating stem cells in muscle.<sup>57</sup>

Targeted nutritional and hormonal therapies may thus help promote wellness and fight the diseases associated with aging through optimizing stem cell production and function.

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#### BETTER LONG-TERM CARDIAC HEALTH

Adult stem cell therapies have also shown clinical benefit in severe chronic heart disease, such as congestive heart failure, of which almost half a million new cases are diagnosed each year. In one study by Brehm and Strauer, bone marrow-derived stem cells were transplanted directly into the heart tissue of 18 male patients who had suffered a heart attack between five months and 8.5 years earlier.<sup>18</sup> These patients had progressive chronic heart failure with reduced left ventricular function. A group of patients who did not receive any cell therapy served as controls. After three months, the researchers found that the area of heart tissue damaged by disease was reduced, while oxygen uptake, energy metabolism and left

ventricular function all increased compared with the control group, who showed no significant changes in these parameters.

In another study, Patel and colleagues studied 20 patients with severe chronic heart disease and very poor left ventricular function classified as chronic heart failure.<sup>19</sup> All 20 patients received bypass surgery to improve blood flow. In addition, half of the patients also received an infusion of adult stem cells during surgery, which were injected into the most severely compromised regions of the heart. Six months after surgery, the left ventricular function of the stem cell-treated group increased substantially compared with the control group. The improvement was so great that the stem cell recipients were no longer defined as having chronic heart failure.

#### BANKING STEM CELLS FOR HEART HEALTH

It has been suggested that an alternative to stem cell infusion is to administer growth factors that are produced naturally in the body. The use of these chemicals, such as granulocyte colony-stimulating growth factor, alone stimulates the endogenous production of stem cells, which might obviate the need for stem cell infusion. However, a defined benefit from this therapy

has not yet been established<sup>20</sup> and some evidence suggests that the use of stem cells immediately after a heart attack may even be detrimental.<sup>21</sup> Furthermore, there is mounting evidence that those factors that precipitate the onset of heart disease—such as hypertension, diabetes, smoking, and others—also impact the effectiveness of stem cells in terms of their ability to migrate, transdifferentiate, and proliferate. The benefits of banking stem cells before the onset of disease will undoubtedly prove to be clinically important as the use of these therapies becomes more widespread. Despite the uncertainties about their mechanisms of action, scientists broadly agree on the potential of regenerating damaged heart tissue using a patient's own stem cells to improve cardiac function and performance.<sup>22</sup>

#### NUTRACEUTICALS KNOWN TO OPTIMIZE ADULT STEM CELLS

- Blueberry
- Green tea
- Catechin (from green tea)
- Carnosine
- Vitamin D3
- Resveratrol (found in red wine)
- Omega-3 fatty acids, including docosahexaenoic acid (DHA)

#### HORMONES KNOWN TO OPTIMIZE ADULT STEM CELLS

- Growth hormone
- Estradiol
- Testosterone

#### AUTOIMMUNE AND NEUROLOGICAL CONDITIONS

Adult stem cells could also offer hope for patients with autoimmune and neurodegenerative diseases.

#### THREE COMMON PROPERTIES OF STEM CELLS

In autoimmune disorders, the body begins to produce a type of white blood cells called T lymphocytes and protective proteins called antibodies, which, instead of protecting the body against invasive microbes and cancers, attack its own cells and organs. There are more than 70 different types of autoimmune disorders, for example, multiple sclerosis,

1. Capable of extensive division and self-renewal
  2. Undifferentiated
  3. Able to develop into specialized cell types
- Adult human hematopoietic stem cells

rheumatoid arthritis, systemic sclerosis (scleroderma), systemic lupus erythematosus, and juvenile idiopathic arthritis. As a class, autoimmune diseases affect approximately 5% of the US population, with common conditions such as systemic lupus erythematosus affecting 1.5 million people, mostly young women. The standard treatment for autoimmune diseases generally consists of immunosuppression, anti-inflammatory medication, or anti-malarial medication, in addition to supportive care. In cases that do not respond to standard treatment or are considered life- or organ-threatening, high doses of immunosuppressive medication have been proposed as a treatment option to eliminate the T cells causing the autoimmune response. However, such high doses also suppress the bone marrow's production of blood cells (known as "myelosuppression"), necessitating rescue therapy with transfused hematopoietic (blood cell-forming) stem cells.

It has been theorized that regenerating bone marrow with transplanted stem cells normalizes the immune system.<sup>23,24</sup> The concept of stem cell therapy following immunosuppressive therapy for autoimmune diseases has led to the publication of consensus guidelines and the initiation of a number of well-controlled clinical trials.<sup>25,26</sup> To date, more than 700 patients have received transplants using their own stem cells as treatment for severe autoimmune diseases,<sup>27</sup> including 183 patients with multiple sclerosis,<sup>28</sup> 76 patients with severe rheumatoid arthritis,<sup>29</sup> 102 patients with systemic sclerosis (scleroderma),<sup>30,31</sup> 103 patients with systemic lupus erythematosus,<sup>32-34</sup> and, most recently, 15 individuals with new onset type I diabetes.<sup>35</sup> Numerous studies using adult stem cells to treat other autoimmune diseases such as Crohn's disease, Behcet's disease, and relapsing polychondritis have also been published.<sup>36,37</sup>



Adult human hematopoietic stem cells

Early studies in patients with neurodegenerative diseases—some of which may represent autoimmune processes—have shown promising results, suggesting that stem cells might offer hope for people with neurological disorders, perhaps even for prevalent conditions such as Parkinson's disease.<sup>38-41</sup>

Although the clinical outcomes of stem cell treatments have been variable, most of the studies in this field have shown significant amelioration of disease activity, improvement in serological (blood) markers, and either stabilization or reversal of organ dysfunction. The preliminary conclusions of these studies are sufficiently encouraging to proceed to randomized prospective trials of stem cell transplantation for autoimmune diseases as a group, and particularly for those that are most severe and debilitating. Similarly, scientists believe that stem cells therapies offer compelling hope for neurological conditions, and are further exploring their applications for these debilitating disorders.

## CURRENT AND FUTURE APPLICATIONS OF STEM CELL THERAPIES

The chart below lists conditions currently treated with stem cell therapy, as well as future applications for this regenerative therapy:

Today	Tomorrow
Leukemias	Spinal Cord Injuries
Lymphoma	Stroke
Multiple Myeloma	Severe Infectious Diseases
Coronary Heart Disease	Lou Gehrig's Disease (ALS)
Radiation Sickness	Breast and Ovarian Cancer
Multiple Sclerosis	Diabetes
Lupus Erythematosus	Osteoporosis
Other Autoimmune Diseases	Autoimmune Neurological Diseases
Tissue Repair & Burns	Amyloidosis
Type I Diabetes	Type II Diabetes
Orthopedics	Others

## CURRENT AND FUTURE STEM CELL THERAPIES

Importantly, all of the studies that have been mentioned so far were carried out using stem cells that were collected after the onset of disease. It is intriguing to speculate on the improvement in outcome that might be achieved if a patient's own stem cells were available before the onset of disease. The table on page 46 summarizes the current status of regenerative therapy, divided into those diseases being treated with adult stem cells today and those in which experimental evidence from animal studies strongly indicates potential benefits in the future.



## CONCLUSION

Adult stem cells may one day yield cures for the most dreaded diseases that plague adults. A plentiful supply of adult stem cells for personal use collected while healthy and available may offer all adults powerful insurance against the consequences of a range of diseases, both chronic and acute, that is growing daily. Only by having a readily accessible source of stem cells can the full benefits of regenerative medicine be realized. While it remains to be seen whether adult stem cells can prevent or reverse aging or extend life span, ongoing research promises to propel the field of regenerative medicine forward. Regardless of these unanswered questions, it is clear that banking stem cells for long-term storage may truly represent a “bio-insurance policy” that can help provide for your optimal health in the future.

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*If you have any questions about the scientific content of this article, please call one of our Health Advisors at 1-800-226-2370.*

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