IQP-DSA-43-5744

CONTROVERSIES IN STEM CELL RESEARCH

An Interactive Qualifying Project Report

Submitted to the Faculty of

WORCESTER POLYTECHNIC INSTITUTE

In partial fulfillment of the requirements for the

Degree of Bachelor of Science

by

Priya Jayachandran

October 24, 2005

APPROVED:

_____

David S. Adams, Ph.D.
Project Advisor

ABSTRACT

Adult stem cells, especially hematopoietic stem cells have been used to treat humans for over 20 years, but the use of embryonic stem (ES) cells has been restricted since their use involves the destruction of a human embryo. Hence, ES cell research is surrounded by ethical, moral, and religious anxieties. This IQP analyzes the controversies surrounding stem cell research, the legislations passed to regulate their use, their applications and their future in regenerative medicine.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Stem cells are unspecialized cells that can be induced to become specialized cells under specific experimental or physiological conditions. They are capable of restoring themselves through cell division over an indefinite period of time. Two main classifications of stem cells have been identified: embryonic and adult. Adult stem cells are obtained from an adult patient or volunteer donor. These cells have the capacity to regenerate only the specific tissue from which they were isolated. Whether all adult tissues contain stem cells remains a controversy, but substantial evidence exists for adult neuronal, heart, and hematopoietic stem cells. Thousands of lives have already been saved using hematopoietic stem cells in bone marrow transplants for cancer patients.

By far the most controversial stem cells are human embryonic stem cell (hES). These cells show greater medical potential due to their true pluripotent nature, but (with the exception of parthenotes) are usually obtained from the blastocyst stage of a fertilized egg which destroys an embryo with the potential for becoming a human.

Due to their pluripotent nature, hES cells can potentially be used to treat a wide variety of degenerative diseases. Patients suffering from Parkinson's Disease, Alzheimer's Disease, and diabetes (both Type 1 and Type 2) are among the top potential benefactors of hES cells. In animal experiments, human ES cells have been used to re-grow damaged spinal motor neurons to treat spinal cord injured rats and they have been used to re-grow cardiomyocytes to replace damaged cells after cardiac arrest in mice. Human trials are underway; however, research with mouse ES cells has already proven successful.

The use of hES cells in regenerative medicine requires the destruction of an embryo. Hence, hES cells have been caught in a web of controversy encompassing three main questions: Is the medical benefit of destroying a human embryo valued more highly than the *potential* life of the embryo? Are there alternative sources of ES cells that do not destroy an embryo? Can adult stem cells medically replace ES cells? To answer these questions, politicians and the general public have turned to religion, as well as two fundamental moral principles: the necessity to both prevent and alleviate suffering, and to respect human life.

The questions of when personhood begins and whether or not an embryo is considered a human being have been explored in great detail, yielding four stances. All four major religions support the use of adult stem cells, so long as they are used to alleviate human suffering. Islam, Hinduism, and Judaism each support the use of hES cells since they associate the beginning of life with 3 to 5 months of gestation, well after the blastocyst stage at which embryos are destroyed to obtain ES cells for research. Christianity is the only faith denouncing hES cell research as they commonly believe life begins when the embryo attaches to the uterine wall, at almost exactly the same time that a blastocyst is formed (which would be destroyed).

Based on religious and scientific stances, the United States created a policy in August 2001 banning the creation of embryos for hES cell research and allowing the use of only stem cells lines derived before that time. In order to conduct research on a topic such as hES cells at a world-class level on a continuous basis, federal funding is required. To try and compensate, private funding is being used, and state legislators in states such as Massachusetts, California, and New Jersey are beginning to use state funding to create stem cell research facilities.

Recently, members of both the Senate and Congress have written letters to Pres. Bush asking him to loosen restrictions on federal funding, as foreign nations are rapidly overtaking the

U.S. in stem cell research. Many of the older ES cell lines had been contaminated with mouse cells used as feeders during the isolation of hES cells, further hindering research progress. The United Kingdom, Korea, China, and Switzerland are among several other countries that are currently allowed to conduct research on hES cell lines, and which are rapidly overtaking the U.S. in this field.

Despite whether the United States loosens restrictions on hES cell research, the ethical anxieties still remain. Hence, an alternative to hES cells presents a promising solution: parthenotes. Parthenogenesis translates to "virgin birth" meaning no sperm or SCNT procedure is needed for the egg to divide and begin developing. During parthenogenesis, oocytes are activated via chemical simulation, and the eggs are incubated *in vitro* to the blastocyst stage where their ES cells can later be extracted for research purposes. Experiments conducted have yielded hES cells and hES cell lines in primates; however, in humans so far only hES cells have been isolated using this promising technique. With an increase in federal funding however, more research may be conducted to allow the isolation of ES cell lines from human parthenotes and thereby replace the need to destroy an embryo.

The author of this report feels strongly that hES cell research must be pursued in greater detail than in the past, despite ethical and moral concerns. She accepts the Hindu, Jewish, and Muslim stance that an embryo represents a human being after taking the form of a fetus. Hence, embryos isolated at the blastocyst stage can be destroyed for medical research. Furthermore, she supports creating embryos for therapeutic cloning once strict regulations are instituted to ban reproductive cloning. The author believes Pres. Bush's August 2001 policy restrictions must be loosened to allow the United States to progress in stem cell medical research. Likewise, an increase in federal funding is required for extended studies on parthenotes as an alternative to

hES cells. So long as hES cell research is not misused for cosmetic therapy or reproductive cloning, the potential benefits of destroying an embryo outweigh the ethical concerns. In the unique circumstances of hES cell research, destroying a potential human is for the greater good of humanity, a fundamental moral principle.

PROJECT OBJECTIVES

The purpose of this IQP was to investigate the controversy surrounding stem cell research, and its ethical and legal implications. The early chapters (One and Two) described the biological nature of stem cells: what are stem cells, what types of stem cells exist, and what does the current and future applications of stem cells consist of. The later chapters (Three and Four) focused on the ethical, religious, and legal anxieties surrounding human embryonic stem (hES) cells: what is the current level of federal and state funding in the United States, what are the guidelines instituted in foreign nations, and what are the stances of the four main religions of the world. The final chapter (Five) summarized and synthesized the earlier chapters, and included the author's view on the key topics surrounding the stem cell controversy.

CHAPTER 1: STEM CELL TYPES, SOURCES, AND ORIGIN

Stem cells are the foundation of all cells within the human body. They are unspecialized cells that can be induced to become specialized cells under specific experimental or physiological conditions. Furthermore, stem cells are capable of restoring themselves through cell division over an indefinite period of time. Currently, two main classifications of stem cells have been identified: embryonic and adult. Each type represents a different level of cell differentiation: totipotent, pluripotent, multipotent, and unipotent.

The Development and Potential of Stem Cells

The characteristics of a stem cell lie in the process of human embryonic development. A sperm and an egg, combine to create a single totipotent cell with the potential to develop into a complete organism. Totipotent cells are capable of generating all types of cells and tissues. The human zygote is one example; it can differentiate into over 200 types of cells: neurons, myocytes, osteocytes, the placenta, umbilical cord, and embryonic tissues. During the first 3-4 days of human development, the embryo follows a series of cell divisions that yield identical totipotent cells up to about the 8-cell stage (see Figure 1.1). Beyond the 8-cell stage, subsequent cells are not totipotent.

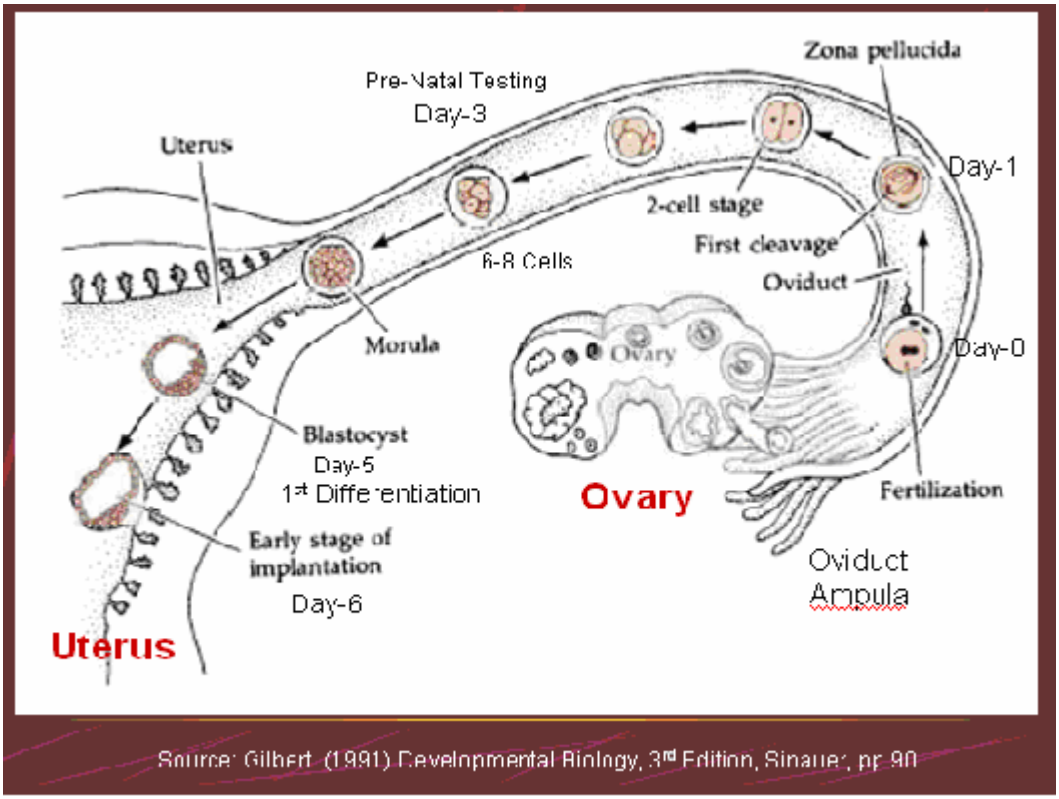

Figure 1.1 Diagram of the First Week of Human Development (Modified from Gilbert, 1991)

On the fourth or fifth day, a hollow sphere of cells known as the blastocyst forms. It contains about 200-250 cells, and is the result of the identical totipotent cells specializing into the outer layer (placenta) and the inner layer (epiblast). The epiblast is commonly known as the inner cell mass, and it houses the embryonic stem (ES) cells (Spiegel and Fischbach, 2000). Embryonic stem cells are pluripotent with the ability to differentiate into a large variety of tissues. Pluripotent is a term used to describe stem cells that produce cells comprising all three embryonic germ layers – mesoderm, ectoderm, and endoderm. The three germ layers produce all cells of the body as shown in Figure 1.2 (Kirschstein and Skirboll, 2001). As of 2000, human pluripotent cells had been isolated from human blastocysts, in addition to the fetal tissue of terminated pregnancies. Since stem cells are self-renewing and limitlessly divide, ES cells

derived from the inner cell mass can be used to create ES cell lines, and can be stored for lengthy periods of time (Spiegel and Fischbach, 2000).

Pluripotent stem cells were initially isolated in 1998 by two different research groups: Dr. James Thomson *et al* and Dr. John Gearhart *et al*. Both research groups identified one distinguishing factor present among stem cells: the ability to produce telomerase, an enzyme that prevents timed death. Most differentiated cells possess chromosomal clocks that dictate the lifespan of a cell. Stem cells chromosomal clocks have been reset allowing them to repeatedly differentiate over the lifespan of an individual (Green, 2001; Thompson *et al*, 1998; Shamblott *et al*, 1999).

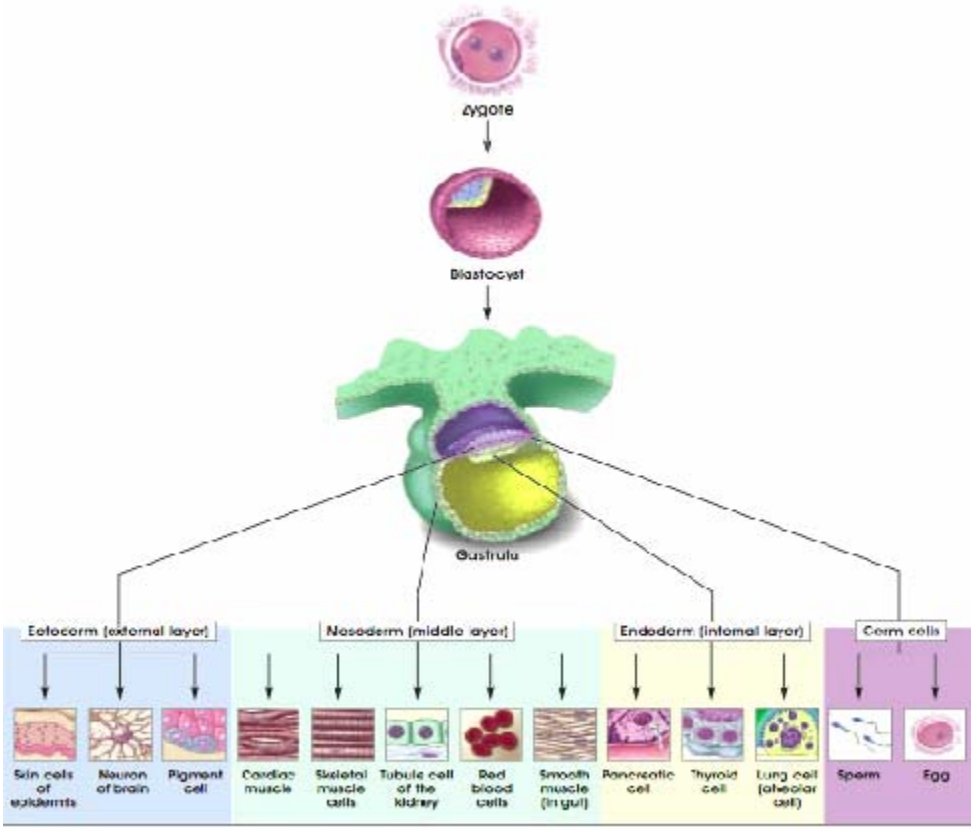

Figure 1.2 Differentiation of Human Tissues (Kirschstein and Skirboll, 2001).

The multipotent stem cell, the offspring of the pluripotent cell, has the potential to become a particular type of cell within an organ. Hematopoietic stem cells (HSCs) obtained from bone marrow or the

umbilical cord represent multipotent stem cells with the ability to differentiate into several kinds of blood cells.

Lastly, the unipotent cell, also known as an adult stem cell, is present in only certain organs and tissues of the body. They are specialized to differentiate along only a single lineage and develop only into cell types of their own tissue ("FAQ", 2004). This cell is unspecialized but is located within a specialized tissue. It develops into one cell type allowing a constant rate of self-regeneration for any particular tissue ("Stem Cells", 2003; Kirschstein and Skirboll, 2001). Neuronal stem cells are an example of this type.

Human Embryonic Stem Cells

A human embryonic stem cell (hES cell) is defined by its origin, the blastocyst phase of an embryo. The team of scientists led by James Thomson that derived the first pluripotent hES cells used embryos obtained for research purposes from an *in vitro* fertilization clinic after the consent of the donors. In order to distinguish a hES cell from all other cells, there are a few specific properties to note: hES cells maintain a diploid karyotype, are capable of long-term self-renewal, and are derived from the epiblast of the blastocyst. Furthermore, hES cells are clonogenic; a single hES cell has the ability to act as a clone, producing a colony of genetically similar cells. Human ES cells can also be induced to either differentiate of proliferate at any given instance of time. They express transcription factor Oct-4 that allows the cells to exist in a non-differentiating and proliferating form by either inhibiting or activating host target genes. Human ES stem cells are unique in that they lack the G1 phase of the cell cycle. Instead, they predominately reside in the S phase during which they synthesize DNA. In addition,

undifferentiated hES cells do not show X inactivation as do all somatic cells within female mammals (Kirschstein and Skirboll, 2001)

Isolating Human Embryonic Stem Cells

The ability to isolate hES cells depends on the condition of the blastocyst where the cells are located. A large, clear inner cell mass is required to yield optimal hES cells. Figure 1.3 provides a visual of such a prime blastocyst (Kirschstein and Skirboll, 2001).

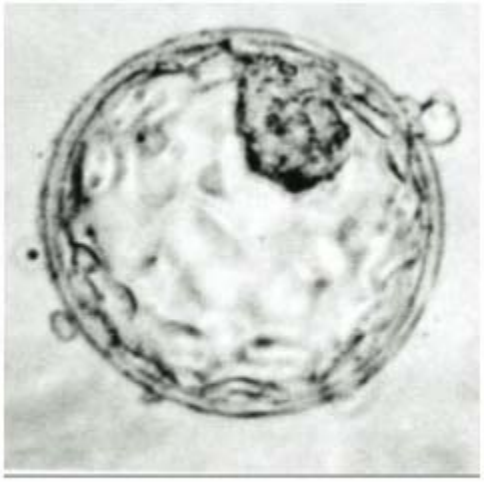

Figure 1.3 Human Blastocyst with Inner Cell Mass (Kirschstein and Skirboll, 2001)

On day 5 of embryonic development, hES cells can be derived from the blastocyst. At this point, there are approximately 200 to 250 cells already present. Unfortunately, only 30 to 35 cells are present in the inner cell mass and can be used for hES cell culture. The rest of the cells are part of the trophectoderm, the extra embryonic section of the ectoderm connected to the mesoderm, and are separated from the inner cell mass by immunosurgery or microsurgery (Kirschstein and Skirboll, 2001).

Tests to Identify Human Embryonic Stem Cells

During the process of generating ES stem cell lines, the process of characterization takes place. Characterization is the use of scientific tests to determine whether or not a cell exhibits the fundamental properties of a hES cell. The National Institutes of Health describes a list of

possible tests that scientists use to identify these properties as indicated in Figure 1.4 ("Stem Cell Basics", 2005).

- growing and subculturing the stem cells for many months. This ensures that the cells are capable of long-term self-renewal. Scientists inspect the cultures through a microscope to see that the cells look healthy and remain undifferentiated.
- using specific techniques to determine the presence of surface markers that are found only on undifferentiated cells. Another important test is for the presence of a protein called Oct-4, which undifferentiated cells typically make. Oct-4 is a transcription factor, meaning that it helps turn genes on and off at the right time, which is an important part of the processes of cell differentiation and embryonic development.
- examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells.
- determining whether the cells can be subcultured after freezing, thawing, and replating. testing whether the human embryonic stem cells are pluripotent by 1) allowing the cells to differentiate spontaneously in cell culture; 2) manipulating the cells so they will differentiate to form specific cell types; or 3) injecting the cells into an immunosuppressed mouse to test for the formation of a benign tumor called a teratoma. Teratomas typically contain a mixture of many differentiated or partly differentiated cell types—an indication that the embryonic stem cells are capable of differentiating into multiple cell types.

Figure 1.4 List of possible tests to identify the fundamental properties of stem cells ("Stem Cell Basics", 2005)

Human Embryonic Germ Cells

Human embryonic germ cells (hEG cells) are derived from primordial germ cells occurring in the gonadal ridge of an embryo. They are isolated between 4 and 5 weeks of development, when the embryo is a fetus. These cells eventually develop into gametes. In 1998, scientist John Gearhart *et al* derived pluripotent stem cells from these germ cells. A concern has arisen from the use of these germ cells as stem cells, however. Since the isolation occurs several weeks into embryonic development rather than a few days, many cells may already be specialized. Currently, not enough research has been performed to verify this concern (Kirschstein and Skirboll, 2001; "FAQ", 2004).

Similarities and Differences between Human Embryonic Cells and Human Germ Cells

The hES cells and hEG cells contain several similarities and differences between them. Although both types of cells are derived from the blastocyst, they differ in tissue origin. A hES cell is derived from an epiblast, whereas a hEG cell is derived from the gonadal region of an embryo. Similarly, both types of cells differ in growth characteristics *in vitro,* and in behavior *in vivo*. Lastly, hES cells have been shown to proliferate several hundreds in population doubling whereas hEG cells have proliferated with only 70 to 80 population doublings (Kirschstein and Skirboll, 2001).

Despite their differences, hES cells and hEG cells are also miraculously similar. They produce female and male cultures, convey markers characteristic of pluripotent cells, do not have chromosomal abnormalities, and are capable of replicating for long periods of time. Both types of cell also have the potential to spontaneously differentiate under the appropriate conditions into the three primary germ layers (Kirschstein and Skirboll, 2001)

Adult Stem Cells

An adult stem cell is an undifferentiated cell found within the tissue of a differentiated organ or tissue. It is capable of long-term self-renewal, and it produces mature cell types with specific functions and individual morphologies. All stem cells produce an intermediate cell type known as a progenitor or precursor cell prior to differentiation. These intermediate cells are partially differentiated and divide to yield fully differentiated cells. Figure 1.5 displays the features of these intermediate cells (Kirschstein and Skirboll, 2001).

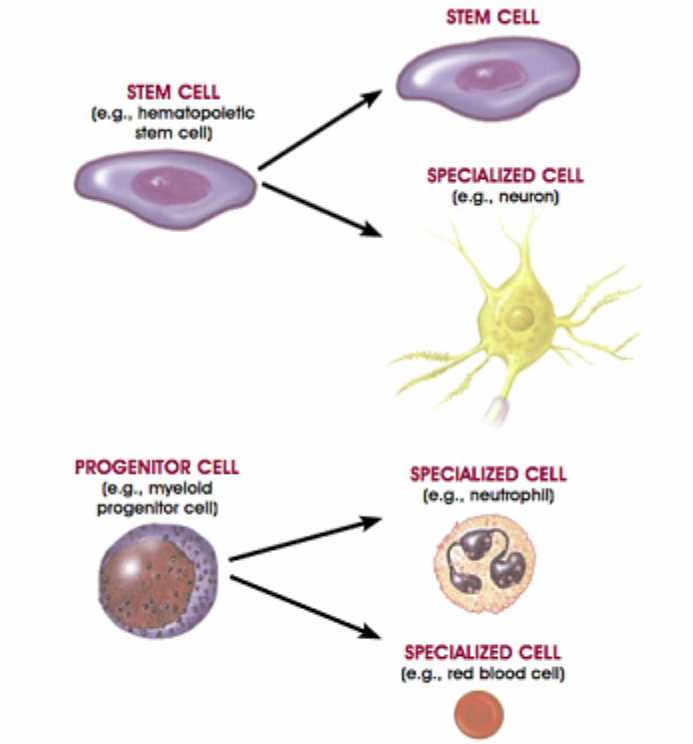

Figure 1.5 Distinguishing Features of Progenitor/Precursor Cells and Stem Cells (Kirschstein and Skirboll, 2001)

The primary function of adult stem cells is to repair and maintain homoeostasis in the tissues in which they are located. Unlike hES cells, adult stem cells do not have a definitive origin. Theories speculate that stem cells are set aside at some point in the fetal development and are prevented from differentiating.

In order to be classified as an adult stem cell, specific criteria must be satisfied. Firstly, the cell must possess the ability to self-renew over the life cycle of the organism. Next, the cell must be clonogenic and be able to produce fully differentiated cells with mature phenotypes. These cells must be fully integrated into and capable of performing the specialized functions of the tissue. The difficulty, however, lies in proving these conditions *in vivo*. Similar to the conditions of classification as a stem cell, there are three methods used to determine whether an aspirant adult stem cell will form a specialized cell. The adult stem cell can be tracked after being labeled *in vivo* or it can be isolated and grown *in vitro*, being manipulated via growth factors or genes that aid in determination of particular differentiated cell types. The third method isolates and labels the adult stem cells, transplants it back into the organism, and monitors its progress within the organism. These three methods combined with the techniques for identifying stem cells provide evidence of the presence of stem cells in an organism (Kirschstein and Skirboll, 2001).

Adult stem cells are most commonly obtained from bone marrow located in the center of all bones. The iliac crest, or the back of the upper hip bone, is an ideal location for harvesting the cells. The bone marrow also contains hematopoietic stem cells, mesenchymal stem cells, and endothelial stem cells ("FAQ", 2004). Recently, adult neural stem cells have also been identified. Most of the cells of the central nervous system are derived during the embryonic and early postnatal periods; however, recently it was determined that the adult mammalian brain continuously produces neurons in specific sections. These neurons are believed to originate from neural stem cells. As shown in 1992 (Reynolds and Weiss, 1992), neural stem cells can be induced to proliferate *in vitro*. They exhibit the standard characteristics of a stem cell: capable of self-renewal and can generate the major cell types of the central nervous system (neurons, oligodendrocytes, and astrocytes) (Reynolds and Lewis, 1996). The neural stem cells are usually isolated from the ventricular system walls or the hippocampus (Lois and Alvarez-Buylla, 1993; Morshead *et al*, 1994; Weiss *et al*, 1996; Palmer *et al*, 1997). Cells from the ventricular walls contain ependymal cells that are now known to be neural stem cells. Ependymal cells express a protein called nestin that is abundant in stem cells and they respond to spinal cord injury by increasing their presence. Hence, ependymal cells have proved to be neural stem cells and their discovery has aided scientists in understanding the response of stem cells to spinal cord injury (Johansson *et al*, 1999).

Limitations of Adult Stem Cells and Comparison to Embryonic Stem Cells

Although adult stem cells are harvested from a patient without many ethical concerns and represent the best chances to avoid immune rejection during therapy (they would be viewed as self by the patient), their differentiation potential is limited. Thus, most scientists today favor

developing both human embryonic stem cells and adult stem cells. It is unclear whether or not every type of cell in the body has an adult stem cell. Even if so, it may be difficult to separate and purify the stem cell since it is quite rare in adult tissues, and sometimes difficult to physically access. An example of such a case is the neural stem cell which is located in parts of the brain that are not easily accessible. In addition, adult stem cells differ from pluripotent cells in both size and number for cell differentiation: they do not self-renew or form specialized cells as rapidly as do embryonic stem cells, but rather have a restricted number of times they can divide. Hence, adult stem cells likely will show a limited use in the development of "cell transplantation therapies". Their resistance to disease once transplanted is also unknown (Spiegel and Fischbach, 2000).

Lastly, scientists are unsure of whether or not adult stem cells have more or less DNA abnormalities than hES cells. There is cause for concern since adult stem cells are exposed to harmful toxins and UV radiation during the lifetime of an individual thereby generating DNA abnormalities ("Stem Cell", 2005). Embryonic stem cells are very young and have not been exposed to the harmful pollutants of the Earth. Consequently, it is currently unwise to claim that adult stem cells are the complete solution to the ethical concerns raised by stem cell research. Instead, it is necessary to embrace the use of both forms of stem cells.

One advantage of using adult stem cells is the lack of immune rejection. The stem cells harvested are from the patient and thus can be expanded in culture and re-injected into the patient without complications. There is a certain level of trepidation for immune rejection within embryonic stem cells. Since pluripotent stem cells are derived from embryos genetically different from the recipient, there is a potential for the body to reject the cells. To resolve this problem, tissue banks would need to be created to ease the transition.

Hematopoietic Stem Cells

Hematopoietic stem cells originate from bone marrow, umbilical cord blood, and placental cord blood ("FAQ", 2004). They form both blood and immune cells, replenishing them when they are either damaged or lost. Blood cells are important to the human body as they maintain and protect the various cell types. Hematopoietic stem cells have two important characteristics: the ability to self-renew and to produce cells capable of differentiating into all types of blood cells. They are also capable of undergoing apoptosis (programmed cell death) and can gather in the circulating blood after leaving the bone marrow (Kirschstein and Skirboll, 2001).

The identification and isolation of HSCs is not easy: they behave very similarly to white blood cells when in culture, and thus are not easily distinguishable by morphology. Instead, identification of cell surface proteins on white blood cells is the only method to differentiate them from HSCs. After performing various experiments on mice, researchers have identified two types of HSCs: long-term stem cells and short-term progenitor/precursor cells. Long-term stem cells are capable of self-renewal over an extended period of time, whereas short-term progenitor/precursor cells are not. They can proliferate but they have limited specialization abilities. In humans, the existence and use of long-term stem cells is rare as they are often very expensive and time consuming to identify (Kirschstein and Skirboll, 2001).

Hematopoietic stem cells are one of the clear examples of stem cells that have been isolated from humans, and currently have the strongest record for saving lives. For the past 40 years, HSCs have been continuously isolated for bone marrow transplants although this fact is either unknown or overlooked by the general public. Hematopoietic stem cells are now used to treat leukemia and various blood disorders. They are also transplanted into cancer patients

recovering from irradiation therapy. As the radiation destroys the body's immune system, new HSCs must be transplanted to replace and restore the immune system. This treatment was also undertaken in sick fetuses and has proved successful ("FAQ", 2004).

Sources of Hematopoietic Stem Cells

As mentioned earlier, HSCs are most frequently obtained from bone marrow. The general procedure requires puncturing a bone (usually the hip) and extracting bone marrow cells of which only 1 in every 100,000 cells will actually contain a long-term stem cell. Hence, the use of stem cells from bone marrow is less preferred than its counterpart, umbilical cord blood.

Umbilical cord blood truly represents the future use of stem cells for treatments of chronic and genetic illnesses. The procedure is harmless, fast, and simple: directly after the birth of an infant, blood from the umbilical cord is stored. In addition, there is a lower rate of disease between graft (area of surgical implantation) and host for umbilical-derived HSCs versus bone marrow-derived HSCs ("Why Cord Blood….2004; "Medical Dictionary….2003). The cord blood cells can be used for the infant throughout its lifetime, and potentially for other family members. Figure 1.6 illustrates the potential benefits of the cord blood stem cells in treating both donor and fellow family members.

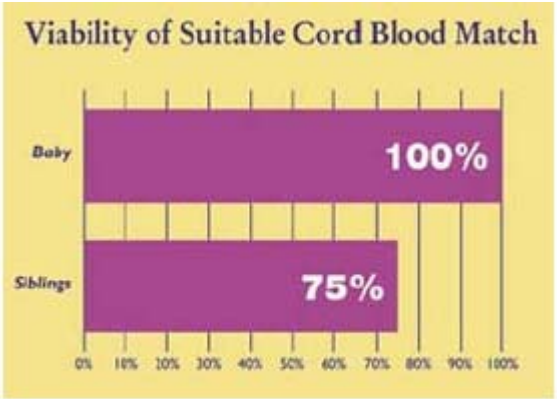

Figure 1.6 Cord Blood Banking ("Cord Blood", 2004)

Today, the New York Blood Center's Placental Blood Program is the largest public umbilical cord blood bank in the United States. It accepts about 13,000 donations annually, and has prolonged the life of ill children by as much as

eight years. Currently there are approximately 40 diseases that can be treated with the aid of umbilical cord stem cells. In the future, researchers hope to have these cells be the ultimate stem cell treatment as it is morally acceptable and painless.

CHAPTER 2: STEM CELL RESEARCH AND APPLICATIONS

As stem cell research progresses, its potential applications are vastly growing. After years of animal studies, researchers are beginning to experiment and understand the potential of human embryonic and adult stem cells in cell-based therapies, drug tests, and human development. Diabetes kills millions of American each year and there is simply no cure. With the use of adult stem cells as precursors for islet cells and embryonic stem cells capable of producing insulin, there is hope for a cure in the near future.

The central nervous system experiences many life-threatening damages that were previously considered irreversible. With the recent discovery of neural stem cells, however, researchers are working to develop cell-replacement therapies that will one day restore function to sufferers of Parkinson's Disease, Alzheimer's Disease, and epilepsy. Furthermore, by exploring and gathering information about enhancing the body's mechanisms and about replacement cells, vital questions may be answered regarding restoring body functions that have been lost.

Cardiovascular disease is the leading cause of death in the United States. Novel experiments have demonstrated the potential of human adult and embryonic stem cells replacing damaged heart tissue and establishing new blood vessels to the heart. Although research is in its early stages, ongoing human clinical trials aim to replicate the positive results achieved in animal research. There are still many questions that must be answered regarding the potential of stem cells in humans. Given time, however, medical professionals and patients will soon have answers.

Potential Applications for Human Embryonic Stem Cells

Future studies of human embryonic stem cells (hES cells) will most importantly aid in developing cell-based therapies for certain diseases. These therapeutic applications represent the basis of the entire field of regenerative medicine, and the main purpose of this chapter is to document examples of these applications, as discussed in the next section. The amount of organs and tissue needed for transplantation far exceeds the amount available. Hence, the generation of specialized cells from, say, the nucleus of a skin cell isolated from that patient, will greatly benefit the human population in need of transplantations. Recently there has been preliminary research in mice and other animals testing to see whether adult stem cells can trans-differentiate into another type of tissue. For example can bone marrow stem cells generate heart muscle cells? Murine bone marrow stem cells were transplanted into a damaged heart and they ultimately grew into heart muscle cells that repopulated the heart tissue. Further studies have demonstrated similar successes with hES cells and adult stem cells in culture ("Stem Cell Basics", 2005).

Prior to using cell-based therapies for treating diseases, it is necessary that scientists be able to properly differentiate, transplant, and engraft the hES cells. Each cell must be able to proliferate efficiently and create ample quantities of tissue. Human ES cells must also be able to differentiate into the cell type in question, and survive within the patient once transplanted. Then the cells must be able to integrate into the environment of the tissue and function throughout the lifespan of the patient. Finally yet most importantly, the transplanted cells must not harm the patient ("Stem Cell Basics", 2005). Once these requirements are met, cell-based therapies can be used to treat the variety of diseases that utilize replacement cells for treatment.

In addition hES studies will help complete the understanding of human development and in testing new drugs. There is a need to identify how stem cells that are undifferentiated become differentiated. Research to date indicates this transition is caused by changes in gene expression; however, how this happens is unknown. By understanding the details of human development, scientists can derive treatments for birth defects and cancer that arise from abnormal cell division and differentiation ("Stem Cell Basics", 2005). Furthermore, by knowing which genes regulate development in stem cells, diseases such as type 1 diabetes and neurological disorders can be interrupted and corrected (Spiegel and Fischbach, 2000).

An additional use of human ES cells is for testing new drugs. Just as cancer cell lines are used to test anti-tumor drugs, pluripotent ES cell lines can be used to test drugs in vitro prior to using them in vivo. The stem cells would differentiate into a desired specialized cell type and the drug would then be tested on the differentiated cell ("Stem Cell Basics", 2005) for toxicity and efficacy.

It is the belief that one day, human pluripotent stem cells will find cures and aid in the better treatment of diseases. By studying the mechanisms behind cell differentiation in humans, there is a hope that abnormalities can be detected and resolved. It is also believed that by studying pluripotent stem cells, researchers will be able to identify the "decision-making" genes and the potential markers that turn them both on and off. Answering the question of how cell specialization occurs will help promote an understanding of cancer and birth defects such as Down syndrome (Kirschstein and Skirboll, 2001).

The use of pluripotent stem cells for "cell transplantation therapies" represents a distant yet very promising future. The need for transplantation organs and tissue drastically exceeds the amount actually available. Hence, both adult and embryonic stem cells can be developed into

specialized cells and used as replacement for damaged or diseased cells. For example, in the case of Parkinson's disease, particular nerve cells that secrete dopamine can be implanted into the patient. These cells will then re-wire the brain and reinstate the proper functions of the brain ("FAQ", 2004). Lastly, the development and testing of drug safety could greatly expand from further research and isolation of pluripotent stem cells. This would allow drugs to be tested within the particular cell lines that are available, and upon success, could be tested in humans, thereby reducing the detrimental effects it can have on living organisms.

Stem Cells and Diabetes

Type 1 (juvenile-onset) and type 2 (adult-onset) diabetes, are good examples of a potential application for hES cells. Nearly 200,000 diabetes patients die each year, making diabetes the seventh leading cause of death in United States. Diabetes is a group of diseases distinguished by a high level of glucose in the bloodstream. The insulin-producing beta cells in the pancreas that generally produce insulin are destroyed by the immune system. Hence, when the insulin level is low, the serum glucose does not enter cells but rather accumulates in the bloodstream. The only known remedy for type 1 diabetes is to increase insulin levels via injections. This method, however, is temporary and complications are vast. Patients with type 2 diabetes must have a balance of diet, exercise, and oral medication. Eventually, insulin therapy becomes the only viable treatment (Kirschstein and Skirboll, 2001). It is believed that with direct differentiation of human embryonic stem cells in cell culture, new cells that produce insulin can be formed. These cells can then be transplanted back into the diabetic patient, curing them of type 1 diabetes (Spiegel and Fischbach, 2000; "Stem Cell Basics", 2005) so long as the

engrafted ES cells are protected from the patient's highly active autoimmune response by encapsulation or by genetic engineering.

Recently, James Sharpiro *et al* developed a protocol to transplant cadaver islet cells into diabetic patients. In a recent study, all seven of the patients tested successfully maintained normoglycemia without insulin injections for over one year. Unfortunately, there are two main disadvantages: there are not enough islet cells for every diabetic patient, and the immunosuppressive therapy needed after transplantation causes patients to become susceptible to a wide range of infections and diseases.

Human ES cells offer a clear solution to the creation of multiple islet cells that is both generally immuno-compatible with the patient and may alleviate the need for immunosuppressive therapy. A question that arises, however, is whether only beta cells should be produced, or if other pancreatic islet cells should also be produced. For example, studies in Bernat Soria's lab (Roche *et al*, 2003) illustrate that beta islet cells alone are less responsive to glucose concentration fluctuations when cultured with other islet cells absent. Islet clusters that contain a mixture of islet cell types release insulin in two distinct phases: high concentrations and low concentrations. This provides a balance of insulin release based on a physiological need (Kirschstein and Skirboll, 2001).

Use of Fetal Tissue for Islet Cells

The use of fetal tissue as a source of islet cells has been researched in depth with mice. Mice were treated with insulin implants from fresh human fetal pancreatic tissue, cultured fetal pancreatic tissue, and purified human islets (Kirschstein and Skirboll, 2001). The results showed that fresh tissue and purified islets yield higher insulin content than the cultured tissue. Over

time, however, whole tissue grafts contained a lower concentration of insulin than purified islet grafts. Then when cultured islets were implanted, the insulin concentrations rose once again. Hence, it was concluded that the cultured islets contained proliferated and differentiated precursor cells that transformed into islet tissue. The purified islet cells, however, were not capable of proliferating after grafting. These cells were already differentiated. Since researchers observed a difficulty in expanding fetal islet progenitor cells in culture (Kirschstein and Skirboll, 2001), this fetal tissue approach may not be feasible long-term.

Use of Adult Tissue for Islet Cells

There has been much thought on the use of adult tissue from cadavers as a source for culturing islet cells. Fred Levine *et al* at the University of California, San Diego has had some success with this experimentation (Itkin-Ansari *et al*, 2003; Itkin-Ansari and Levine, 2004). The research team grew islet cells isolated from cadavers by adding special cell proliferation genes to the DNA. These cells were then engineered to produce insulin and were tested in mice. The results yielded a secretion of insulin as expected, but not in quantities equal to normal islet cells. In 2000, research on mice conducted by Peck *et al* and Ramiya *et al* (personal communication in Kirschstein and Skirboll, 2001) indicated a reversal of diabetes; pancreatic ductal epithelial cells were cultured to yield structures resembling islet cells and were then implanted in diabetic mice. With further research, there is a possibility that reversal of diabetes in humans will soon be possible (Kirschstein and Skirboll, 2001).

Trans-differentiation and Diabetes

Recently in April of 2005, a group of researchers at Stanford University were able to induce immature brain stem cells into insulin-producing islet cells. A chemical cocktail was added to brain cells from aborted fetuses and was implanted in the kidneys of mice (where other insulin-producing cells have been shown to survive). The results indicated that when the blood sugar levels increased, insulin was released by the brain stem cells in the mouse kidney. Hopefully, this trans-differentiation approach can eventually replace the use of ES cells for patients suffering from type 1 diabetes ("Brain Stem Cells…", 2005).

Human Embryonic Stem Cells in Diabetes

The possibility of using hES cells for treatment of human diabetes is promising since ES experiments in mice have already proven successful. Human ES cells can be grown, kept ready for transplantation, and genetically engineered to evade immune rejection. In 2000, mouse embryonic stem cells were used to reverse diabetes in mice. Bernat Soria *et al* added DNA that contained a section of the insulin gene linked to an antibiotic resistant gene to murine ES cells. The cells activating the insulin promoter survived and were cloned and cultured. Once placed in the STZ diabetic-induced mice, they inhibited the diabetes.

Although progress reversing diabetes in animals has proven successful, in humans there is still a need for more experimentation. In 2000, research conducted by Melton, Nissim Benvinisty and Josef Itskovitz-Eldor (Schuldiner *et al*, 2000) demonstrated hES cells manipulated in culture to express a gene known to control insulin transcription: *PDX-1*. Human ES cells were induced to spontaneously form embryoid bodies which were then treated with eight growth factors, especially nerve growth factor. Results indicated that regardless of NGF

treatment, both sets of embryoid bodies expressed *PDX-1*. Hence, beta stem cells (which are directly related to *PDX-1*) may be capable of spontaneously differentiating within embryoid bodies. In addition, research conducted by scientist Jon Odorico supports these results (personal communication in Kirschstein and Skirboll, 2001).

Further research by Itskovitz-Eldor *et al* indicates that about 1 to 3 percent of the cells within the embryoid body are beta-islet cells capable of producing insulin. Genes crucial to the secretion of insulin and the function of beta cells have also been expressed by cells of the embryoid bodies (Kirschstein and Skirboll, 2001). In March of 2005, the Diabetes Research Institute determined a novel way to transform stem cells into insulin-producing cells. Results were published in the March issue of *Diabetes* and indicated that pancreatic cell differentiation has been promoted by protein transduction domains (PTD). Previously, there was little understanding of which molecular signals turn on and off genes that activate pancreatic development. The PTD's, however, represent a "protein therapy" that accelerates differentiation of stem cells ("Diabetes Research Institute….2004).

Stem Cells and the Central Nervous System

Human embryonic stem cells have the potential to cure several neurological disorders through the replacement of lost nerve cells. Until the mid 1990's, it was believed that neurons from the brain and spinal cord could not regenerate. Further research, however, produced evidence of neural stem cells present in particular sections of both the fetal and adult brain. These neural cells were capable of producing neurons as well as oligodendrocytes and astrocytes (neural-support cells) (Reynolds and Weiss, 1992; Weiss *et al*, 1996; Palmer *et al*, 1997; Johannson *et al*, 1999).

Past research in animals indicates that stem cells can be forced to differentiate and replace the dopamine cells lost in Parkinson's Disease. In the future, a similar procedure may be used to produce lost acetylcholine nerve cells for Alzheimer's disease, or inhibitory cells to restrain electrical activity in epilepsy (Spiegel and Fischbach, 2000). Stem cells also have the potential to replace supporting glial cells that insulate nerves and cause them to conduct electrical impulses quickly as in multiple sclerosis. Furthermore, in inherited birth defects such as Tay-Sach's disease, the stem cells could migrate throughout the brain and deliver a missing enzyme that could ultimately cure a child of this fatal substrate accumulation disease. Stroke victims have hope in stem cells regenerating complex brain tissue and neural tissue for spinal cord injuries (Spiegel and Fischbach, 2000). As more research is completed, applications of stem cells broaden.

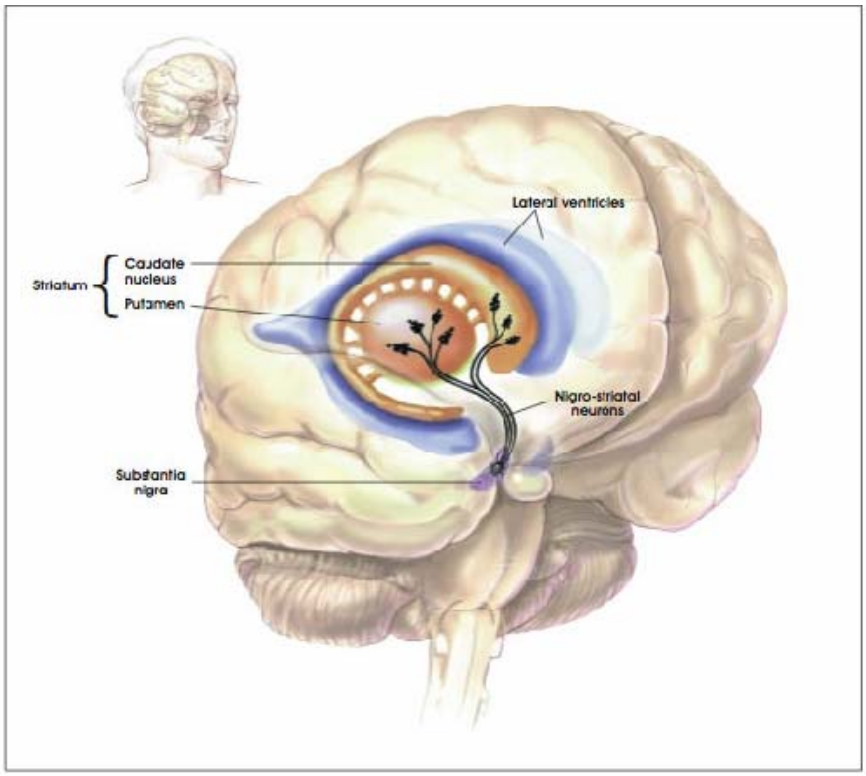

Figure 2.1 Neuronal Pathways that Degenerate in Parkinson's Disease (NIH, 2001)

Stem Cell Research for Parkinson's Disease

Parkinson's Disease is induced by the death of a particular set of neurons deep within the brain. The neurons that die connect the substantia nigra with the striatum as illustrated in Figure 2.1 (Kirschstein and Skirboll, 2001). These neurons are known as "nigro-striatal" neurons that release dopamine to the target neurons located in the striatum. When the cells die, there is a decrease in the amount of dopamine produced. Hence, patients exhibit difficulty in movement: hand tremors followed by difficulty in walking and in initiating involuntary movement (Kirschstein and Skirboll, 2001). The best known medication is a drug named "levodopa"; the side effects, however, are difficult to endure causing frustration among doctors and helplessness for patients.

The solution to Parkinson's Disease is quite simple to state but very difficult to execute: replace the lost "nigro-striatal" neurons by implanting new dopamine-releasing cells (Kirschstein and Skirboll, 2001). Completely differentiated dopamine neurons do not survive transplantation and do not make connections to the target neurons in the striatum. There have, however, been successful experiments with animals that have been based on transplanting dopamine neurons from fetal brain tissue. These studies promoted human trials in centers throughout the world.

During the 1970's one group of researchers transplanted fetal tissue from nigro-striatal parts of embryonic mice into an adult rat's anterior eye chamber (Olsen and Malmfors, 1970; Dunnett, 2001). The cells continued to develop into fully mature dopamine neurons. Research progressed into the early 1980's with experiments that resulted in a reversal of Parkinson's-like symptoms in monkeys and mice. Human trials for Parkinson's Disease using this fetal cell transplant technique in the mid-1980's resulted in a decrease in the severity in symptoms, as well as an increase in the function of dopamine neurons in the striatum. Autopsies conducted on

patients who had died due to other causes also indicated a strong survival of grafted neurons. Recently, Warren Olanow has been conducting a very similar double-blind experiment (unpublished).

It is a widely accepted belief among the scientific community that cell-implantation will ultimately lead to a cure for Parkinson's Disease. The greatest concern is the source of cells: the amount of recovery of neurons from human fetal tissue is considerably low. Hence, biotechnology companies such as Genzyme and Diacrin have run experiments in which Parkinson's patients received neural cells from fetal tissue of pigs. The results, however, were not satisfactory. A very small percentage of the pig cells survived once transplanted. Hence, cells grown within the laboratory may be the only acceptable solution to the shortage of available cells for transplantation. Two methods exist for the growth of these cells. In the first method undifferentiated cells grow into specialized dopamine neurons under appropriate cell culture conditions and then they are implanted in the patient. The second method implants undifferentiated cells in the patient and relies on environmental factors to guide the cell to differentiate into dopamine neurons.

Although success reversing Parkinson's disease has been achieved in animals using human fetal tissue transplants or mouse ES cells, there is uncertainty about the potential of adult neural cells. Similarly, there is no documented evidence of lab-grown cells that have differentiated into dopamine neurons.

Stem Cells and Spinal Cord Injuries

Using cell-therapies to completely restore lost functions in spinal cord damaged patients will be difficult to achieve in the near future. When a spinal cord is damaged, several types of

tissues are destroyed. For example, if a neuron is destroyed, it is difficult to connect neurons on either side of an injury site. Hence, full restoration is less likely to be resolved; however, there is hope for restoration of particular functions such as bladder control, or the partial use of a limb (Kirschstein and Skirboll, 2001).

In January 2005, researchers at the University of Wisconsin-Madison induced hES cells to differentiate into spinal motor neurons. These neurons relay messages between the brain and the rest of the body. The results, published in the February issue of *Nature Biotechnology* (Li *et al*, 2005) explained how a replacement of deteriorating motor neurons will help restore the mobility of spinal cord injured patients as well as relieve symptoms of degenerative diseases such as ALS. Furthermore, motor neuron modeling systems can be developed to screen drugs ("Scientists Grow…", 2004).

In May 2005, Keirstead *et al* at the Reeve-Irvine Research Center at the University of California, Irvine derived a treatment for human embryonic stem cells to improve the mobility of rats with acute spinal cord injuries. Results were published in the May 11 issue of *The Journal of Neuroscience* explaining how using human ES cells, the scientists were able to restore the rat's neuron insulation tissue, and thereby its motor skills, in just one week after the injury occurred. The results, however, could not be replicated with rat's that had been injured 10 months previously ("Stem Cell Treatment…", 2004; Keirstead *et al*, 2005). This treatment has the potential to be replicated in humans. If similar results are obtained, the procedure may be used in treating patients with recent spinal cord injuries. The hES cells differentiated into oligodendrocyte cells (myelin building blocks). When myelin is removed, sensory and motor skills are lost. The oligodendrocyte cells were implanted in rats with a partial spinal cord injury that created a walking impairment. Two groups were tested: 7 days and 10 months after injury.

It was determined that myelin tissue was capable of growing after 7 days of injury and yielded rats capable of walking. The rats with 10 month old injuries lost all motor skills ("Spinal Cord Injury", 2004; Keirstead *et al*, 2005).

Stem Cells and the Heart

Cardiovascular disease is the leading cause of death in the United States, claiming the lives of nearly 1 million people each year. Congestive heart failure (CHF), the most common pathway in cardiovascular disease, is a deterioration of the heart over a period of time. The heart becomes unable to supply all parts of the body with the required oxygen and blood flow due to a loss or dysfunction in cardiomyocytes (heart muscle cells). CHF can be instigated by a wide variety of factors: high blood pressure, coronary artery disease (CAD), and myocardial infarctions (heart attacks) ("Cardiovascular Disease", 2004, Kirschstein and Skirboll, 2001). Despite the many surgical procedures and mechanical devices that have been developed, most patients do not survive over five years after diagnosis. By using stem cells, scientists can create replacement cells for dead or damaged cardiomyocytes that will allow the heart muscle to recover pumping abilities (Kirschstein and Skirboll, 2001).

Adult and hES cells can be used to develop three important types of cells: cardiomyocytes, vascular endothelial cells, and smooth muscle cells. Cardiomyocytes contract to remove blood from ventricles of the heart. Vascular endothelial cells form the inner lining of new blood vessels, and smooth muscle cells form the walls of blood vessels. There is, however, no proof of stem cells that can differentiate within the heart. Through cell culture in a laboratory, stem cells are being induced to proliferate and differentiate into cardiomyocytes and vascular endothelial cells.

The potential for growing replacement cells and tissue to repair damaged hearts in humans originates from experiments in mice and rats in which heart attacks are induced by coronary artery cannulation. Orlic *et al* experimented with hematopoietic stem cells in regenerating heart tissue. Heart attacks were induced by cannulation of the left main coronary artery of mice and a specific group of adult primitive bone marrow cells were selected for implantation into the damaged wall of the ventricle. Nine days after implantation, cardiomyocytes, vascular endothelial cells, and smooth muscle cells formed generating de novo myocardium and replacing 68 percent of the older, damaged section of the ventricle. Hence, the hematopoietic stem cells responded to the environmental factors of the damaged myocardium and in response, proliferated and differentiated into new cardiomyocytes (Kirschstein and Skirboll, 2001).

Jackson *et al* conducted another experiment in which mouse adult stem cells were used instead of human adult stem cells. Hematopoietic stem cells were obtained from a genetically engineered mouse strain and were injected into the marrow of a mouse 10 weeks after an induced heart attack. The survival rate was 26 percent between 2 and 4 weeks. The astounding result of this experiment, however, is that hematopoietic stem cells can be injected directly into cardiac tissue or through a bone marrow transplant to achieve re-growth of damaged cardiac tissue. This breakthrough yields another potential therapy in the treatment of heart disease.

In another research study, human adult stem cells extracted from bone marrow and injected into rats showed growth of vascular endothelial cells. The stem cells isolated displayed plasticity or the capability to differentiate into cell types of tissue different from their intended purpose (Kocher, 2001). Figure 2.2 demonstrates the process by which the adult stem cells repair damaged heart muscle tissue.

In February of 2005, researchers at the University of California, San Diego School of Medicine discovered the presence of rare cardiac progenitor cells (isl1+ cells) in the atrium of the heart of newborn humans (Laugwitz *et al*, 2005). These cells are programmed to develop into mature heart muscle while in fetal growth. When placed with neighboring fibroblasts, these cells became spontaneously beating cardiac cells.

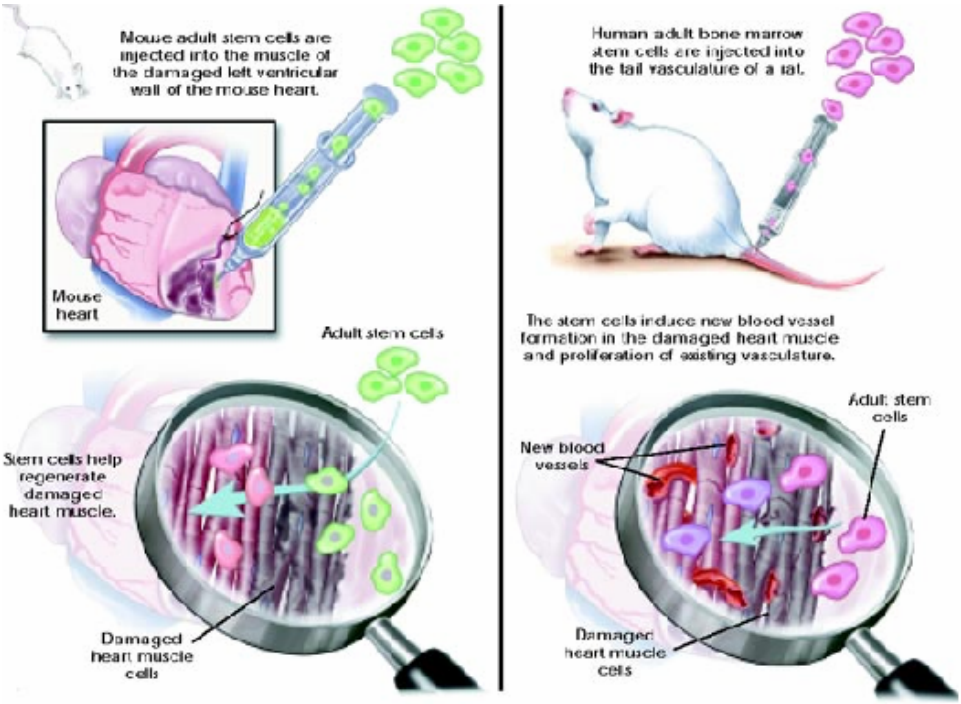

Figure 2.2 Heart muscle repair with adult stem cells (NIH, 2005)

There are several potential benefits in the discovery of the isl1+ progenitor cells. Patients can utilize their own cells for cell-therapy treatments of pediatric cardiac diseases. The cells also have the potential to function as biological pacemakers in children born with heart blocks. Furthermore, isl1+ cells have the remarkable ability to proliferate in cell culture within a laboratory. Hence, cells can be isolated from a patient, be allowed to multiply, and then be replaced into the patient. In addition, a developmental lineage marker located on these cells aids in identifying cardiac precursors which are undifferentiated.

Recently, a clinical trial began in May 2005 at the University of Pittsburg Medical Center in which a patient's own hematopoietic stem cells were transplanted into heart muscle to repair a

damaged heart. If successful, this procedure could become a potential treatment for congestive heart failure. Furthermore, this procedure will aid in understanding how and why stem cells differentiate in heart muscle. Once a ventricular assist device (VAD) is connected to the heart's ventricle, CD34+ cells, bone marrow stem cells with a high therapeutic potential, will be isolated from the hip bone of the patient and injected directly into 25 to 30 sites on the diseased heart ("Novel Stem Cell Trial….2004).

As an increased number of human stem cell studies are undertaken, there will hopefully be answers to a few pressing questions. For example, can a patient at risk of a heart attack reserve stem cells in advance? Furthermore, can stem cells be genetically programmed to travel to an injured location and begin to synthesize the required heart proteins? Answers to these questions may be well into the future; however, progress is being made (Kirschstein and Skirboll, 2001).

Future Endeavors

Since hES cells were first discovered in 1998, there have been numerous breakthroughs in the development and implementation of hES cells in cell-therapies and drug tests. Furthermore, the experiments conducted are leading to a better understanding of human development and the behavior of stem cells after implantation. In May 2005, scientists in Seoul, South Korea presented groundbreaking research in the May 20, 2005 issue of *Science* and *Science Express* (Hwang *et al*, 2005). These researchers grew 11 batches of stem cells originating from the skin cells of patients suffering from spinal cord injuries, diabetes and various genetic immune disorders. What is most remarkable is that these cells were obtained from a procedure known as somatic cell nuclear transfer (SCNT) and are a genetic match to the

donor's body, thus the transplants will not be rejected. In the future, this procedure will be used to harvest replacement cells for cell-therapies. Prior to this endeavor, however, scientists must first determine how these stem cells develop and how to control them. Ultimately, this procedure will allow scientists to determine how particular diseases occur, how to treat them, and how to prevent them from occurring (Hwang *et al*, 2005). By allowing stem cells to be produced from adult cell nuclei, SCNT represents the future of the field of regenerative medicine and will broaden stem cell research and applications.

CHAPTER 3: STEM CELL ETHICS

Since the discovery and isolation of human embryonic stem cells (hES cells), controversies have arisen regarding their use in scientific research. Numerous experiments within the last six years have demonstrated the enormous potential of hES cells in curing degenerative diseases, spinal cord injury, and growing organs for transplants, as discussed in Chapter 2. Since ES cells are usually obtained from the inner cell mass of a blastocyst derived from a fertilized egg, using ES cells to save lives requires embryos to be destroyed. Hence, the heart of the stem cell debate perches on three important questions: Is the medical benefit of destroying a human embryo valued more highly than the potential life of the embryo? Are there alternative sources of ES cells that do not destroy an embryo? Can adult stem cells medically replace ES cells? To answer these questions, the moral standing of human embryos will be considered from both a scientific and religious standpoint. Furthermore, other ethical and moral questions regarding donating embryos will be addressed. How can unethical practices about exploitation of embryos for personal prestige or financial gain be minimized? What alternatives are there for using embryonic stem cells lines? Lastly, three main categories to unite ethics and medical benefits will be explained. With the support of examples, this chapter will ultimately help to educate the reader and aid in creating a well-informed opinion on stem cell research.

Moral Standing of Human Embryos

The moral standing of human embryos embraces two principles: the necessity to both prevent and alleviate suffering, and to respect human life. Stem cell research will provide an array of therapies for treating debilitating diseases thereby satisfying the first moral principle.

Human ES cell research will, however, destroy a human embryo (unless parthenotes are used) thereby restricting the creation of a human life. Hence, both moral principles cannot be satisfied. The heart of the stem cell research debate is now unraveled: Is it more important to alleviate and prevent current human suffering or is it more important to respect and thereby not destroy potential human life (Rickard, 2002)?

The debate over stem cell research that has plagued America for years is based solely on moral beliefs and can be both accredited and discredited by a standard of ethics. First, however, the difference between morality and ethics must be explored. Morality represents a concern in distinguishing what is good and evil. It varies per person and even per religion. Ethics, however, is a set of rules governing moral conduct. Social policies made within society are governed by ethics ("Morality" and "Ethics", 2005).

The moral debate over stem cell research is based on two fundamental questions: When does personhood begin, and what does an embryo represent? Biologically, the embryo is not a recognizable human being. When the sperm and egg unite, an embryo is created that possess the framework necessary for it to develop into a human being, so long as it receives appropriate nutrients, growth factors, protection, etc. provided by the uterus. The fertilized egg develops into a blastocyst that is a collection of undifferentiated tissue containing an inner and outer cell mass. It is only the inner cell mass that develops into a full embryo. Furthermore, the embryo does not attach to the uterine wall until 2 weeks after conception. Some argue that the embryo has the potential to become a human; however, it is not a human. As Thomas Shannon, social ethicist, argues, potency is not act. The embryo is a human in potency so it is not actually a human (Shannon, 2001). Morally, there are four views of when personhood begins, and four views of what an embryo represents.

When does human personhood begin?

There are four accepted moralistic views of when life beings. The first view assumes life to begin at the moment when the egg and sperm unite creating a fertilized egg. Supporters of this view are incapable of supporting hES cell research since life would be destroyed with any use of the zygote or subsequent stages. The second view, historically belonging to the Catholic Church, is that life begins at embryo implantation in the uterine wall. This takes place at approximately day 6, one day after blastocyst formation at day 5. With these two processes so close in timing, the Catholic Church is against using blastocysts even if not implanted and not yet a "person". The third view assumes life to begin after formation of the primitive streak, a biological term referring to the point at which a band of cells moves along the axis of the embryo to form a groove through which cells move to form the mesoderm ("Medical Dictionary...", 2003). The primordial streak represents clear evidence of cell specialization and does not form until approximately 2 weeks after fertilization, well after blastocyst formation from which ES cells are isolated. Thus, holders of this view would have no problem sacrificing an embryo at the blastocyst stage exhibiting no evidence of a primitive streak. The fourth view assumes life to begin at the moment of birth, when the child enters the surrounding world (Derbyshire, 2001). The latter two views are capable of supporting hES cell research since the isolation and destruction of the embryo occurs prior to when personhood is believed to begin. Supporters of all four viewpoints are capable of supporting all other forms of stem cell research (i.e. adult stem cells or parthenotes) that do not involve an embryo or fetal tissue.

What does an embryo represent?

Four stances have been formed regarding what am embryo represents and thus what its use is for stem cell research. The extremes are represented by two beliefs: an embryo is a human being or an embryo is a mass of tissue. These two extremes represent two fundamental questions of the moral status of an embryo. While there are advocates of both extremes, the general acceptance is somewhere in between both positions. In the paragraphs that follow, all four stances will be explored to aid in forming an unbiased decision on the status of the embryo.

Position 1: The embryo is a human being and must not be destroyed or used for research purposes. It must be treated and protected as an individual of the human society.

Supporters of position 1 believe a human embryo to be an individual whose destruction would be considered immoral and murderous. They strongly oppose ES cell research as it involves the destruction of an embryo. Their proposed solution is to use adult and umbilical cord stem cells since their medical benefits have clearly been illustrated within the last 20 years. A subsection of the supporters do not believe destroying the embryo is a form or murder, but simply immoral. Most supporters feel that the ends do not justify the means: the potential medical benefit does not justify the destruction of a human embryo ("Human Stem Cells…, 2005).

In addition, the use of embryos that are already destroyed is acceptable since the act of killing is irreversible. No new embryos, however, may be destroyed. This status represents the current federal policy under the Bush Administration as of August 9, 2001. One problem that arises from this policy is "complicity". Working with the previously destroyed embryos is

viewed as participating in the immoral act. Hence, some supporters of position 1 disagree even with President Bush's federal policy ("Human Stem Cells…, 2005).

Position 2: The existence of an embryo is considered valuable but it does not share the same status as a baby or a fetus. Thus, it can be used for research purposes.

Supporters of position 2 reason that an embryo is not worthy of the rights of a baby or fetus, and therefore its existence is dulled by the rights and potential benefits for people currently alive. An embryo possesses the ability to become a human being, but it is not yet a human being. Moreover, its destruction will benefit people who are alive and suffering and therefore, it is deemed worthy for scientific research. Supporters of this stance believe that the advancement in locating cures for life-threatening diseases must not be hindered by the inability to use embryos ("Human Stem Cells…, 2005). Although adult stem cells are less controversial to work with, their existence in all cell types is unknown, and their medical applications are more restrictive. Also, further research must be conducted in inducing these cells to differentiate correctly, which would only be made possible through isolation and use of embryonic stem cells and embryonic germ cells.

Position 3: Embryos should not be created for research purposes; however, what is left of IVF procedures may be used in scientific research.

Position 3 is known as the "nothing is lost" principle. If embryos are not to be used for their intended purpose of reproduction and are to be discarded, then they may be used to aid in scientific research. No embryos, however, should be created or cloned on the grounds of research only. Most of these discarded embryos are obtained from *in vitro* fertilization clinics. Essentially, the "intention" of the embryo matters to certain ethicists. Furthermore, a couple who

has finished all reproductive treatments with the clinic may issue consent to donate their embryos for research purposes ("Human Stem Cells…, 2005). Ethical concerns arise in this situation: a woman must indeed give consent and must not be paid to do so. An analysis of such concerns will be presented later in the chapter.

Position 4: Embryos are a cluster of cells similar to somatic cells and thus can be used and destroyed for scientific research.

The fourth position takes a purely biological standpoint. Embryos are a cluster of undifferentiated cells that posses the *ability* to create a human being, but are not yet a human being. This specific ability makes them unique and invaluable to scientific research. Furthermore, the intent for creating an embryo is irrelevant. For this position, embryos may be used from IVF procedures or created from somatic cell nuclear transfer procedures (SCNT). Many advocates for stem cell research support the SCNT procedure since it is used to generate tissue that will restore the function of damaged organs. There is hope that this therapy will be more successful than organ transplantation since stem cells obtained from a patient may be used to create transplant tissues viewed as self by that patient's immune system. Hence, the medical benefit of SCNT procedures is viewed highly ("Human Stem Cells…, 2005), and is the basis for all the excitement surrounding the recent Korean success preparing ES cells lines from 11 different patients (Hwang *et al*, 2005).

Religious Standing of Human Embryos

The four major religions of the world (Christianity, Islam, Hinduism, and Judaism) each represent different views on the concept of stem cell research. Most views are based on the first

moral principle: to alleviate and prevent suffering. For this reason, specific aspects of stem cell research are supported by all major religions (Chapman *et al*, 2005).

The Roman Catholic Church holds the strongest views, accepting stem cell research only under particular conditions. The religious debate asks two questions, one concerning the heart of the moral debate, and one representing complicity: Is it morally justified to destroy a human embryo (a potential human being) for medical advancement and if so, is a researcher who is utilizing an embryo destroyed by someone else also engaging in an immoral act?

The Roman Catholic Church supports stem cell research but opposes research in which stem cells are obtained by destroying human embryos. As explained by Father Tadeusz Pacholczyk, director of the National Catholic Bioethics Center, the Roman Catholic Church agrees with research conducted on adult stem cells, umbilical cord blood cells, and stem cells from miscarriages known as embryonic germ cells. Furthermore, there is more evidence of the benefits of non-embryonic stem cell research over the past 20 years than there is on hES cells thereby showing no need to rely heavily on destroying embryos (Cioffi, 2004). These thoughts are echoed by the newly elected Pope Benedict XVI who stated that killing embryos for research purposes would ultimately lead man "to a descent into hell" (Sweeney, 2005). Carlos Bedate of the Autonomous University of Madrid, a Jesuit priest and doctorate in molecular biology, claims that recent progress in the field of developmental biology indicates that an embryo is considered viable depending on both its environment and DNA. Hence, there is not enough information in the early embryo (3 to 5 day blastocyst) to complete development into a human being, freeing it to be used for research purposes. With future research into embryos, the Vatican and the entire Christian faith may soon come to a consensus that hES research is acceptable if used solely for the greater good (Reichhardt *et al*, 2004).

Within the Islamic faith, all perspectives on stem cell research are based on the Shari'ah, the divine Muslim code of conduct. In accordance with the Qur'an and the Shari'ah, stem cell research is viewed as acceptable. The interpretation of Chapter 23, verse 12-14 in the Qur'an implies the fetus to be a human life as indicated by the phrase "thereafter We produced it as another creature". The embryo develops into a fetus after the fourth month in pregnancy. Furthermore, the Shari'ah distinguishes between actual life and potential life claiming the former to have more protection. Hence, an embryo or a fetus aborted before the end of the fourth month of pregnancy is not viewed as a person and can be safely used for stem cell research. In addition, it is considered a "societal obligation", as stated by the Washington based Islamic Institute, to use extra embryos for research purposes rather than discarding them because the Islamic law prohibits surrogate parenting or adoption due to parentage and inheritance rights. Hence, extra embryos can freely be used for research purposes in particular since the Islamic faith believes in pursuing further scientific knowledge for the benefit of society i.e. treatment of degenerative diseases (Ahmed, 2001; Weckerly, 2005).

Traditional Hindu beliefs mark conception as the beginning of life or rebirth according to the theory of reincarnation. Other Hindu beliefs mark the beginning of personhood between three and five months of gestation (Cousins, 2004). Although it is unclear when life actually begins, Swami Tyagananda, a Hindu chaplain at the MIT Religious Activities Center in Cambridge, MA, believes that destroying an embryo would be permitted if it is an "extraordinary, unavoidable circumstance" or it is "done for greater good". Furthermore, India, the country with the largest population of Hindus, does not object to stem cell research. Hence, the Hindu religion is shown to permit hES cell research because the embryo does not represent a human (Reichhardt *et al*, 2004).

Buddhism follows the same traditional principle as Hinduism in that life begins at conception. Most Buddhists believe that destroying an embryo violates a fundamental tenet that living objects should not be harmed. Cloning embryos, however, does not cause concern as it does not involve the destruction of an embryo (Reichhardt *et al*, 2004).

Judaism takes a very similar stance to Islam on hES cell research. According to the Jewish biblical and Talmudic law, "ensoulment" does not occur until 40 days after gestation when the fetus begins to take the form of a human. Prior to that, the embryo is referred to as "water". Hence, the Jewish faith accepts and endorses ES cell research; Iran recently developed stem cell lines under the acceptance of their leader, Ayatollah Ali Khamenei (Reichhardt *et al*, 2004).

Donating Embryos

Donating embryos for hES cell research has proven to be as controversial an issue as organ donation. Payment for organ and tissue donation is currently illegal in the United States under the National Organ Transplantation Act (NOTA) established in 1984. Donation of organs alleviates suffering for those in need, but there are concerns of uneven distribution of organs to patients with higher financial qualifications. Similarly, women can be compensated for donating eggs for fertility treatments just as in blood and plasma donations.

More importantly, there is apprehension that researchers may use research advances for financial gain and personal prestige. Unethical practices may then arise. In order to minimize such practices, several countries are considering placing bans on patents for stem cell research and on stem cell-related products. This will prevent researchers from claiming to hold a patent on a lung or heart function ("An Ethical Overview", 2005).

United Nations Resolution

In an effort to institute a set of ethical rules to govern stem cell research, and unite both national and spiritual concerns, the United Nations drafted a cloning compromise on November 19, 2004. Within the non-binding declaration, member states were asked to ban reproductive cloning (using somatic cell nuclear transfer to insert the nucleus from an adult cell into an enucleated egg, and implanting the embryo into a uterus) and implement legislation to respect "human dignity" (McCook, 2004; Reichhardt *et al*, 2004). The ways in which this statement can be interpreted may vary and will undoubtedly raise questions in the future.

Alternative Source for Embryonic Stem Cell Lines - Parthenotes

To reduce some of the current ethical concerns surrounding the destruction of fertilized embryos to obtain ES cells, an alternative solution has been developed: parthenotes. Parthenogenesis is a Greek word meaning "virgin birth", hence no sperm or SCNT procedure is needed for the egg to divide and begin developing. During parthenogenesis, oocytes are activated via chemical simulation, and the eggs are incubated *in vitro* to the blastocyst stage where their ES cells can be extracted for research purposes (Kiessling, 2005). Some female amphibians, insects, reptiles and turkeys have been known to develop via parthenogenesis and recently, researchers have succeeded in obtaining blastocycts from primates; primate parthenote blastocysts were obtained in 2002 (Holden, 2002) and provided ES cell lines. Human parthenote blastocysts were also obtained in 2002 (Cibelli *et al*, 2002) but provided no ES cell lines. In 2004, murine parthenote pups were obtained that developed into adult mice (Kono *et al*, 2004). Development of mammalian parthenotes to adults is difficult because biparental reproduction is normally needed and parent-specific epigenetic modifications in the genome occur during

gametogenesis which can alter the ability of DNA from one parent to be fully viable. Hence, there is an unequal expression of imprinted genes from both mother and father (Kono *et al*, 2005). Recent experiments, however, have shown the development of mouse parthenotes with expression of specific genes (*Igf2* and *H19*) that are sometimes silenced which affirms the need for paternal imprinting for parthenogenesis to occur (Kono *et al*, 2005).

Recently, in humans, the discovery of the presence of dermoid cysts of the ovary and teratomas imply parthenogenesis in humans. If the ovarian sack does not rupture, dermoid cysts are formed. The egg then self-induces cell division. The teratomas have been shown to contain various cell types including skin, bone, and muscle, hence proving the presence of pluripotent stem cells (Kiessling, 2005).

If ES cell lines can be isolated in humans, parthenogenesis would reduce a large portion of the ethical concerns related to hES cell research ("Human Stem Cells…, 2005; Kiessling, 2005). Since parthenotes cannot develop into people, the question that arises is whether or not the parthenotes are as morally significant as embryos (Weiss, 2001). The stem cell lines could be used to help other tissue-matched individuals and thereby eliminate embryo stem-cell banks ("Human Stem Cells…, 2005; Kiessling, 2005). One ethical concern that arises, however, is whether or not it is morally acceptable to collect eggs from women's ovaries for therapeutic reasons rather than reproductive reasons. Hence, with proper terminology to describe this new process, policy makers may be able to fully appreciate and understand the full capabilities of eggs (Kiessling, 2005).

Based on the religious stances taken for hES cell research, however, it is hopeful but not certain that the four major religions will accept the use of parthenotes as a substitute for destroying embryos. Since the Hindu, Islamic, and Jewish faith already accept hES cells and the

destruction of an embryo, the use of a parthenotes should be acceptable to those religions. There is even potential for the Catholic Church to accept parthenotes since no fertilized embryos will be destroyed. The only ethical concern that arises and which has not been investigated yet is the use of a woman's eggs for therapeutic rather than reproductive purposes. All religions may or may not accept women freely donating eggs since they are a prized possession given by God to be used for creating children. First, however, there needs to be more scientific research conducted and made available to religious authorities.

Bone Marrow Transplants: Low Ethical Concern, High Medical Benefit

Not all stem cell applications use highly controversial ES cells. Stem cell research incorporates treatments that require either hES cells or non-hES cells. Non-hES cell treatments utilize adult stem cells, including hematopoietic stem cells (HSCs) from bone marrow, umbilical cord or peripheral blood. One such treatment, bone marrow transplantation, traditionally employs bone marrow stem cells to restore stem cells that have previously been destroyed from chemotherapy or radiation therapy for cancer treatments. Bone marrow transplantations are usually used for leukemia, lymphoma, neuroblastoma, and multiple myeloma patients. The hematopoietic stem cells are harvested from the marrow within the pelvic bone or, in rare instances, the sternum ("Cancer Facts", 2004).

The use of bone marrow stem cells has already saved a multitude of lives. As stated in the 2001 Biennial Report of the National Bone Marrow Registry, the National Marrow Donor Program (NMDP) has conducted 13, 453 transplants between 1987 and 2001. In the year 2001 alone, 1,743 transplants occurred implying an average of 30 transplants a week. Hence, more than 13,000 patients have been cured of leukemia and a host of anemia and immune disorder

diseases. Approximately 12,000 transplants were performed for malignant cases of which the majority, nearly 4,000, was for various forms of leukemia. Approximately 1,500 transplants were performed for non-malignant cases for immune, metabolic, and platelet disorders ("Biennial Report", 2001).

Evidence of the astounding number of lives saved through the use of non-hES cells is a clear indication that there are reasons for people to support at least adult stem cell research, in particular by those who do not endorse the destruction of an embryo. Bone marrow transplants rely completely on hematopoietic stem cells and hence do not result from the destruction of an embryo. There are few if any ethical concerns surrounding bone marrow transplantations. Based on the statistics illustrated, the author of this report strongly supports the use of adult stem cells for treatments due to the low ethical conflicts and high medical benefit. No human being is harmed from the isolation and use of adult stem cells; patients only gain. Furthermore, all four of the major religions support this form of stem cell research thereby eliminating spiritual conflicts.

Cosmetic Therapy: High Ethical Concern, Low Medical Benefit

The use of hES cells in cosmetic therapy for beautification purposes is an example of a treatment with low medical benefit yet high ethical concern. There is simply no need to destroy a human embryo for someone else to improve their physical image. Perhaps there should be a greater importance placed on using hES cells in health treatments prior to beautification applications. Even if adult stem cells replace the need for hES cells in cosmetic therapy, ethical concerns arise on another front as well. Should such importance be placed on physical image and what effects will it have on younger children and teenagers? What age groups will these

treatments be available to? Although the use of stem cells for breast augmentation could help provide information on graft optimization and their detrimental effects to the body, will this, however, cause more teenagers to make use of such treatments? Perhaps a more immediate concern is whether or not these procedures will be affordable for people of all social classes. Other examples for cosmetic therapy include eliminating baldness in both men and women, as well as removing or reducing wrinkles. There is a large difference between using ES cells to grow hair on the top of one's head, versus growing new inner ear hairs in the cochlea to restore an individual's hearing loss.

As of now, more research must be conducted before any treatments (cosmetic or not) can be brought to clinical trials. In addition, safety and complications must be considered. For example, Gennady Sukhikh, a stem-cell scientist at the Russian Academy of Sciences, suggested that implanting stem cells in patients with low immunity may cause the development of cancer. Currently in Russia, stem cell clinics are bustling, but the authenticity of the treatments is highly questionable (Titova and Brown, 2004). In the future if cosmetic therapy becomes a reality, strict guidelines will have to be placed in order to minimize this doubt and fear for patients. As of now, the author of this report does not support the use of embryonic stem cells for cosmetic therapy, but does support the use of adult stem cells for cosmetic therapy once health applications have been fully attended to, and so long as other tax payers do not have to pay for it.

The four religious standpoints on cosmetic therapy are unknown; however, based on each of their stances on stem cell research, their potential responses can be deduced. The Catholic Church would not be expected to support cosmetic therapy if hES cells are used; however, the Islamic, Jewish and Hindu faith would be expected to support it so long as it "raised the common good or alleviated suffering". A cosmetic procedure to improve someone's face following an

automobile accident might rank higher than making hair grow on top of someone's otherwise healthy head. A supporter of hES cell research may not necessarily support cosmetic therapy. The marketing strategy used to display cosmetic therapy to the public will ultimately draw supporters.

hES Cells to Treat Spinal Cord Injury: High Ethical Concern, High Medical Benefit

The use of hES cells to repair a spinal cord after injury or paralysis is a strong example of the high medical benefits and high ethical concerns surrounding using hES cells in treatments. Success has been achieved with human ES cell therapy for rat spinal cords (Keirstead *et al*, 2005). Although only animal trials have been conducted so far, there is a strong indication that results may be replicated in humans. Recently, there has been a tremendous amount of progress in spinal cord research. One particular company, Spinal Research, is working to regenerate four centimeters of the spinal cord of a paralyzed person. This procedure may eventually allow the person to breathe unaided, or to use their arms or legs. Spinal cord neurons are not self-repairable and so neural stem cells can be used to re-grow nerve fibers in the injured region ("Spinal Cord Repair", 2005).

Washington University School of Medicine (St. Louis) focuses research on the mechanisms of spinal cord injury and repair via hES cells. As described by Dr. John W. McDonald, ES cells were once used in the creation of knockout mice and the same technology can be used for cell cultures and integrated into spinal transplantation research. This would provide researchers with novel insights into the link between genes and a body's ability to recover from injury. With the continued use of hES cell lines, a treatment for spinal cord injured patients will soon be made possible (McDonald, 2005).

The use of embryonic stem cells carries all the ethical concerns and religious stances laid out earlier in the chapter; however, in this example the medical benefit is very relevant as well. Allowing a paralyzed patient to either regain movement or speech are medical opportunities that must to be considered. Although a potential human being may be destroyed, a severely suffering human being will be cured. The question that arises once again is whether it is ethical to take a potential life in order to save a life. The author of this report supports hES cell research due to its paramount potential for treating debilitating diseases and the belief that a blastocyst does not possess full human characteristics prior to being destroyed. It is more difficult and therefore more important to alleviate and prevent human suffering than to create a human being.

Each individual is entitled and encouraged to form individualized opinions on a matter as controversial and discerning as embryonic stem cell research. The ultimate goal of this chapter is to alert the reader of the ethics surrounding the use of hES cells and in turn help shape a well-informed reason for their decision. The future of stem cell research in the United States relies on individuals who are well educated in both the science and ethics of stem cell use.

CHAPTER 4: STEM CELL LEGALITIES

The legal status of human embryonic stem (hES) cell research in the United States is a topic of high dispute and paramount concern. Beginning in the early 1970's after the development of the first "test-tube baby", the use of human embryos in research has held a variety of viewpoints. State and federal legislations (often in conflict with one another) as well as commissions have been formed in an attempt to control the rights of an embryo. New policies are issued every time a new president is elected. The current Bush Administration has created the strongest policies to date. Since the first isolation of hES cell lines in the United States, nations throughout the world have caught up and even surpassed America in stem cell research. Countries such as China and Switzerland are in the nascent stages of research, but have demonstrated the potential to rise further in the future. Australia has formed strict regulations although more lax than the United States. Lastly, the United Kingdom has become one of the forerunners in stem cells research. Within this chapter, the legal status of hES cell research and therapeutic cloning (for obtaining hES cells) in both the United States and foreign nations will be discussed, drawing together a worldwide view on stem cell research.

A History of Human Embryonic Laws

The dispute over the use of human embryos in research began over 30 years ago after the 1973 U.S. Supreme Court legalization of abortion in the case of *Roe vs. Wade*. During that time frame, the advent of *in vitro* fertilization (IVF) (and its ability to manipulate a fertilized embryo outside the human body) also stirred a political controversy in which each research application was to be verified by the Ethics Advisory Board (EAB) (Boonstra, 2001). On May 4, 1979, the

EAB granted the use of federal funding to support IVF procedures after reviewing ethical considerations. The EAB dissolved in 1980, however, after its recommendations were not accepted by the Health and Human Services (HHS). Since all human IVF procedures that were federally funded were to be approved by the EAB, a "de facto moratorium" resulted on IVF procedures and other research on early human embryos including stem cell research. The moratorium was finally lifted when the NIH Revitalization Act of 1993 was enacted (Johnson, 2001; Boonstra, 2001). This act now provided federal funding for embryonic research and embryos created through IVF procedures all made possible by Pres. Bill Clinton. The U.S. Congress then withdrew the position, and instead enacted a new ban on federal funding for any research that involves the destruction or discarding of an embryo (Boonstra, 2001).

Human Embryo Research Panel

The NIH created the Human Embryo Research Panel (HERP) to evaluate the moral and ethical issues surrounding the human embryo after Pres. Clinton allowed federal funding to be given for stem cell research (Dunn, 2005). They created a set of recommendations, released in September 1994 that focused on the need for federal funding for SCNT, stem cells (particular conditions) and embryos created for medical research purposes only. In addition, areas deemed unacceptable or requiring a further analysis were listed. The report was accepted on December 2, 1994 by the NIH Advisory Committee to the Director (ACD) (Johnson, 2001).

Following the acceptance of the report by the ACD, Pres. Clinton issued a directive to the NIH to not allot resources to "support the creation of human embryos for research purposes". Parthenotes and "spare" embryos were not included in the directive (Johnson, 2001). Furthermore, one month after March 4, 1997, after the Dolly announcement (the cloning of the

world's first mammal, Dolly the sheep), Pres. Clinton issued a memorandum to make it "absolutely clear that no federal funds will be used for human cloning." Hence, the congressional ban on human cloning was extended to all research supported by federal funds (Johnson, 2001). In 1995, funding for all research that involved the creation or destruction of an embryo was banned, known more formally as the Dickey-Wicker Amendment after its two authors, Representative Jay Dickey, Republican of Arkansas, and Representative Roger Wicker, Republican of Mississippi. Attached to the appropriations bill for the HHS, the ban passed as a rider, and the ban is renewed yearly limiting all forms of human embryo research to the private funding (Dunn, 2005).

In January 1999, the release of a legal opinion from Atty. Harriet Rabb of HHS transfigured the hES cell research stance by the Clinton Administration. Rabb concluded that since hES cell lines "are not a human embryo within the statutory definition", the Dickey-Wicker amendment could not apply; federal funds were not to be used to derive stem cell lines because it involves the destruction of an embryo (Dunn, 2005). Hence, NIH could federally fund experiments involving the stem cell lines.

National Bioethics Advisory Commission

The National Bioethics Advisory Commission (NBAC) was created by the Executive Board in 1995, and gathered for the first time in 1996 ("Former Bioethics…", 2005). Combining efforts with NIH, the *NIH Guidelines on Stem Cell Research* was published under the Clinton Administration. These guidelines clearly stated no funding would be issued for research in which "human stem cells are used for reproductive cloning of a human; human stem cells are *derived* using SCNT; or, human stem cells that were derived using SCNT are *utilized* in a

research project" (Johnson, 2001). These set of guidelines were supported by the Bush Administration and incorporated into Pres. Bush's August 2001 policy as will be discussed in subsequent paragraphs.

The Current Status of Human Embryonic Research in the United States

The politics behind hES cell research is complicated, with federal and state legislators each issuing their own set of rules. Most importantly, in order to conduct research on a topic such as hES cells at a world-class level on a continuous basis, federal funding is required (private funding is a good source, but can not match that of the federal government over long periods of time). Pres. Bush's policy on stem cells ultimately helps to clarify what can and cannot be supported by federal funding. Currently, it is illegal to destroy, create, or clone a human embryo within experiments that are supported by federal funds. It is legal to do so with private funds, however. Deciding on how much cloning to outlaw is a question that is highly being debated within Congress. Two legislations have been passed in the House (2001 and 2003) to outlaw human cloning in all forms: for producing human beings, and for biomedical research such as stem cells. The legislations have been delayed in the Senate. Stem cell lines, however, follow a different set of rules. According to the federal funding ban issued by Congress, all research involving existing stem cell lines is acceptable as they did not fall under the ban. Hence, in August 2001, Pres. Bush extended the ban to include limited research on existing stem cell lines (Dunn, 2005).

Federal Funding

When President George W. Bush took office in January 2001, he assured the general public that he would review the status of federal funding for human embryonic stem (hES) cell research. He also asked that the HHS to examine the current NIH guidelines. On August 9, 2001, Pres. Bush announced the availability of federal funding for research on all presently existing stem cell lines only. No federal funding was to be made available for the future destruction of human embryos. The embryos from which these stem cell lines were derived have already been killed and cannot develop into humans (Duffy, 2002; "Remarks", 2001). Pres. Bush believes this restricted funding will promote the sanctity of life "without undermining it" ("Fact Sheet", 2001). This avoids the moral anxiety of using taxpayer funding to promote and encourage the further destruction of human embryos while permitting scientific researchers to investigate the potential of hES cells in treating degenerative diseases ("Remarks", 2001). Pres. Bush's policy reduces the amount of federal funding available for hES cell research present during the Clinton Administration (Dunn, 2005).

Under Pres. Bush's hES cell policy, several guidelines must be met for research on the approximately 64 existing cell lines. The following criteria were obtained from the Stem Cell Fact Sheet distributed by the Office of the Press Secretary within the White House ("Fact Sheet", 2001).

> Federal funds will only be used for research on existing stem cell lines that were derived:
>
> 1. With the informed consent of the donors;
> 2. From excess embryos created solely for reproductive purposes; and
> 3. Without any financial inducements to the donors.
>
> In order to ensure that federal funds are used to support only stem cell research that is scientifically sound, legal, and ethical, the NIH will examine the derivation of all existing stem cell lines and create a registry of those lines that satisfy this criteria.

> No federal funds will be used for:
>
> 1. the derivation or use of stem cell lines derived with newly destroyed embryos;
> 2. the creation of any human embryos for research purposes; or
> 3. the cloning of human embryos for any purpose.
>
> Today's decision relates only to the use of federal funds for research on existing stem cell lines derived in accordance with the criteria set forth above.

Pres. Bush awarded $250 million of federal funding for the pursuit of research in non-embryonic stem cell research such as umbilical cord placenta, adult, and animal stem cells. Furthermore, the President created the President's Council on Bioethics to explore both the human and moral consequences of future developments in biomedicine and behavioral science such as stem cell research (embryonic and non-embryonic), cloning, gene therapy, and euthanasia among others. The Council is chaired by biomedical ethicist Dr. Leon Kass of the University of Chicago "Remarks", 2001).

State Funding

In addition to federal legislations, a variety of state legislations have been passed both endorsing and banning all forms of hES cell research. California was the first state to officially sanction hES cell research as of 2002. Therapeutic cloning was also permitted, with the exception of cloning to produce a human being. Then in 2004, a bond measure known as Proposition 71 was passed providing $3 billion for stem cell research over a time span of 10 years. Also in 2004, New Jersey followed in California's footsteps and created the first stem cell, state-supported research facility (Dunn, 2005).

In comparison to other states, Massachusetts has sustained the greatest fight on stem cell research. It is home to Harvard University and the distinguished faculty who comprise some of the nation's top stem cell scientists. Governor Mitt Romney supports stem cells being derived

from left over embryos of IVF procedures. He opposes the creation of cloned embryos, however. Recently, in March of 2005, Romney delivered a veto threat that forced state lawmakers to vote in favor of pursuing cloning hES cell research. The bill, called the "radical cloning bill", passed by a veto-proof margin causing Romney to state that he would veto it anyway (Dunn, 2005).

In early June of 2005, the Legislature overrode Romney's veto by more than a two-thirds vote in both the House and the Senate (112-42 in the House, and 35-2 in the Senate). Therefore, the new law will now revive a previous plan to construct a center for regenerative medicine directly linked to both the University of Massachusetts Medical School and the surrounding biotechnology research firms in Worcester, MA. When constructed, the new center will provide incentives for private research expansion, as well as create an adult stem cell cord blood bank in UMASS Memorial Medical Center. In a similar situation, the Connecticut House of Representatives recently accepted a $100 million plan over a 10 year time span to conduct stem cell research (Monohan, 2005).

Since 2001, many new stem cell lines have been created in the private sector. They are easier to access, maintain and convert into desired cell types. These lines have much more potential to create human cell therapies for treating diseases. Furthermore, unlike the earlier lines approved by Pres. Bush, the newer stem cell lines have not been contaminated with mouse cells. Both Democrats and Republicans alike have recognized the hindrance caused by Pres. Bush's policy and have voiced their opinions through letters addressed to the President. Beginning in April of 2004, 206 members of the U.S. House of Representatives signed a letter asking for an expansion of federal funding for stem cell lines. Following suit, in June of 2004,

58 U.S. Senators signed a similar letter, and 48 Nobel laureates including former NIH director Harold Varmus (in the Clinton Administration) approved John Kerry's presidential candidacy (Dunn, 2005; Garfinkel, 2004a). In essence, there is a strong belief among political leaders that Pres. Bush's restrictions are preventing new medical discoveries. The general public has voiced similar support. In a recent poll in February of 2005 conducted by Results of America (project of Civil Society Institute), 72 percent of America supports an expansion of federal funding i.e. a loosening of Pres. Bush's restrictions ("American Views On…", 2005). Hence, in March of 2005, the House Republican leadership agreed to vote on a bill to reduce the current restrictions on hES cells. Once again, the debate over the status of the human embryo will be opened, hopefully for the betterment of medicine and science (Dunn, 2005).

Laws on Human Embryonic Stem Cell Research in Foreign Nations

The United Nations initially intended to institute a worldwide ban on human cloning. This proposal, drafted by the United States, Honduras, Australia and various other Catholic nations, was placed aside until 2004 (Garfinkel, 2004b; Wroe, 2005). It was intended to ban all forms of reproductive and research cloning. Several other nations, including Great Britain, objected to a potential ban on research cloning since that would prevent investigation into medical breakthroughs (Garfinkel, 2004b). The proposal currently awaits the testimony of other nations currently partaking in ES cell research. Below, the laws governing human cloning in the United Kingdom, Australia, and Switzerland will be considered.

Australia

As of March 2005, Australia has banned the use all forms of reproductive and research cloning, thereby supporting the United Nations declaration (Wroe, 2005). Additionally, it has banned a technique known as embryo splitting (among others including parthenotes) that will prevent cloning without fertilization. The use of embryos left over from assisted reproduction created before April 5, 2002 is allowed for research, however. This new federal law currently surpasses all state laws regarding hES cells and cloning (Garfinkel, 2004b).

United Kingdom

As of 1990, the United Kingdom has allowed the use of embryos obtained from assisted reproductive procedures for research purposes. Creating embryos was also permitted for research purposes only. The Human Fertilisation and Embryology Authority (HFEA) outlines such research protocols and, as of 2001, has expanded to include many forms of basic research including reproductive biology (Garfinkel, 2004b).

As reported in the October 2003 issue of Reproductive BioMedicine Online, the first reported hES cell lines were derived in the UK. The quality of embryos previously used was not suitable for deriving stem cell lines. In this derivation, however, stem cells were obtained from fertile couples (Pickering *et al*, 2003). The study became the first scientific publication headed under government guidelines (pertaining to stem cell research) regarding stem cell isolation. The UK then created a stem cell bank to organize all newly created cell lines; it is overseen by the HFEA and run by the Medical Research Council (Garfinkel, 2004b).

Recently, as of August 11, 2004, the HFEA granted a license to the Newcastle Center for Life, permitting researchers to create colonies of human stem cells. These stem cells can only be used for research purposes and not for creating a cloned human being. The license expires in one year, after which researchers may work only on established stem cell lines ("HFEA grants…". 2005).

Switzerland

The Swiss Parliament is currently deliberating whether to allow stored, frozen embryos for therapeutic research. All eligible embryos must be seven or fewer days into development, which allows the use of blastocysts and ES cells. In addition, embryos cannot be created for research only and soon, a limited number of stem cell cultures from other foreign countries may have to be used. The Swiss Constitution is very strict, controlling even the number of eggs that may be fertilized and developed outside a female body. Hence, between 1,000 and 5,000 embryos are currently frozen, compared to nearly 400,000 in the United States. If this new legislation is accepted, Switzerland may overturn its strict stance, and soon be among the leading nations in stem cell research (Garfinkel, 2004b).

China

China began its stem cell research shortly after the United States isolated its first embryonic stem cell line. China's first stem cell line was isolated by a team lead by Xu Zhing *et al* and was published in the Zhongshan Medical School Journal (Sleeboom, 2002). China currently permits therapeutic cloning of embryos for hES stem cell research. As stated by Chen Hanbin, a member of the Chinese People's Political Consultative Conference (CPPCC) National

Committee and a professor at Guiyang Medical College in Southwest China's Guizhou Province, therapeutic cloning must not be banned due to its humanitarian benefits (healing wounded and rescuing dying people) ("China needs…", 2005). Furthermore, researchers at medical schools and at the China Academy of Sciences are requesting National People's Congress (NPC) officials to create stricter laws banning reproductive cloning. As of now the boundary between reproductive and therapeutic cloning is blurred. In order to prevent cloning misuse, government administrations such as the Ministry of Health must first institute regulations on research followed by formulations of a law by the government.

The full potential of hES cells is still not known causing both political leaders and the general public to claim that the medical potential of these cells may just be a hoax. In order to fully recognize the possibilities of hES cells, more research must be conducted. Hence, nations must begin to loosen their strict regulations against human cloning and allow for therapeutic cloning. The U.S., United Kingdom and China are prime examples. It is the author's view that the United States must reduce strict regulations against human cloning: it must allow therapeutic cloning while continuing to ban reproductive cloning. This act will allow medical research to vastly improve thereby implementing humanity's fundamental moral principle: to alleviate and prevent human suffering (See Chapter 3).

CHAPTER 5: CONCLUSIONS

Stem cell research is beginning to revolutionize modern medicine in the 21st century. Despite cultural and religious barriers, there is evidence that stem cells (either adult, embryonic, or both) have great potential to eliminate a plethora of degenerative diseases that has plagued humankind for centuries. Breakthroughs obtained from animal experiments indicate a similar response in humans, and human trials are at last being conducted with promising results. Stem cell research's greatest hindrance is its ethical standpoint, in particular for human embryonic stem (hES) cells more than with adult stem cells. Currently, both animal and human data are extremely strong for the successful use of adult hematopoietic stem cells (HSCs) to treat cancer patients following radiation or chemotherapy. Some animal evidence supports the existence of adult neuronal stem cells and heart cells, but such adult stem cells have not yet been used in humans. Human ES cells are believed to be even more valuable, however. Despite strong restrictions placed on hES cell research the United States, there is evidence that the rest of the world is rapidly making advances. Furthermore, alternatives to using hES cells such as parthenotes must be investigated and their lower ethical concerns presented to the public. Once the majority of strong ethical concerns and religious beliefs are ironed out, all forms of stem cell research present a bright future in the new medical field of regenerative medicine.

Stem cells are pluripotent, possessing the ability to differentiate into an array of cells, thereby allowing them to replace damaged or lost cells and treat a variety of degenerative diseases. The two types of stem cells, adult and embryonic, hold great potential; however, adult stem cells may not be found in every organ of the human body and can only differentiate into cells of the particular organ from where they are extracted. Researchers believe hES cells hold

greater potential since they are capable of differentiating into all cell types. The future of hES cell research rests in whether or not it is morally and ethically acceptable to destroy an embryo since ES cells are obtained from the blastocyst stage of a fertilized embryo.

To determine the moral status of an embryo, four views have been conjured up to determine when personhood begins and what an embryo actually represents. Embryos are considered humans either from the moment of conception, from implantation in the uterine wall, from the formation of a primitive streak, or from the moment of birth. Furthermore, embryos are believed to represent either a human being, a mass of undifferentiated tissue, or somewhere in between. This valuable entity that can be used for scientific purposes, however, cannot currently be newly created for research purposes in the United States.

Each of the four major religions (Hinduism, Judaism, Christianity, and Islam) has voiced their stances on these two questions. The Catholic Church holds the strongest views against hES cell research believing than an embryo is considered human after implantation on the uterine wall, which negates using the blastocyst stage (which forms just prior to implantation) to obtain ES cells. Hindus, Jews, and Muslims each support hES cell research since an embryo is considered human between 3 and 5 months of gestation, after the embryo has taken the form of a fetus (and well after the blastocyst stage), so long as the research is used to support the common good.

Embracing both the religious and ethical anxieties over hES cell research, the United States drafted a policy to ban the further destruction and creation of human embryos for research purposes. Only "spare" embryos from IVF trials are allowed to be used in conjunction with stem cell lines established prior to August 2001. Recently, various members of the Senate and Congress have tried to loosen Pres. Bush's restrictions since federal funding is essential for

progress to be made in experiments. In the meantime, state legislators are creating stem cell research facilities through private and state funding. California, Massachusetts, and New Jersey represent the leading states in stem cell research. Foreign nations such as the United Kingdom have permitted researchers to grow colonies of human stem cells. Switzerland and China are catching up, and will soon supersede the United States if Pres. Bush does not loosen restrictions.

The author of this report feels strongly that hES cell research must be pursued in greater detail than it has in the past, despite ethical and moral concerns. She supports the belief that an embryo represents a human being after taking the form of a fetus, supporting the Hindu, Jewish, and Muslim stances on hES cell research, allowing research to be performed freely on the blastocyst stage from which ES cells are obtained. In addition, she supports the creation of embryos for therapeutic cloning only if strict regulations are placed to ban reproductive cloning. The author believes Pres. Bush's August 2001 policy restrictions must be loosened in order for the United States to proceed in developing treatments using hES cells. Although adult stem cells have shown some potential, hES cells appear more promising. In order to obtain maximum benefit, additional research must be conducted through the aid of federal funding. Embryonic stem cells have transformed into insulin-producing cells to treat diabetes, as well as spinal motor neurons to treat spinal cord injured patients. In addition, the author believes the use of parthenotes must be further explored and supported by federal funding as an alternative to hES cells. Most of the general public is unaware of their potential and low ethical anxieties; however, once funding has increased, further research may deem parthenotes more useful. In essence, as long as hES cell research is not misused for cosmetic therapy or reproductive cloning, society's potential benefit far outweighs any ethical concerns of this author, so it must be pushed forward.

Even if it is believed to destroy a potential human being, it is for the greater good of humanity, a fundamental moral principle.

REFERENCES

Ahmed, Ayesha. "U.S. Muslims Give Support to Embryonic Stem Cell Research – Survey". Islam Online. August 28, 2001. Accessed May 29, 2005. <http://www.islam-online.net/english/News/2001-08/29/article6.shtml#top>

"American Views on Stem Cell Research: Summary of Survey Findings". Results for America, A Project of Civil Society Institute. February 15, 2005. Opinion Research Corporation. Accessed June 8, 2005. <http://resultsforamerica.org/calendar/files/021505%20CSI%20RFA%20stem%20cell%20survey%20report%20FINAL.pdf>

"Biennial Report (2001) of the National Bone Marrow Donor Registry". National Marrow Donor Program. August 2002. U.S. Department of Health and Human Services, Health Resources and Service Administration, Office of Special Programs, Division of Transplantation and the National Bone Marrow Donor Registry. Contract number: 240-97-0036. Accessed May 31, 2005. <http://www.marrow.org/NMDP/biennial_report_2001_1.pdf>

Boonstra, Heather. "Human Embryo and Fetal Research: Medical Support and Political Controversy". The Guttmacher Report on Public Policy. February 2001. Volume 4, Number 1. Accessed June 6, 2005. <http://www.guttmacher.org/pubs/tgr/04/1/gr040103.html#table>

"Brain Stem Cells to Cure Diabetes". British Broadcasting Center (BBC) News. April 25, 2005. Accessed May 24, 2005. <http://news.bbc.co.uk/2/hi/health/4480875.stm>

"Cancer Facts – Bone Marrow Transplantation and Peripheral Blood Stem Cell Transplantation: Questions and Answers". National Cancer Institute. August 31, 2004. Cancer Information Service. Accessed May 31, 2005. <http://cis.nci.nih.gov/fact/7_41.htm>

"Cardiovascular Disease". SynCardia Systems, Inc.. 2004. Accessed May 26, 2005. <http://www.syncardia.com/patients2.php>

Chapman, Audrey R., Mark S. Frankel, Michele S. Garfinkel. "AAAS/ICS Report on Stem Cell Research". American Association for the Advancement of Science and The Institute for Civil Society. Accessed May 30, 2005. <http://www.aaas.org/spp/sfrl/projects/stem/report.pdf>

"China needs law to prevent cloning misuse". People's Daily Online: English. March 12, 2005. China Daily. Accessed June 9, 2005. <http://english.people.com.cn/200503/12/eng20050312_176531.html>

Cibelli J.B., K.A. Grant, K.B. Chapman, K. Cunniff, T. Worst, H. Green, *et al*. "Parthenogenetic Stem Cells in Non-human Primates". Science. 2002**.** 295: 819.

Cioffi, Fr. Alfred, "The Truth About Stem Cell Research". The Florida Catholic. October 28, 2004. Christian Patriots for Life. Free Public. Accessed May 29, 2005. <http://www.freerepublic.com/focus/f-news/1410722/posts>

Cousins, Jennifer. "Religions' Take on Embryonic Stem Cell Research and When Life Begins". Science and Theology News. December 2004. Accessed May 30, 2005. <http://www.stnews.org/archives/2004_december/feat_focus_1204.html>

Derbyshire, Stuart. "Stop Stemming the Research". Spiked Science. November 29, 2001. Accessed May 28, 2005. <http://www.spiked-online.com/Articles/00000002D309.htm>

"Diabetes Research Institute Demonstrates New Approach To Transform Stem Cells Into Insulin-Producing Cells". Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 25, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/March_2005.htm#8>

Duffy, Diana. "Background and Legal Issues Related to Stem Cell Research". Almanac of Policy Issues. June 12, 2002. Congressional Research Service. Accessed June 5, 2005. <http://www.policyalmanac.org/health/archive/crs_stem_cell.shtml>

Dunn, Kyla. "Dispatches: The Politics of Stem Cells". NOVA scienceNOW. April 13, 2005. Public Broadcasting Service (PBS). Accessed June 7, 2005. <http://www.pbs.org/wgbh/nova/sciencenow/dispatches/050413.html>

Dunnett, S.B., A. Bjorklund, and O. Lindvall. "Cell therapy in Parkinson's disease—stop or go?" Nat. Rev. Neurosci. 2001. 2: 365–369.

"Fact Sheet: Embryonic Stem Cell Research". White House. August 9, 2001. Office of the Press Secretary. Accessed June 5, 2005. <http://www.whitehouse.gov/news/releases/2001/08/20010809-1.html>

"Former Bioethics Commissions". The President's Council on Bioethics. Accessed June 9, 2005. NBAC and HHS. <http://www.bioethics.gov/reports/past_commissions/>

"Frequently Asked Questions on Stem Cell Research". International Society for Stem Cell Research. September 17, 2004. Accessed May 20, 2005. <http://www.isscr.org/science/faq.htm>

Garfinkel, Michele (a). **"**New Support for Stem Cell Research Seen in U.S. Congress". GNN – Genome News Network. June 8, 2004. Accessed June 8, 2005. <http://www.genomenewsnetwork.org/articles/2004/06/08/stemcellpush.php>

Garfinkel, Michele (b) (compiler). "Stem Cells: Policies and Players". GNN – Genome News Network. 2004. Accessed June 8, 2005. <http://www.genomenewsnetwork.org/resources/policiesandplayers/>

"HFEA grants the first therapeutic cloning license for research". Human Fertilisation and Embryology Authority. Accessed June 8, 2005. <http://www.hfea.gov.uk/PressOffice/Archive/1092233888>

Holden C. "Primate Parthenotes Yield Stem Cells". 2002. Science. 295: 779-780.

"Human Stem Cells: An Ethical Overview". University of Minnesota's Center for Bioethics. Starr Foundation, Brenda Paul, Carol Tauer, Elizabeth Chambers, Jeffery Kahn, M.P.H., and Dianne Bartels. Accessed May 29, 2005. <http://www.bioethics.umn.edu/publications/Stem_Cells.pdf>

Hwang W.S., S.I. Roh, B.C. Lee, S.K. Kang, D.K. Kwon, S.J. Kim, .S.W Park, H.S. Kwon, C.K. Lee, J.B. Lee, J.M. Kim, C. Ahn, S.H. Paek, S.S. Chang, J.J. Koo, H.S. Yoon, J.H. Hwang, Y.Y. Hwang, Y.S. Park, S.K. Oh, H.S. Kim, J.H. Park, S.Y. Moon, G. Schatten . "Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts". Science Express. May 19, 2005: 1-11.

Itkin-Ansari P., I. Geron, E. Hao, C. Demeterco, B. Tyrberg, F. Levine. "Cell-based therapies for diabetes: Progress towards a transplantable human beta cell line". Ann N Y Academy of Science. 2003. 1005: 138-147.

Itkin-Ansari P., F. Levine. "Sources of beta-Cells for Human Cell-Based Therapies for Diabetes". Cell Biochemistry Biophysics. 2004. 40: 103-112.

Jackson, K.A., S.M. Majka, H. Wang, J. Pocius, C.J. Hartley, M.W. Majesky, M.L. Entman, L.H. Michael, K.K. Hirschi, and M.A. Goodell. "Regeneration of ischemic cardiac muscle and vascular endothelium by adult stem cells". J. Clin. Invest. 2001. 107: 1–8.

Johansson, Clas B., Stefan Momma, Diana L. Clarke, Mårten Risling, Urban Lendahl, and Jonas Frisén. "Identification of a Neural Stem Cell in the Adult Mammalian Central Nervous System". Cell. January 9, 1999. 96: 25-34.

Johnson, Judith A. "CRS Report for Congress – Human Cloning". Congressional Research Service – Library of Congress. December 19, 2001. Domestic Social Policy Division. Order Code RS21096. Accessed June 6, 2005. <http://fpc.state.gov/documents/organization/7943.pdf>

Keirstead H.S., G. Nistor, G. Bernal, M. Totoiu, F. Cloutier, K. Sharp, O. Steward. "Human embryonic stem cell-derived oligodendrocyte progenitor cell transplants remyelinate and restore locomotion after spinal cord injury". J Neurosci. 2005. 25: 4694-4705.

Kiessling, Ann A. "Eggs Alone – Human parthenotes: an ethical source of stem cells for therapies?" Nature. March 10, 2005: 434.

Kirschstein, Ruth and Lana R. Skirboll. "Stem Cells: Scientific Progress and Future Research Directions". National Institutes of Health, Department of Health and Human Services. 2001. Accessed May 17, 2005. <http://stemcells.nih.gov/info/basics/>

Kocher, A.A., M.D. Schuster, M.J. Szabolcs, S. Takuma, D. Burkhoff, J. Wang, S. Homma, N.M. Edwards, and S. Itescu. "Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function". Nat. Med. 2001. 7: 430–436.

Kono, Tomohiro, Yayol Obata, Quiong Wu, Katsutoshi Niwa, Yukiko Ono, Yuji Yamamoto, Eun Sung Park, Jeong-Sun Seo, and Hildehiko Ogawa. "Birth of parthenogenetic mice that can develop into adulthood". Nature. April 22, 2004. 428: 860-864.

Laugwitz K.L., A. Moretti, J. Lam, P. Gruber, Y. Chen, S. Woodard, L.Z. Lin, C.L. Cai, M.M. Lu, M. Reth, O. Platoshyn, J.X. Yuan, S. Evans, K.R. Chien. "Postnatal isl1+ cardioblasts enter fully differentiated cardiomyocyte lineages". Nature. 2005. 433: 647-653.

Li X.J., Z.W. Du, E.D. Zarnowska, M. Pankratz, L.O. Hansen, R.A. Pearce, S.C. Zhang. "Specification of motoneurons from human embryonic stem cells". Nat Biotechnol. 2005. 23: 215-221.

Lois, C., and A. Alvarez-Buylla. "Proliferating subventricular zone cells in the adult mammalian forebrain can differentiate into neurons and glia". Proc.National Academy of Science. USA 1993. 90: 2074-2077

McCook, Alison. "UN Proposes Cloning Compromise". The Scientist. November 23, 2004. Accessed May 28, 2005. <http://www.the-scientist.com/news/20041123/02>

McDonald III., John W. "Mechanisms of Spinal Cord Injury and Repair". Washington University in St. Louis School of Medicine. Accessed May 31, 2005. Department of Neurology. June 1, 2005. <http://research.medicine.wustl.edu/ocfr/research.nsf/s/3B4119393F3FD1C786256ECC006616E6>

"Medical Dictionary: Graft". Medline Plus. February 4, 2003. Merriam-Webster, U.S. National Library of Medicine, National Institutes of Health, Department of Health and Human Services. Accessed May 17, 2005. <http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=graft>

"Medical Dictionary: Primitive Streak". Medline Plus. February 4, 2003. Merriam-Webster, U.S. National Library of Medicine, National Institutes of Health, Department of Health and Human Services. Accessed May 28, 2005. <http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=primitive%20streak>

Monohan, John J. "Stem cell override trumps veto: New law expected to lead to center". Telegram and Gazette. June 1, 2005: A1, A6.

"Morality" and "Ethics". Dictionary. 2005. Accessed May 28, 2005. <http://dictionary.reference.com/>

Morshead, C.M., B.A. Reynolds, C.G. Craig, .M.W. McBurney, W.A. Staines, D. Morassutti, S. Weiss, and D. van der Kooy. "Neural stem cells in the adult mammalian forebrain: a relatively quiescent subpopulation of subependymal cells". Neuron. 1993. 13: 1071-1082.

"Novel Stem Cell Trial In Heart Failure Patients To Begin At The University Of Pittsburgh Medical Center". Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 26, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/May_2005.htm#2>

Olsen, L and Malmfors. "T Growth characteristics of adrenergic nerves in the adult rat. Fluorescence histochemical and H-noradrenaline uptake studies using tissue transplantation to the anterior chamber of the eye". Acta Physiol. Scand. 1970. 348 (S1-S112).

Palmer T.D., J. Takahashi, F.H. Gage. "The Adult Rat Hippocampus Contains Primordial Neural Stem Cells". Mol Cell Neurosci. 1997. 8(6): 389-404.

Pickering, S., P. Braude, M. Patel, C.J. Burns, Virginia Bolton, S. Minger. "Preimplantation genetic diagnosis as a novel source of embryos for stem cell research". Reproductive BioMedicine Online (RBM). October 2003. Volume 7. Number 3. Accessed June 8, 2005. <http://www.rbmonline.com/4DCGI/Article/Detail?38%091%09=%201074%09>

Reichhardt, Tony, David Cyranoski, and Quirin Schiermeier. "Religion and Science: Studies of Faith". Nature. December 8, 2004. doi:10.1038/432666a. Accessed May 31, 2005. <http://www.nature.com/news/2004/041206/pf/432666a_pf.html>

"Remarks by the President on Stem Cell Research". The White House. August 9, 2001. Office of the Press Secretary. Accessed June 6, 2005. <http://www.whitehouse.gov/news/releases/2001/08/20010809-2.html>

Research Directions". National Institutes of Health, Department of Health and Human Services. 2001. Accessed May 17, 2005. <http://stemcells.nih.gov/info/basics/>

"Researchers Discover Specialized, Rare Heart Stem Cells In Newborns". Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 26, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/February_2005.htm#2>

Reynolds, B.A and S. Weiss. "Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system". Science. 1992. 255: 1707-1710.

Reynolds, B.A and S. Weiss. "Clonal and population analyses demonstrate that an EGF-responsive mammalian embryonic precursors is a stem cell". Developmental Biology. 1996. 175: 1-13.

Rickard, Dr. Maurice. "Key Ethical Issues in Embryonic Stem Cell Research". Department of Parliamentary Library. Current Issues Brief No. 5 2002-03. November 12, 2002. Information,

Analysis, and Advice for the Parliament. Accessed May 30, 2005. <http://www.aph.gov.au/library/pubs/CIB/2002-03/03cib05.pdf>

Roche E., M.P. Sepulcre, R. Ensenat-Waser, I. Maestre, J.A. Reig, B. Soria. "Bio-engineering inslulin-secreting cells from embryonic stem cells: a review of progress". Med Biol Eng Comput. 2003. 41: 384-91.

Schuldiner M., O. Yanuka, J. Itskovitz-Eldor, D.A. Melton, N. Benvenisty. "Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells". Proc National Academy of Science USA. 2000. 97: 11307-11312.

"Scientists Grow Critical Nerve Cells". Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 26, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/January_2005.htm#7>

"Scientists Make Major Advancement In Stem Cell Research"**.** Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 26, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/May_2005.htm#3>

Shamblott M.J., J. Axelman, S. Wang, E.M. Bugg, J.W. Littlefield, P.J. Donovan, P.D. Blumenthal, G.R. Huggins, J.D. Gearhart. "Derivation of Pleuripotent Stem Cells From Cultured Human Primordial Germ Cells". Proc. National Academy of Science. USA 1999. 95: 13726-13731.

Shannon, Thomas A. "Human Embryonic Stem Cell Therapy". Theological Studies. September 15, 2001. 62: 811-824.

Sleeboom, Margaret. "Stem Cell Research in China: An Intertwinement of International Finances, Ambition and Bioethics". IIAS Newsletter. November 2002. 29. Accessed June 9, 2005. <http://www.iias.nl/iiasn/29/IIASNL29_49.pdf>

Soria B., E. Roche, G. Berna, T. Leon-Quinto, J.A. Reig, F. Martin. "Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice". Diabetes. 2000. 49: 157-162.

Spiegel, Allen M. and Gerald D. Fischbach. "Testimony of Pluripotent Stem Cell Research". National Institute of Neurological Disorders and Stroke. April 26, 2000. National Institutes of Health and U.S. Department of Health and Human Services. Accessed May 19, 2005. <http://accessible.ninds.nih.gov/news_and_events/congressional_testimony/spieg_fisch_testimony.htm>

"Spinal Cord Repair". Spinal Research. Accessed June 5, 2005. International Spinal Research Trust. <http://www.spinal-research.org/display_section.asp?section=cord_repair>

"Stem Cell". Wikipedia, the Free Encyclopedia. May 21, 2005. Accessed May 19, 2005. <http://en.wikipedia.org/wiki/Stem cell>
"Stem Cell Basics". National Institutes of Health, Department of Health and Human Services. May 4, 2005. FirstGov. Accessed May 17, 2005. <http://stemcells.nih.gov/info/basics/>

"Stem Cell Treatment In Rats Improves Mobility After Spinal Cord Injury". Stem Cell Research Foundation. 2004. American Cell Therapy Research Foundation. Accessed May 25, 2005. <http://www.stemcellresearchfoundation.org/WhatsNew/May_2005.htm#1>

Sweeney, Kathleen. "Election of Pope Benedict XVI Welcomed with Delight by Pro-lifers". Editorial. National Right to Life News. May 2005. Outreach Department. Accessed May 29, 2005. <http://www.nrlc.org/news/2005/NRL05/PopeBenedict.html>

Thompson J.A., J. Itskovitz-Eldor, S.S. Shapiro, M.A. Waknitz, J.J. Swiergiel, V.S. Marshall, J.M. Jones. "Embryonic Stem Cell Lines Derived From Human Blastocysts". Science. 1998. 282: 1145-1147.

Titova, Nadya and Frank Brown. "Stem Cell Rip-off". Newsweek International. November 8, 2004. International Edition and MSNBC. Accessed June 1, 2005. <http://www.msnbc.msn.com/id/6370140/site/newsweek/>

Weckerly, Michele. "The Islamic View on Stem Cell Research". Rutgers University. Accessed May 29, 2005. <http://www.camlaw.rutgers.edu/publications/law-religion/new_devs/RJLR_ND_56.pdf>

Weiss, Rick. "'Parthenotes' Expand the Debate on Stem Cells". Washington Post. December 10, 2001: A11. Accessed June 5, 2005. <http://www.washingtonpost.com/ac2/wp-dyn/A18046-2001Dec9?language=printer>

Weiss S., C. Dunne, J. Hewson, C. Wohl, M. Wheatley, A.C. Peterson, and B.R. Reynolds. "Multipotent CNS stem cells are present in the adult mammalian spinal cord and ventricular neuroaxis". Journal of Neuroscience. 1996. 16: 7599-7609.

"What are stem cells?". American Federation for Aging Research. April 24, 2003. Accessed May 18, 2005. <http://www.infoaging.org/404.html>

"Why Cord Blood is the Premier Source of Stem Cells". Viacord, a Viacell Company. 2004. The Bone Marrow Foundation. Accessed May 18, 2005. <http://www.viacord.com/index.asp?p=206>

Wroe, David. "Australia backs stem cell ban call". The Age. March 10, 2005. Accessed June 8, 2005. <http://www.theage.com.au/news/National/Australia-backs-stem-cell-ban-call/2005/03/09/1110316091357.html?oneclick=true>