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Stem Cells and Society

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STEM CELLS AND SOCIETY

An Interactive Qualifying Project Report

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ABSTRACT

Stem cell research is a major source of both controversy and promise. The goal of this paper will be to provide an introduction to this complex topic, and to help dismiss some common misconceptions. Stem cells are not all alike, and each type has different ethical considerations. Adult stem cells (ASCs) have been medically used for decades in the case of bone marrow transplants, and have fewer ethical considerations than embryonic stem (ES) cells which usually destroy an embryo to obtain them. My analysis shows that three of the five major world religions believe that life begins before the day-5 embryo stage at which ES cells are obtained, and such embryos should not be destroyed. My analysis also shows that both ASCs and ES cells are capable of providing viable medical treatments, drug modeling systems, and disease modeling. Therefore, with such incredible potential, research regarding these cells will affect politics, litigation, moral views, and therefore society in general, worldwide.
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PROJECT OBJECTIVES

The objective of this IQP report was to discuss the topic of the controversial science of stem cell research and the effects of stem cell technology on society. The compilation of material was written to so that it can be easily understood, and taken from reliable sources to provide accurate up to date information. The purpose of chapter-1 was to describe the sources and types of stem cells. This chapter showed that there are a variety of different types, which provides a background to individuals unfamiliar with stem cells. The purpose of chapter-2 was to present a variety of uses for stem cells, in both animal experiments or in human clinical trials if available. Here the reader should gain insight as to what has actually been accomplished versus what remains in the future. The purpose of chapter-3 was to evaluate the ethics of stem cell science, including the ethical stances of various groups in our society. The purpose of chapter-4 was to examine the legal history of stem cells, as well as the current laws that govern research today. Finally, the author makes conclusions about stem cell technology.
CHAPTER-1: Stem Cell Technology

The Importance of Stem Cells

Stem cells represent an enormous opportunity for advancement in the scientific and medical communities. The study of stem cells gives a wealth of knowledge about how cells in the body are capable of differentiating into mature cells, how they react to various growth factors, how diseases develop, how to treat these diseases. As a contribution to medicine, stem cells have enormous potential, and are the basis for what some scientists argue is the medicine of the 21st century, regenerative medicine. Degenerative diseases such as Parkinson’s disease, ALS, and Tay-Sachs disease, to name a few, all involve the deterioration of tissues and organs, and can be fatal. Currently, certain degenerative diseases have some form of treatment options, however no cure exists for these. An example of such an affliction is Rheumatoid Arthritis (RA). RA is an autoimmune disease, meaning that the body is unable to distinguish its cells from foreign cells. The body then initiates an immune response to fight off what it assumes are invading cells. With RA, the body causes inflammation, typically but not limited to the cartilage within the body. This can cause extreme pain and even deformation. There is no cure for RA, however treatments can include steroids or anti-inflammatory medications. For this disease, among countless others, stem cells could potentially cure some of the most rampant, debilitating, and fatal medical conditions by regenerating damaged tissues. However in order to understand how such boasts are plausible, it is necessary to understand the physiology, location, and unique characteristics of stem cells, as a prelude to subsequent chapters on their uses, ethics, and legalities.
A Basic Understanding of Cells

As important as stem cells are, much of the terminology discussed within this project will relate to distinguishing stem cells from mature cells. So to allow for optimal clarity, a quick overview of cell physiology will follow.

The cell is considered to be one of the smallest living biological entities. The cell itself will begin as a stem cell, and from this it will differentiate, or mature, into a highly specialized cell. This specialized cell will interact with other cells of its kind to form a tissue, and a collection of tissues forms an organ, and a compartmentalized set of organs will yield an organism. So there is a hierarchy within the human body in which even the smallest contributor, being the cell, plays a vital role in the overall cooperation that allows our bodies to function efficiently. However, within each cell is a myriad of compartmentalized "machines" known as organelles. Each organelle has a specific duty in the cell that it must carry out for the cell to continue to live and perform its specific function (PDE Cell, 2009).

The composition of a cell can have an enormous effect on its physiology, and therefore the overall physiology of the tissue in which it resides. The cells in our body have their contents enclosed by a phospholipid bilayer, which can selectively allow certain molecules to enter or exit. This can occur pending solubility, size, or shape of the molecules, or with the aid of protein channels and transporters. One additional, and highly important feature of the lipid membrane is the membrane-bound carbohydrate and protein receptors present. These extend from the membrane to interact with various molecules. An example of this is an insulin receptor which, when bound to insulin, causes a cascade of events to unfold that allow glucose to enter the cell via a glucose protein transporter (Colorado State, 2009). Such receptors are often so precise that they specifically bind only one type of molecule and no other. The types of molecules located on
the surface and within a cell are critical in identifying specific cell types within the body. Often in order to isolate stem cells from other cells, they are sorted from undesirable cells simply by specific receptors present on their membranes.

**Types of Stem Cells**

Where do stem cells come from, and how are they different from each other and from other cell types? The greatest difference between a typical stem cell and a mature cell is that mature cells can no longer differentiate to another stage in development. Stem cells are unspecialized, so they have the ability to divide for long periods of time, and are capable of differentiating into more specialized cells. And contrary to popular belief, stem cells are not all alike. There are many types of stem cells within the body, and each type has its limitations, advantages, disadvantages, and location. However, stem cells can be divided into two main classes, somatic (adult) stem cells (ASCs), and embryonic stem (ES) cells (Stem Cell Basics, 2005).

When a sperm and egg fertilize, they form a zygote. This type of cell is referred to as a *totipotent* cell in that it can form any cell within the body and extra-embryonic tissues such as the placenta (Figure-1). As the embryonic cells begin to divide, cells through about the 8-cell stage remain totipotent. However, after several divisions occurring over approximately 3 to 5 days, the cells begin to specialize and are no longer totipotent. These newly specialized cells are known as embryonic stem (ES) cells that are *pluripotent* since they can divide into any cell in the body with the exception of extra-embryonic tissues, such as the various components of the placenta. Pluripotent cells are then further specialized to *multipotent* stem cells. These cells are typically located in a specific area of the body in order to replace dead or dying cells within
specific tissues. Hematopoietic stem cells (HSCs) are a good example of multipotent stem cells. They can form several types of blood cells, but do not normally differentiate outside the blood-forming pathway. Not shown in the figure are progenitor cells that are often *unipotent*, and are able to differentiate into only one cell type. Stem cell division is asymmetric. This means that they are able to divide into a cell identical to themselves, or into cells that are more differentiated (Stem Cell Basics, 2005).

**Figure 1: Diagram of the Various Levels of Stem Cell Potencies.** The highest level of stem cell potency is a totipotent cell (diagram upper center), which specializes into a pluripotent cell (i.e. ES cell), which specializes into a multipotent stem cell (i.e. hematopoietic stem cell), that ultimately differentiates into a variety of mature specialized cells (diagram lower). Also note the cyclic arrows present at each level, showing the asymmetrical division of cells so that the stem cell line can continue while differentiation can also occur. (Whitehead Institute for Biomedical Research, 2006)
Embryonic Stem Cells

Easily the most controversial aspect of stem cell medicine is the experimentation with embryonic stem (ES) cells. ES cells were originally discovered in 1981 in mouse embryos (Evans and Kaufman, 1981). The knowledge provided by subsequent studies eventually allowed for human ES cells to be derived from human embryos in 1998 (Thomson et al., 1998). The method in which ES cells are obtained requires a basic knowledge of the cellular differentiation process after fertilization has occurred. After approximately 3-5 days post-fertilization, the embryo is known as a blastocyst (Figure-2). This is comprised of 3 distinct features: the inner cell mass, the blastocoele, and the trophoblast. The inner cell mass is the group of cells that will eventually divide into the embryo. The blastocoele is the cavity of the blastocyst. The trophoectoderm is the outermost layer of cells that encapsulates the blastocoele and the inner cell mass. At the 3-5 day stage the blastocyst has not implanted itself upon the uterine wall.

Figure 2: Diagram of Early Human Embryogenesis. As an egg matures in the ovary (diagram center) it is released into the fallopian tube lumen (lower left), where it is fertilized by a sperm. The fertilized egg moves towards the uterus (diagram center), undergoing cell divisions. At the 5-day mark (center right), the embryo is a blastocyst. The inner cell mass is apparent and the embryo has not implanted into the uterine wall. (NIH Static Resources, 2009)
Since ES cells can differentiate into almost any kind of cells, they have great deal more potential than adult stem cells, whose differentiation is limited to the certain tissues. The issue with ES cell use is largely an ethical one, which will be discussed further in Chapter 3. However, it should be noted that the ES cells experimented on has largely been isolated from embryos created for reproductive purposes during in vitro fertilization (IVF). With donor consent, these excess embryos can sometimes be used for research purposes depending on laws regarding embryo use (which will be discussed in Chapter 4).

To use ES cells experimentally, egg and sperm are united in vitro, and the embryo is grown about 5 days to the blastocyst stage, then the inner cell mass is extracted. The inner cell mass is placed into a culture on a plastic dish containing nutritional supplemental broth in order to keep it alive and dividing, and a "feeder layer" which is a layer of differentiated mouse fibroblast cells which allows the inner cell mass cells to have a point of attachment. If the cells survive and continue to divide, the subsequent generations of ES cells are put into additional dishes so that more can be grown. If this culture process is successful for 6-8 months without cell differentiation, the cells are known as a "cell line" (National Institute of Health, 2005). The application of these ES cells will be discussed further in Chapter 2.

**Adult Stem Cells**

Adult stem cells (ASCs), also known as somatic stem cells, are multipotent and unipotent stem cells found in organs and tissues in adult organisms. This category basically includes all types of stem cells other than ES cells, and loosely includes umbilical cord stem cells. As mentioned before, their multi or uni-potency means they are capable of differentiating into the cells within the tissue it resides. They are located in highly specific areas of the body so that they
may be present to replenish those cell types. However, ASCs are typically quite difficult to acquire and grow in culture compared to ES cells. Therefore ASCs are critically important to the health and maintenance of the body, but are not nearly as versatile as ES cells.

Similar to ES cells, ASCs have asymmetrical division capability, in that they can divide into two cells, one of which is a stem cell, and the other is a more specialized cell. The cells they mature into will have a highly specific function depending on their origin. Sometimes the maturation process involves the production of progenitor cells that are one stage removed from end stage differentiated cells.

**Adult Hematopoietic Stem Cells**

Hematopoietic stem cells (HSCs) are the most characterized of all the stem cell types, and these cells have been investigated for over 50 years. After the bombings in Hiroshima and Nagasaki at the conclusion of the Second World War, it was found that individuals exposed to radiation could not regenerate sufficient amounts of white blood cells. White blood cells are critical in the body’s immune response to pathogens, and therefore with diminished immune systems many died from normally non-lethal infections. In the 1950s, this immunodeficiency was investigated with a series of radiation tests on mice. Mice whose bones were unshielded to radiation suffered from decreased immune response due to poor blood cell regeneration, while the mice with bones shielded from the radiation were unharmed. It was also found that when mice were injected with bone marrow cells from other mice, the mice that could not formerly produce blood cells were rescued from hematopoietic failure (NIH Stem Cell Information, Chapter-2, 2006).
Hematopoietic stem cells can differentiate into a myriad of blood cells (Figure 3). Granulocytes, such as neutrophils, basophils, eosinophils, and macrophages, are types of white blood cells necessary to fight infection. Platelets, also known as thrombocytes, derive from cells known as megakaryocytes, which reside in the bone marrow. These thrombocytes are essential for blood clotting to occur so excessive bleeding can be avoided. These important cells have an average lifespan of approximately 8-12 days, and therefore a compromised hematopoietic reproductive system would mean that the blood could no longer clot effectively after a relatively short period of time. The final type of blood cell is the red blood cell. The main function of this cell is to bind oxygen inhaled through the lungs, and deliver it to tissues within the body. These cells also have a finite lifespan, and live for approximately 120 days. Therefore it is imperative that all types of blood cells be replenished by hematopoietic stem cells (NIH Stem Cell Information, Chapter-2, 2006).

Figure 3: Diagram of Hematopoietic Stem Cell Differentiation. The hematopoietic stem cell (left center) differentiates into lymphoid or myeloid progenitor cells, which give rise to a variety of blood cells (diagram right). (ISSCR, 2009)
Though bone marrow has traditionally been the largest source of adult HSCs, other less invasive sources have also been identified that do not require anesthesia. The first method is saving the umbilical cord of an infant after childbirth. In recent years it was found that multipotent HSCs are present in cord blood (Viacord, 2007). This is a very useful option as the cord blood can simply be frozen and stored until required by the patient. Also, the blood will already be compatible with the same patient, so there will be less chance of the body rejecting the transplant.

Another additional method for acquiring HSCs is stimulating their release into the peripheral blood. These are known as mobilized peripheral bone marrow. The methodology of this will be discussed further in Chapter 2 of this paper, however it should be noted that the general method involves injecting the patient with hormones to stimulate release of HSCs from the bone marrow into the peripheral blood, where they are collected from an arm vein. This too is a useful approach that does not require painful isolation from bone marrow or anesthesia, and should not cause any compatibility issues as the source of blood is from the same patient.

**Adult Neuronal Stem Cells**

Neuronal stem cells (NSCs) are found only in two regions of the brain, and therefore are quite difficult to obtain. NSCs are capable of differentiating into three major cell types: nerve cells, astrocytes, and oligodendrocytes. Nerve cells, also known as neurons, are required for processing and transmitting electrical signal information within the body. Neurons make up the nervous system, which includes the brain, spinal cord, and peripheral nerves, and allow humans to relay information between the brain and all other parts of the body. Astrocytes are cells found in the brain and spinal cord. They are non-neuronal cells whose main function is to provide
nutrients to the nervous tissue, as well as repairing and scarring the brain upon injury. Oligodendrocytes, like astrocytes, are also non-neuronal cells. Their main function within the body is to insulate nerve cells. This is accomplished by forming a fatty layer around them, known as the myelin sheath, so that electrochemical impulses quickly pass from one nerve cell to another to make communication between the brain and the rest of the body efficient (NIH Stem Cell Information, Chapter-8). Diseases such as multiple sclerosis and transverse myelitis result from demyelination, and manifest with symptoms such as weakness of arms and legs, lack of coordination, and loss of dexterity (Mayo Clinic Foundation for Medical Education and Research, 1998).

Adult Cardiac Stem Cells

Cardiovascular disease has been the number one cause of death in America since 1900, with the exception of 1918 (with its unusual combination of deaths from WWI and a pandemic flu). When the heart suffers from a prolonged lack of oxygen, there is significant cell death and subsequent scarring of the heart. Currently the only treatment for this is surgery, however the heart is still often left misshaped, with thinning heart walls, and its pumping action is inefficient. However, as will be discussed further in Chapter 2, cardiac stem cells (CSCs) may represent a treatment for various heart conditions in which cellular regeneration needs to occur.

Only recently have scientists discovered that cardiac stem cells exist in the heart (Oh et al., 2003). For quite some time, scientists believed that the number of cells in the heart was an established number at birth. However patients who suffered from heart disease showed signs of minimal cell division and repair. The pools of cells found within the heart can give rise to multiple cell types important for heart function, including myocytes, smooth muscle, and
endothelial cells (Beltrami et al., 2003). Cardiac myocytes are a type of muscle cell that respond to the electrochemical impulses that govern heart rate to allow contraction. Smooth muscle typically forms hollow structures, such as heart arteries and veins, and is also capable of contracting. Endothelial cells form an interface between blood and the vein or artery walls surrounding it. Their main function is to aid in the speed with which blood is able to flow by reducing its turbulence.

**Adult Epithelial Stem Cells**

In the human body, epithelial cells line the surfaces and cavities of organs and structures while performing a wide variety of functions. The term epithelial can be subdivided into two main types: simple and stratified. Simple epithelial cells are only one cell thick and have four subdivisions of cells. The exact functions and uses of all of these types is beyond the scope of this paper, however a few examples can be explored. Cuboidal cells are a type of simple epithelium found in secretive tissues such as glands, as well as in germinal epithelium, which contribute to the formation of egg and sperm cells. Simple columnar epithelium is a cell type that lines the stomach and intestines and secretes mucous. Simple epithelium differs from stratified epithelium, in that simple has only one layer of cells while stratified has multiple layers. This allows for these stratified cell groups to have a stronger constitution than simple epithelium, and therefore are found in areas of the body in which chemical or mechanical stress to the cells can either be withstood (University of Nebraska, 1997). Being able to replace epithelial cells would have strong medical applications for treating burn patients, and disorders of organ linings.

The adult epithelial stem cells can be found in the skin itself, as well as within the digestive tract. The high rate of epithelial cell death requires frequent regeneration, and therefore
to maintain homeostasis within the body there must be a source to replenish dead and dying cells (National Institute of Health, 2005).

**Adult Mesenchymal Stem Cells**

Mesenchymal stem cells (MSCs) were discovered in the 1950s in bone marrow. These extremely versatile cells are capable of generating bone, cartilage, fat, blood, and fibrous connective tissue cells. Because of their strong multipotency, ease of isolation from bone marrow, and relatively few ethical concerns (no embryo is destroyed), MSCs have become a very hot topic of research in the stem cell field in the past few years (Jackson et al., 2007).

**Adult Intestinal Stem Cells**

Unlike the majority of adult stem cells in the body, which divide approximately once per month, intestinal stem cells divide rapidly every day. Hans Clevers of Hubrecht Institute-KNAW and the University Medical Center Utrecht, states that 200-300 grams of intestinal cells are created by the dividing of intestinal stem cells each day, and over a period of 5 days the intestinal lining is replaced in its entirety (ScienceDaily.com, 2009). The intestinal lining is made up of peaks known as villi, and valleys known as crypts. Intestinal stem cells are found in the crypts. These intestinal stem cells have the surface marker protein Lrg5, and are epithelial stem cells that give rise to absorptive cells, goblet cells, paneth cells, and enteroendocrine cells (Barker et al., 2007).

The absorptive cells are simple columnar epithelial cells, and aid in the transport of digestion and transport of molecules from the intestine. The goblet cells are another form of simple columnar epithelial cells that secrete mucous to lubricate the intestinal tract. The paneth
cells play a critical role in the protection of the adult intestinal stem cells. These cells possess the enzyme lysozyme, which is capable of destroying certain types of bacteria. The final types of cell produced by adult intestinal stem cells are enteroendocrine cells. These are a specific type of endocrine cell, which secrete various types of hormones involved in digestion (National Institute of Health, 2005).

**Adult Eye Stem Cells**

Stem cells within the eye are present in a variety of places, and continue to proliferate even into old age. **Figure-4** details the anatomies of the human eye to help understand where the stem cells are and what function they have.

**Figure 4: Diagram of the Anatomy of the Human Eye.**
With respect to stem cell location, the areas of focus will be the cornea (diagram left), the conjuctivia (a transparent tissue covering the sclera) (upper left), and the ciliary margin of the ciliary body (lower left). (ISSCR, 2009)
The cornea of the human eye is the outermost part of the eye. This part of the eye is subject to damage on a daily basis, and therefore requires a source of stem cells to replenish and repair the corneal cells. The area in which these stem cells are located is in the area between the cornea and the sclera, known as the limbus. The conjunctivia is the transparent tissue that covers the sclera. Its function is to secrete oils and mucous that lubricates and moistens the eye. Similar to the cornea, it is exposed to daily wear and tear, and as such, must be constantly replenished by stem cells. These particular stem cells are goblet epithelial cells, which excrete mucin. The ciliary margin of the eye is adjacent to the ciliary body. The ciliary body is a group of muscles that allows the eye lens to contract. The adult stem cells present in the ciliary margin are able to produce the mature cells of the retina, as well as the clear fluid that fills the front of the eye (Siegel, 2005).

**Parthenotes**

Typically for mammals, female eggs must be fertilized for division and embryonic development to occur. This is a necessary aspect in human physiology, as two pairs of 23 chromosomes are required for correct development. However, some animals, especially insects like bees and ants, can reproduce asexually, by stimulating egg divisions without fertilization. Parthenogenesis (virgin birth) does not normally occur in mammals, but the female egg can be tricked into not excluding its extra set of chromosomes during egg production, by using chemicals, that will be discussed in Chapter 2. Human parthenote embryos were first produced in 2001 (Cibelli et al., 2001). The tricked egg begins replication, and if the embryo can survive to the blastocyst stage, ES cells can be isolated. Since mammalian parthenote embryos cannot produce a baby, some ethicists argue the embryos have less moral status than IVF embryos, so
may be an alternative source for ES cells. Parthenote ethics will be discussed in Chapter 3 of this paper, to see whether these parthenote cells are indeed a solution to the controversial subject of ES cell use (Barry, 2007).

**Induced Embryonic Stem Cells (iES Cells)**

Induced embryonic stem (iES) cells are adult stem cells that, through artificial genetic manipulation revert back to an ES-like cell state. Human iES cells were first derived in 2007, by transfecting DNA encoding four transcription factors into skin fibroblast cells (Takahashi et al., 2007; Yu et al., 2007). The transcription factors induce the cells to a de-differentiated state. The technique was later refined down to two transcription factors (Kim et al., 2008), especially avoiding the use of the original c-Myc, which tended to make tumors. Because iES cells are produced from adult skin fibroblast cells, no embryo is destroyed (so the cells have fewer ethical concerns), and the produced ES-like cells are genetically identical to the skin cell donor, so the patient would not reject the ES cells. Because of these features, iES cells have become the hottest topic in all of stem cell research in the past two years.

Though it has been shown that these iES cells are pluripotent, it has not been shown if they have the full differentiation capacity of true ES cells. iES cells possess ES cell markers unique to ES cells. And they are capable of differentiating into 3 distinct types of germ layers. These layers are formed after the blastocyst stage of embryonic development, in which the inner cell mass undergoes a process known as gastrulation and forms into 3 distinct germ layers (the ectoderm, mesoderm, and endoderm). The ectoderm is the outermost layer of cells, and gives rise to the nervous system, sensory organs, as well as the skin. The mesoderm is the middle layer, and gives rise to bone, muscle, connective tissue, and the kidneys. The endoderm is the
innermost layer of cells and eventually becomes the lungs, and the digestive organs (National Institute of Health, 2005).

**Somatic Cell Nuclear Transfer**

Somatic cell nuclear transfer (SCNT) involves the removal of a nucleus from a skin fibroblast cell, and its subsequent implantation into an unfertilized female egg that had its DNA removed. Then the egg is chemically "tricked" into believing it had been fertilized, and it begins developing. As with parthenogenesis, the blastocyst inner cell mass is harvested, and ES-like stem cells are created. As with iES cells, ES cells prepared by SCNT are genetically identical to the patient from whom the fibroblast nucleus was obtained, so that patient would not reject the ES cells. But unlike iPS cells, this SCNT process destroys an embryo, and is a type of human cloning, so ethically it is not as advantageous as iES cells, and is outlawed in the U.S and internationally. This topic will be discussed in greater detail in chapter-2 and chapter-4 (Mollard, 2005).

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CHAPTER-2: Stem Cell Applications

Introduction

Now that the various types of stem cells has been discussed, a brief compilation of what has been accomplished with each type of stem cell can give us an idea of which applications have been, or soon will be applied to humans, and which applications are far off in the future. The examples discussed in the following sections are by no means an exhaustive list of the accomplishments occurring in the field, but they provide a basis for discussion of near term versus long-term medical promise, and allow a distinction between animal studies versus human clinical trials. And new advances are being made every day.

Stem Cell Differentiation

Chapter 1 introduced the idea that some stem cells can differentiate into any kind of cells in the body. However, what was not discussed was the means by which this occurs in cells, and this is an important topic for how stem cells would be used clinically to fight specific diseases. The cellular pathways by which cells specialize into mature cells are known as determination. Such a process is controlled by the action of genes (Yu and Thomson, 2006). When a cell becomes differentiated, genes are expressed that result in a pattern of protein production characteristic of a specialized cell. Usually the conversion is one way, with unspecialized stem cells giving rise to more specialized cells, however as discussed in Chapter-1, with iPS cells the treatment of some differentiated cells (skin fibroblast cells) with a combination of genes encoding two to four transcription factors can reverse the differentiation pathway to produce pluripotent cells (Takahashi et al., 2007).
In order to differentiate stem cells, usually external stimuli are received from surrounding cells. One type of stimulus is known as a growth factor. As the name implies, a growth factor is important in the stimulation of cellular growth, but they often also function in differentiation. Examples of such growth factors are hormones, which bind to receptors extending from the cell membrane to trigger a "cascade" of intracellular signaling which results in differentiation (Yu and Thomson, 2006; NIH Chapter-2, 2006).

**Graft Versus Host Disease**

When patients use their own tissue in a transplant, it is known as an "autologous graft." When a patient receives a transplant from another patient with similar histocompatible markers, it is known as an "allogenic graft." The advantages and disadvantages of each type depend on "graft versus host disease" (GVHD). GVHD is an autoimmune response by the patient to the transplanted cells, which can cause a variety of complications (Domen et al., 2006). When an autologous graft is employed there is no incompatibility, as the transplant is coming from the same donor. However, when an individual's health is too poor to provide a good graft source or the organ is too diseased, this autologous approach is not possible, so doctors usually attempt to find histocompatible donors for allogenic grafts. However, depending on the type of tissue needed, finding a donor with a histocompatible match for the patient can be quite difficult (Domen et al., 2006; NIH Chapter-2, 2006). With respect to stem cell use, the new type of iPS cells discussed in Chapter-1 would provide ES cells genetically identical to a patient and would provide a type of allogenic graft.
Adult Hematopoietic Stem Cell Applications

Adult hematopoietic stem cells (HSCs) are the most characterized of all the stem cell types, and have been used since 1957 in human bone marrow transplants to treat specific types of cancer (Thomas et al., 1957). As discussed in Chapter-1, HSCs have several hallmarks that allow them to be clinically useful. They can be obtained from bone marrow, cord blood, or mobilized peripheral blood, they readily differentiate in vivo into all types of blood of cells, and they rarely de-differentiate (which would form cancer) (NIH Stem Cell Information, 2006). Marker proteins have also been identified for HSCs (CD34) that allows HSCs to be isolated from cell mixtures with relative ease (Negrin et al., 2000).

In human patients, HSCs have been used to treat leukemia, lymphoma, bone marrow failure, aplastic anemia, thalassemia, sickle cell anemia, and a variety of autoimmune diseases (BMT Success Stories, 2006). Such treatments are very desirable in developing countries as one shot treatments are much more financially feasible than chronic therapy (Bordignon, 2006). In 1995 alone 40,000 bone marrow transplants had occurred worldwide (NIH Stem Cell Information, 2006). Thus, providing examples of stem cell therapy using HSCs is a very strong response to criticism that human stem cell applications remain far in the future (Earll, 2005).

In addition, non-traditional HSC applications have been tested in which the plasticity of HSCs is used to treat non-blood disorders. For example, human umbilical cord HSCs has been used to treat Alzheimer’s disease mice to reduce senile plaque formation (Nikolic et al., 2008). Alzheimer’s disease is the most common type of progressive dementia. It has been characterized by the deposition of a plaque of molecules known as amyloid-β (Aβ). Aβ is thought to be a key cause of neuron degeneration in the brain. The use of HSCs to partially restore brain cells in an Alzheimer’s mouse model is a great step forward in the treatment of Alzheimer’s disease.
Another example of non-traditional HSC applications is the treatment of spinal cord injuries. In a testimony given by physician and neuroscientist Michael Lévesque, the spinal cord patients treated with HSCs have shown significant improvements (Levesque, 2005).

Treatment of Parkinson’s Disease

Parkinson’s disease (PD) is a degenerative disease that affects the substantia nigra area of the brain. It is not yet known how it initiates, but PD can cause an impairment of motor control, speech, and other bodily functions. These symptoms arise because the brain cells that produce a chemical known as dopamine begin to die. Dopamine is a neurotransmitter necessary for communication between the body and the brain, functioning in speech and coordination. Patients with advanced stages of Parkinson’s disease have 80% less dopamine in their brain cells than the average healthy individual.

Adult neuronal stem cells (NSCs) are present in the brain, and are remnants of stem cells that have existed since the fetus began developing that organ. NSCs actively divide to replace dead cells when the body has undergone trauma. However, as discussed in Chapter 1, these stem cells are only located in a few sections of the brain, so one of the greatest challenges is to obtain them without incurring any brain damage, or to obtain them from cadaver sources. So far, experiments have been performed on rodents and primates with either adult NSCs or ES cells to attempt to treat models of degenerative diseases such as amyotrophic lateral sclerosis (ALS), Huntington’s disease, and Parkinson’s disease. Eventually NSC applications could also be used on patients who have suffered from spinal or cranial trauma.

With respect to cell therapy treatments, most of the early work was performed on rat models of the disease. An improvement in symptoms was achieved in rat models treated with
adult NSCs (Studer et al., 1998); ES cells (Bjorklund et al., 2002; Kim et al., 2002), or NSCs derived from ES cells (Ben-Hur et al., 2004). Before their treatment the rats were unable to make side steps, and would turn continually. After treatment these symptoms were significantly reduced. Upon a post-mortem examination it was also found that the injected stem cells had differentiated into dopamine producing cells (Ryan, 2004). With respect to human PD patients, substantial work has been performed with fetal tissue transplants (Madrazo et al., 1988; Lindvall et al., 1989; Freed et al., 2001, Mendez et al., 2002), but none of those studies directly used stem cells, and the public has strong opposition to using fetal tissue in experiments. However one study has demonstrated that human ES cells are capable of differentiating into dopamine-producing cells (Perrier et al., 2004).

**Spinal Cord Repair by Stem Cells**

Embryonic stem (ES) cells have been used to treat spinal cord injuries in rat models, but as of 2009 are only now in human clinical trials with spinal cord patients. The first evidence that transplanted ES cells survive, differentiate, and promote recovery in rat models was provided in 1999 (McDonald et al., 1999) who showed partial recovery in an injured rat model. This initial study was subsequently verified in 2004 in an injured rat model (Harper et al., 2004; Stem Cell Treatment, 2004), and by a series of rat studies in 2005 (Keirstead et al., 2005; Nistor et al., 2005; University of California, 2005). In all these studies, the best results were obtained in those rats who received the transplants soon after the injury, as those rats had not formed scar tissue yet. The injected ES cells migrated to the injured area of the spine, differentiated into mature oligodendrocytes, and within two months the rats showed significant improvement in walking.
With respect to human spinal cord patients, in January of 2009 the FDA approved the first clinical trial of ES cells to treat spinal cord injuries. Data was provided to the FDA from the rodent experiments to help approve the protocol, and it currently is in phase I, meaning that the safety of the treatment will be the main concern, not efficacy. The patients accepted into the trial had their injuries occur within 7-14 days, as there is no evidence that stem cells can be an effective treatment after this point in the recovery process. Though this clinical study will require quite some time to obtain efficacy data, it is a great leap forward for stem cell therapy (New York Times, 2009).

**Stem Cell Treatment of Heart Failure**

According to the National Institute of Health approximately 2,600 Americans die each day from cardiovascular disease (NIH Stem Cell Information, 2006). Symptoms can include hypertension, coronary heart disease, stroke, and congestive heart failure. These can cause scarring within the heart, a thinning of the cardiac walls, and it becomes misshapen. Heart surgery can provide treatment, however the heart is often left with a much less efficient pumping system. A heart transplant is another means of correcting this problem, however donor hearts are very difficult to obtain.

Stem cell experiments for treating heart attacks are based on animal experiments that are too numerous to go into here. With respect to human studies, human ES cells have been shown to be capable of differentiating into cardiac lineages (Kehat et al., 2001), and so have human adult cardiac stem cells (Beltrami et al., 2003). Human heart attack patients have been treated with adult cardiac stem cells or skeletal myoblasts (NIH Stem Cell Information, 2001; Britten et al., 2003) and with bone marrow stem cells (Lunde et al., 2006; Schachinger et al., 2006). In the
2001 patient experiment using adult skeletal myoblast injections, after approximately five months the heart showed more efficient pumping and improved tissue health. Thus in the presence of these injected myoblasts, repair and differentiation occurred, but this does not necessarily mean it is due to the differentiation of the myoblasts.

There is some information on treating a human patient with ES cells, although this information did not appear in a refereed medical journal. In 2003, while attempting home repair, a 16-year-old boy was shot in the heart with a nail gun. He was taken to the hospital and underwent heart surgery, during which he had a heart attack. In order to survive he required a heart transplant or an experimental stem cell procedure. He chose to try the stem cell procedure. His heart was injected with human embryonic stem cells and this therapy continued for 5 days. On the fifth day he was considered recovered enough to be allowed to return home (Philipkoski, 2003).

**Stem Cell Treatment of Diabetes**

Over 700,000 Americans suffer from Diabetes Mellitus, also known as Type 1 diabetes. This is an autoimmune disease that destroys the body's pancreatic islet beta cells (Norman, 1997). These cells produce insulin, which allows sugar to be taken into cells from the bloodstream. Without insulin the body suffers from hyperglycemia. Classic symptoms of this include frequent urination, thirst, and hunger (Norman, 1997). Prolonged hyperglycemic conditions can lead to cardiovascular disease, stroke, or kidney failure. Typically, injections of insulin are given to regulate the blood glucose levels; however transplants of the pancreas or islet cells can treat the problem. The primary obstacle with this approach is the lack of donors and rejection of
transplantation. Aside from donor tissue however, there is no cure for the disease (Suheir et al., 2001).

Though it is debated within the field of stem cells, it is largely believed that progenitor cells can differentiate into insulin producing beta cells exist with the pancreas. However the mechanism by which these cells can be stimulated into producing more cells and differentiate is not known. Progenitor cells are also not being produced at a rate fast enough to combat the destruction of beta cells, and therefore diabetes is still quite rampant. So as possible therapies, ES cells are being tested. A study published in Diabetes, an American Diabetes Association journal, showed that when human ES cells were examined in vitro they differentiated into a variety of cells including cells with characteristics similar to that of the insulin-producing beta cells (Assady et al., 2001). When these cells were isolated they secreted insulin into the medium. These differentiated ES cells also possessed the same unique markers as beta cells (Assady et al., 2001).

There have also been reports that adult stem cells within the liver, spleen, central nervous system, and bone marrow can be treated with specific growth factors in order to coax them into differentiating into insulin producing beta cells. By culturing these cells they could theoretically be given to patients either by direct transplant into the pancreas, or through the blood stream in the hope that they will get to the pancreas. As described prior, each of these methods has its advantages and disadvantages, but even if this is successful it will not alone cure the disease. Since type-1 diabetes is an autoimmune disease the body will still target and destroy these cells. Therefore controlling the immune response of the body is a critical factor in the success of stem cell transplantation for autoimmune diseases like diabetes. It has successfully been shown in mice however that the immune response can be stopped by transplanting bone marrow into a
human that was diabetes resistant. This allowed for the T-cells which attacked the beta cells to eventually be replaced by the new blood cells that did not cause any immune response (Goldwaithe, 2006).

The Use of Stem Cells in Gene Therapy

Gene therapy entails the elimination of a faulty gene, or the reparation or reactivation of a necessary gene. For example, cystic fibrosis is a heritable disease in which the mucous of the lungs becomes dense and thick, making it difficult to breath. The cause of this potentially fatal disease is a single faulty CFTR gene with only one mutated amino acid. Such a small change in such a vastly complex protein shows how important it is that our genes be functional (National Heart Lung and Blood Institute, 2009).

Gene therapy can be performed by direct DNA transfer into a patient, or by DNA transfer into stem cells. As to delivering DNA to cells, this can be accomplished by making a vesicle package constructed from the same materials as our body's cellular membranes. Genes can be packed into these vesicles and delivered into the body through the bloodstream and into a target cell. Viruses can also be used to deliver DNA to cells. The viruses are genetically altered to be benign and not cause any sort of disease but carry the treatment genes. Once the genome of the specific stem cell has been permanently altered, it will divide, and in that division the new genetic material will be present in the new cells.

Adult hematopoietic stem cells can be selected with genetic markers such as CD34, and can be manipulated in vitro to take up DNA for therapy, and then subsequently perfused into a patient. Mesenchymal stem cells can also be used. These cells are found in the bone marrow, and are capable of forming cartilage, bone, and adipose cells. The first successful clinical trials
treated monogenic (treatment of only 1 gene) disorders, such as cystic fibrosis or SCID (when the lymphocyte system has a defect).

The largest danger in treating disorders with gene therapy is activating an adjacent or nearby gene that could potentially cause cancer, known as an oncogene. These genes are typically dormant, however the activation process and location of these genes is highly complex and not entirely understood. Therefore in order to attempt to be as informed as possible, scientists from a variety of fields, such as genetics, virology, and biochemistry, work together. But it is clear that there is great promise with this field both now and in future studies to come.

Chapter-2 Conclusions

Stem cell research has had many real world successes in both humans and animals. Yet of the potential stem cells have is not even close to being reached. Understanding of stem cell differentiation pathways, migration through the body, and safety issues, are all aspects of research that have yet to be fully documented. Once all of these are thoroughly understood stem cells should provide almost limitless potential in the field of regenerative medicine.

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Chapter-3: Stem Cell Ethics

Introduction

Since their discovery, embryonic stem (ES) cells have gathered more attention than any other kind of stem cell. This is because an in vitro fertilized (IVF) egg approximately 5 days into development must be destroyed to obtain the inner cell mass containing the ES cells. This process is considered by many factions to be the destruction of potential life. Others believe life has not yet started at that point. Depending on one’s moral and possibly religious viewpoint, the ES cell debate is a debate about whether the fertilized egg has the same rights as a person.

But this is not the only ethical issue in stem cell research. The development of parthenotes and iPS cells as alternative sources of ES cells have entered the debate. As outlined in Chapter 1, parthenotes are female eggs that use a second set of genetic material within them to begin embryonic development. This presented what many hailed as a solution to the embryonic stem cell debate, as there is no true fertilization, and therefore no life to protect. Opposing this however is the idea that in the future scientists could figure out how to allow parthenote embryos to develop into a viable life form, and therefore is no different than embryonic stem cell research. iPS cells are ES-like cells induced from skin fibroblast cells. This process does not involve an embryo at all. The last issue that will be discussed is therapeutic cloning, also known as somatic cell nuclear transplantation (SCNT) as a method to produce stem cells. SCNT produces ES-like cells by removing genetic material from the female egg, followed by the transplantation of DNA from an adult donor cell. The zygote believes it has been fertilized and undergoes embryonic development, and can have its ES cells retrieved in much the same way as with IVF embryos.
There is much to debate and many misconceptions that should be fully explored and understood before taking a stance. Though this paper cannot possibly depict every viewpoint, it will provide the necessary information so that one can come to informed conclusions. At the end of each section I will provide my own viewpoint, which is by no means a correct one, and serves only to provide an additional argument.

**Kantianism V. Utilitarianism**

A great deal of the stem cell debate comes down to two opposite philosophies. The first is known as *Kantianism*, and is named after the 16\textsuperscript{th} century philosopher Immanuel Kant. He felt that when it comes to our actions, *intent* is all that matters. It is not the end point of our actions that decides if we have acted morally, but the intent upon which we act that defines it. He also felt that as individuals we have certain rights that absolutely cannot be infringed upon. Kant justified this by speaking of two types of worth: Price and Dignity. Price is something that can be exchanged for something of equal value. Dignity is something that has intrinsic and incomparable value, and therefore has inherent rights. The only way it could be moral to disregard these rights however, would be if consent were given. For example, if there were to be a situation in which one person would be sacrificed against their will to save many, a Kantian would say that this is morally wrong and that we must respect that individual’s inherent rights. However if consent were given it would no longer be considered morally wrong (McCormick, 2006).

The opposing argument is known as *Utilitarianism*. The fundamental belief is that the morality of a decision is based on the worth, or *utility*, of the end result. Therefore it is not important what the intent of the action is; only the *overall gain*. It is a very mathematical idea
that can easily be compared to a business model. The principle by which they judge gain is known as the Greatest Happiness Principle. This states that an action will be moral if the greatest amount of good is provided for the greatest amount of people. In this case, if a person were to be sacrificed to save many, a Utilitarian would sacrifice that person so that the greatest number of people would be saved at the expense of one (McCormick, 2006).

These two philosophies obviously have very different views of what is moral and what is not. Each has a very reasonable viewpoint when applied to a variety of situations. Hopefully this background will be an adequate guide in discovering where one stands on the position of stem cell research (McCormick, 2006).

**Ethics of Embryonic Stem Cell Research**

When the egg has been fertilized, whether done via normal human reproduction or *in vitro*, after 5 days it forms the blastocyst. At this point the embryo is approximately 100 cells, unattached to the uterine wall if fertilized by regular human reproduction, and the inner cell mass of the blastocyst must be extracted to harvest the ES cells. Should they survive the culturing process these ES cells can form into almost any kind of cell in the body. This is potentially one of the most powerful tools in regenerative medicine in our possession.

So why would anyone object to the use of this? This is objected to because this is quite often perceived as the destruction of human life or the destruction of *potential* human life, depending on when an individual believes life begins. Moreover, according to stem cell research experts, there is a large chance that a patient will not be compatible with or accept the ES cells. Therefore to account for the large number of diseases they can treat, and the number of different types of resistance to transplants, over four million human embryos would have to be destroyed.
to generate the number of cell lines necessary (Doyle, 2007). Although such high numbers of ES cell lines diminishes down to one if one uses iPS cells or SCNT where the donated ES cells would be genetically identical to the patient.

In order to better understand exactly what specific arguments are, the various religions, proponents, and objectors will be outlined here. Although the religious views explored are documented opinions and official stances of various religious leaders or law, it by no means speaks for the entire population of that religion.

**Judaism**

Jewish law believes that an unborn child does indeed have the potential for human life. Yoel Jakobovits of Johns Hopkins University Medical School attests that they do not believe that life begins at the moment of conception. Rather, once the fetus has the means to become a viable it has potential for life, and cannot be aborted for the purpose of stem cell research. This means that while the embryo has not attached itself to the uterine wall it is cannot develop into a viable fetus, and therefore Jewish law has no opposition to harvesting the embryo for research (Castillo, 2006).

**Hinduism**

Although there appears to be a consensus that for Hindus life begins at conception (*in vitro* or *in vivo*), there is no consensus among Hindus concerning ES cell research. For many the destruction of an embryo is a terrible act to commit, and there will be karmic retribution. For others it is ethically permissible to destroy an embryo if it spared the life of the mother. There is yet another group within these groups who have a bit more of a utilitarian viewpoint and feel that
it is should at least be considered, due to the overwhelming promise stem cells possess should the research be successful. Though it should be noted that the latter group also is aware that the extent to which we are willing to help those at the costs of others is not clear (Castillo, 2006).

Christianity

One of the most vocal branches on ES cell research has been the Catholic Church. Just as the Hindus believe life begins at conception, so do most Catholics. Because of this, they feel that in order to potentially help others at the expense of a human life is morally wrong. The Catholic Church has been opposed to similar types of research, such as IVF since its first success in 1978 (Deech, 2008).

Given that the Catholic Church believes the embryo is potential life at the blastocyst stage, the Catholics act as Kantians in that the individual embryo has rights, and the embryo cannot give consent to its own destruction (Castillo, 2006). In 2006, Pope Benedict XVI stressed that the church must draw a distinct ethical line against this type of research, as it does not respect the "dignity of the human person." He further mentioned it to be "not only devoid of the light of God, but also devoid of humanity" (Pope Benedict XVI, 2007).

Outside the Catholic Church, a number of other Christian groups are actually in favor of ES cell research. Some Protestants, such as the American Presbyterian Church, believe that ES cell research is ethical if it results in new medical therapies (Teaching About Religion, 2006). The Episcopal church believes the early embryo is not a viable human being until the fourteenth day post-fertilization when the primitive streak forms (i.e. when the spinal cord begins to develop) (Kohsl, 2008). In general, most Protestants hold that ES cell research should be limited
to embryos less than 15 days old, obtained by consent from discarded IVF embryos (Teaching About Religion, 2006).

*Buddhism*

The Buddhist stance on ES cell research is not a clear one. Roland Peters of the Diamond Way Buddhist Center says that though life begins at conception, until the fetus has attached to the uterine wall, it does not have a mind. Therefore if it does not have a mind, it is not immoral to use the early embryo experimentally. However not all Buddhists share this opinion, and Peters remarked that only one such as that Dalai Lama could give a definitive answer (Castillo, 2006).

*Islam*

The argument about when human life begins is not the main focus of debate within Muslim circles. Imad-Ad-Dean Ahmad of the Minaret of Freedom Institute explains that life does not necessarily begin at conception. At the 4-month period in pregnancy it is believed that the fetus receives its soul. Therefore Islamic Law does not object to the use of ES cells for research (Castillo, 2006).

*Ronald Green*

Ronald Green, a professor of the study of ethics at the Dartmouth Ethics Institute, believes that religion should not have any influence on the stem cell litigation. He feels that religious groups act unjustly and disrespectfully when they impose their particular and non-publicly shared moral beliefs on others (Green, 2001). This means that while various religious sects have a right to an opinion, this should not affect the laws that we have in place. The
reasoning behind this opinion is that there is meant to be a fundamental separation of church and state within the United States in order to allow for religious tolerance, as well as a protection of our freedom to think independently. Therefore, no one religion that has gained a majority will enact laws that govern those of other religions.

Guido de Wert and Christine Mummery

Guido de Wert and Christine Mummery work for the Institute of Bioethics, and the Netherlands Institute of Developmental Biology, respectively. Concerning the ethics of ES cell research, they pose a few unique positions as to whether we can consider the inner cell mass of the blastocysts as life, or whether it can be dubbed potential life. They suggest that when the inner cell mass is removed, it does not cease to be an embryo; it simply ceases to have the specific nourishment provided by the trophoblast (ectoderm) of the blastocyst. This can be considered analogous to removing the yolk from the egg of a chicken. The argument posed by Mummery and de Wert is that without specific growth factor nourishment, ES cells have no potential for life, and therefore should not be treated as such (de Wert and Mummery, 2003).

Another point that these authors make is that the blastocyst is never guaranteed life, not all eggs successfully attach to the uterine wall. This information about survivability simply cannot be known at the 5 day point, and therefore they argue that without such knowledge a 5 day old embryo should not be attributed moral status. By this logic a woman’s oocyte as well as a man’s sperm should all be given moral status as they all have the potential for life. This would also imply that any contraceptive device would be inherently immoral as it blocks life. Because a 5 day old embryo has not yet chosen a specific developmental pathway, de Wert and Mummery argue that until the 14 day point, the embryo can still choose to become more than
one child and that without any sense of identity it cannot be afforded moral status (de Wert and Mummery, 2003).

Their final argument is that the intent of the research is very important. This means, for example, that if the destruction of embryos in order to treat infertility in couples is successful, then it is morally sound. This represents a utilitarian argument as to whether the potential good from ES cell research can outweigh what many perceive to be the death of a living organism (de Wert and Mummery, 2003).

*John Robertson*

John Robertson wrote an article in *Nature Reviews: Genetics*, about his view on ES cell research. He divided the objectors into two groups, and kept the proponents in one group. The objectors are first categorized as people who believe the embryo is in fact a person who deserves rights. This implies that the use of embryos for research purposes would be considered murder. The second group of objectors is those who believe the embryo is not yet a person, but they have the potential to be. This view argues that even if the 5 day old embryo is potential life, using it leads to a slippery slope in our appreciation for the sanctity of life, so its use should be avoided. Robertson then described the proponents for ES cell research as those who simply view the blastocyst nothing more than a collection of cells. Such people would attempt to turn the tables on those who say that our appreciation for human life is waning by asking: what kind of a society protects a mass of cells that are not guaranteed to become life, when their potential use is going to greatly benefit the people who are alive now (Derbyshire, 2001)?
Author’s Input on ES Cell Research

I believe that the issue of ES stem cell research is about the value of human life. If you feel that life does not begin until an infant is born and capable of living on its own, then it is likely you would not have any issue with ES cell research. Also if you do respect human life, but take a utilitarian point of view and feel that the sacrifice of some to help the majority is acceptable, then you also would have very little problem with this type of research. If it is your belief that life begins upon conception (Kantian category), then you may have an objection to this and view it as murder. The debate truly focuses on when human life begins, and what sort of intrinsic worth we can assign to a 5 day old embryo.

My personal view is that the potential for life is not life, and we should not attach high moral standing to the potential for life. If we assign potential life as worthy of moral status, then all sperm and egg should be afforded this status. With this in mind, it would be murder donate sperm or eggs to a fertility clinic while knowing that only a small chance of these cells will actually become a child. Such cells can also form life even without somatic cell nuclear transfer, and therefore will form a viable fetus. Some may argue that it is the intent to create life that justifies donating sperm and egg cells while knowing that not all that are fertilized will become fetuses. Therefore this is a clash between a Kantian and Utilitarian view, in that you cannot say life is sacred, begins upon conception, and that it is still morally acceptable to destroy many fertilized egg for the success of one.

As far as sources of embryos to derive ES cells, I believe that IVF embryos created for research or reproductive purposes, as well as aborted embryos, are all acceptable means of obtaining ES cell lines. I abide by the notion that life truly begins when the fetus is clinically viable by itself. This means that should the mother give birth or undergo a Caesarian Section,
the child would be capable of living on its own. However, this is not quite as cut and dry as it may sound. With technology growing so sophisticated, it may one day be possible to have a 5-day embryo survive outside the mother keeping it alive only with machinery. Should this one day become a reality my ethical position may need to be re-evaluated.

Parthenotes: Is “Virgin Birth” an Ethical Solution?

Parthenogenesis is the artificially induced cell division of an oocyte using a second identical set of chromosomes within the egg. An egg is treated with a chemical, such as strontium chloride, to stimulate the retention of the normally discarded second set of chromosomes, and to begin cell division. This “virgin birth” is considered by some to be a unique solution to the ES cell debate, as this would produce an embryo clone of the woman from which the egg came. It is not known whether this will create a viable embryo, as scientists currently can only grow human parthenote embryos for just a few cell divisions (Cibielli et al., 2001).

SCNT is a similar idea, since a nucleus from a somatic cell is injected into an enucleated egg, however the difference is that with SCNT the embryo might be capable of surviving if implanted into a uterus. SCNT creates an embryo with the same genetic material as the donor, and in this case the nucleus donor could be either male or female, while with parthenogenesis the donor is only a female. Since there is no uniting of a sperm and egg in either process, some deem this as a lack of true fertilization and therefore it is not morally wrong.

For parthenogenesis, because no chemically stimulated egg has ever been implanted into a uterus, there is much ambiguity concerning whether this could produce a viable fetus, and many are reluctant to take a firm stance. The Roman Catholic Church for example has not
officially embraced or opposed this idea, as they are not convinced whether a parthenote embryo has the potential for life. Kevin Fitzgerald, a Jesuit Priest and Geneticist, feels that because human parthenogenesis does not occur naturally, such an embryo does not have high moral status. In 2005, the United States Presidential Council of Bioethics said that human parthenote embryos are “assumed by most commentators to lack entirely the potential for development as a human being.” Therefore it will be some time and require a greater understanding of the parthenogenesis developmental pathways before any conclusions can be made (Barry, 2007).

With respect to SCNT, the process is also known as “therapeutic cloning” because it uses the same DNA as the donor to create an embryo. One worry that the HUGO Ethics Committee has outlined is the slippery slope from therapeutic cloning (to create ES cell lines from blastocyst embryos), to reproductive cloning (creating viable embryos for implantation into a uterus). Reproductive cloning was used to create life, such as Dolly the sheep. Some argue it could be used to create early life for the donation of various organs should the patient require some sort of transplant in their life. Reproductive cloning is currently outlawed in all countries (to be discussed in Chapter-4).

Obviously since it is not known whether these two processes can produce viable human embryos, it is difficult to take a firm ethical stance. However important points to consider are: 1) is it right to create embryos from somatic cells to obtain ES cells, 2) is it morally right to clone humans, 3) can cloned fetuses have the same rights that adult humans do, and therefore is it morally right to keep clones for the purposes of transplantation. Such ethical queries are not easily answered, and until this technology is better understood it may be prudent to be very cautious of their applications (Hugo Ethics Committee, 1999).
Author Input on Parthenotes and SCNT

Concerning parthenotes, I feel that if it is discovered that these cells cannot possibly become viable fetuses, we should not assign them the same rights and dignity of normal embryos. However until that time, they should be afforded the same moral value as IVF embryos, as they are still potential life. As stated previously, I do not consider potential to life to be life, and therefore feel that both IVF embryos and parthenotes are morally acceptable means of obtaining stem cells.

With respect to SCNT therapeutic cloning, I have a similar stance. Though an egg is fertilized with the same genetic material as the skin cell nuclear donor, I see it as no different than any embryo, and therefore I apply the same arguments as for ES cells. The fact that a sperm did not unite with the oocyte does not change the fact that the embryo is developing and could potentially become a human life, but as I said before, I do not believe the potential for life is life and therefore a SCNT embryo does not deserve the same dignity and rights we enjoy.

As for reproductive cloning, I feel this is a topic beyond the scope of the paper, as it does not involve the use of stem cells. However I included it as a potential "slippery slope" result of therapeutic cloning discussed above that one should be cognizant of, and I note that it is currently illegal in the U.S. and elsewhere.

Induced Embryonic Stem Cells: A Possible Answer to the Moral Dilemma?

One large misconception is that many religions, especially the Catholic Church, are against all stem cell research. In fact, Catholics have been quite vocal about their support of adult stem cell research, especially in the case of induced ES stem cells. This method involves taking a mature skin cell and, using genetic manipulation, revert it back to cells that have many
characteristics of ES cells. It should also be noted that these iPS cells cannot form oocytes or sperm, and therefore do not have the potential for life. Dr. Marie Hilliard of the National Catholic Bioethics Center remarked, “From both a practical and moral perspective this advance represents a significant benefit over ES cell research” (Doyle, 2007).

The only problem with this is that scientists have yet to prove that iPS cells have the same medical potential as embryo derived ES cells, so it may be years in the future before we know whether such cells will be as useful as ES cells. So for now, ES cells remain the most versatile stem cells. Initially there was a high tendency of iPS cells to become cancerous and grow tumors, but recently omitting one of the four inducing transcription factors, c-Myc, has considerably minimized tumor formation (Kim et al., 2008). Still for now, the best therapeutic option remains ES cells (Doyle, 2007).

Author’s Input on iPS Cells

I feel that this is a technique that is still in its infancy as far as becoming therapeutic. However scientifically, this appears to be the best solution to the ES cell debate. As I am not morally opposed to using ES stem cells, I do place great weight on finding alternatives to ES cell use, such as parthenotes or iPS cells. I feel that ES cells should be used while iPS cells are being studied. However I understand the vehement moral objection others have to ES cells, and therefore unless some sort of consensus can be reached, ES cells should not be created when such a promising alternative as iPS cells is present.
Chapter-3 Conclusion

I do admit that much of what I believe could easily change as more is learned in the field of ES cell research. I encourage all readers, as well as myself, to continue to keep up to date and not to claim one position steadfastly. Rather, keep an open mind and hear each case presented and then judge it on its own merit.

Chapter 3 Works Cited


Chapter-4: Stem Cell Legalities

Introduction

When science and new technology begin to pose ethical issues, it is important to regulate and monitor it. In the U.S., although the government has never outright banned ES cell research, federal funding has been withdrawn in a variety of instances to dissuade the derivation of new ES cell lines and the destruction of new embryos. Embryo legislation has been in place in the United States since 1974, and continues to change with each new presidency. In this chapter, a short summary of important U.S. legislations will be provided, followed by a brief discussion of international policies.

U.S. Embryo and Stem Cell Policies

Early U.S. Embryo Policies

On July 12, 1974, a ban on all federally funded research was instated for those using fetal tissue. The ban was put in place until the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research could examine the types of research being done and create guidelines by which to regulate it. The purpose of this ban was to prevent the mistreatment of human subjects during scientific or medical research. In 1975, an Ethics Advisory Board was established to oversee research on fetal tissue originating from abortions. With the development of in vitro fertilization (IVF) in 1978, the Ethics Advisory Board recommended that the board receive federal funding to investigate the safety of this new IVF technology. However by 1981, newly elected President Ronald Reagan did not renew the charter
for the Ethics Advisory Board, so the earlier 1974 ban on federal funding for embryo research continued (Stem Cell Tracker, 2009).

In 1988, a Human Fetal Tissue Transplantation Research Panel voted 18-3 to approve federal funding of embryo research, however under the conservative President Reagan, the panel was unsuccessful in overturning the 1974 ban. The senate testimony of several conservatives in the Department of Health and Human Services helped the ban continue, by arguing that federal funding for embryo research would increase the number of abortions in the country, which would be unethical. In 1990, when congress attempted to overturn the ban on funding, the legislation was vetoed by President George H.W. Bush (Stem Cell Tracker, 2009).

President Clinton’s Embryo Policies

In 1993, under an executive order by newly elected President Clinton, the moratorium on federal funding on embryo research was lifted. Embryo research was also supported by the National Institute of Health advisory commission. However, this ban was short lived, as in 1994 under pressure from the public flooding him with emails, Clinton reversed his position and restarted the ban on embryo research. In 1995, the Dickey-Wicker Amendment was created by congress. The amendment prohibited federal funding for research to create human embryos for research purposes, for research involving the destruction of human embryos, and for research in which the fetus within a human female’s uterus could be at risk for death (Stem Cell Tracker, 2009). It should also be noted that parthenotes are considered embryos, and therefore were forbidden under the Dickey-Wicker amendment.

In 1998, the monumental event of James Thomson’s isolation of human ES cells occurred at the University of Wisconsin, and he was able to isolate the inner cell mass and show that these
cells could rejuvenate and differentiate into specific tissues (Thompson et al., 1998). This finding increased the ethical dilemma as to whether or not the destruction of an embryo was allowable as the potential for saving human lives became so great. In 1999, it was decided by the Department of Health and Human Services advisory committee that the Dickey-Wicker amendment did not apply to ES cells, arguing that the blastocyst stage is not the same as an embryo, so ES cells could be researched but the cells would have to be derived without federal funding (Stem Cell Tracker, 2009).

On August 25, 2000, the National Institute of Health (NIH) published its guidelines for federal funding of ES cell research. There were several important points within this paper. First, human ES cells must be derived using private funds from the frozen cells at IVF clinics. Secondly, these cells must have been created with the intent for fertility treatment purposes, and not for research purposes. And finally, the embryos must have been obtained with the consent of the donor.

Bush’s 2001 Stem Cell Policy

However in spite of the NIH recommendation on embryos, on August 9th of 2001, newly elected President George W. Bush put a ban on the federal funding of any research that used ES cells derived after August 9th (Stem Cell Tracker, 2009). This ban on federal funding to derive new ES cell lines became quite controversial, as the number of pre-existing ES cell lines dwindled over time, as many cell lines died. Of the 64 ES cell lines initially considered eligible for federal funding, only 21 lines survived in culture (Abbott et al., 2006). And in 2008, an investigation on the consent forms for federally funded ES cell lines for the 21 surviving ES cell lines showed that only 16 were ethically obtained and viable (Stem Cell Tracker, 2009).
In an effort to move ES cell research forward, the National Academy of Sciences released a paper called “Guidelines for Human Embryonic Stem Cell Research” in April of 2005. The main goal of this paper was to address the guidelines that all stem cell researchers should abide by to safely and responsibly bring stem cells into the clinical setting. In May 2005 the President's Council on Bioethics released a paper called “Alternative Sources of Pluripotent Stem Cells.” This paper addressed many important issues in stem cell research. The first point addressed was whether the blastocyst can be considered a living human, and whether moral status should be given to it. Following this council recommendation, the alternative of somatic cell nuclear transfer (SCNT) to create embryonic-like stem cells was addressed. It brings up the notion that it is important for researchers to create embryonic-like cells because if it is similar to an embryo but has no potential for life it is not ethically wrong to destroy them. The final point touched on by this paper was the ability to induce pluripotency in mature cells. It states that there would be nothing ethically wrong with this, unless of course a totipotent cell could be derived, and then this could potentially be deserving of moral status (The Presidents Council on Bioethics, 2005).

On June 20th of 2007, President George W. Bush issued an executive order to encourage the research of alternative sources of pluripotent stem cells. He also had the Department of Health and Human Services change the name of the Human Embryonic Stem Cell Registry to be renamed to the Human Pluripotent Stem Cell Registry.
Individual State’s Stem Cell Policies

President Bush’s ban on using federal money to derive new ES cell lines did not negate state funding for such purposes. In fact, the ban significantly increased state funding in several key states. In December 2002, Stanford University announced it was going to privately fund ES cell research, by floating a 3 billion dollar state bond to fund an International Stem Cell Center in San Francisco. Also within the same year Johns Hopkins University and the University of California opened similar research institutes (Check, 2002). On February 12, 2004, South Korean scientists announced they had successfully cloned a human embryo, however this research was subsequently withdrawn due to fraud. But the claim started an intense debate as to whether creating embryos could be moral if its intent was to derive ES cells (Godoy et al, 2006).

In June, 2004, New Jersey legislators included 9.5 million dollars within their state budget to fund both ES and adult stem cell research. This made New Jersey the first state to actually approve state funding of ES stem cell research, as California’s bond required public approval. In November, 2004, California approved a proposition allowing for 3 billion dollars to be used in the research of ES cells over a ten-year period (Hayden, 2008). In 2005, Connecticut approved a similar proposition allowing 100 million dollars to be provided over 10 years for adult and ES cell research. In Florida, an initiative was passed that allowed for 200 million dollars to be used to fund ES cell research over a ten-year period. However, this was met with a petition to ban this type of research, and it did not succeed (Stem Cell Tracker, 2009). Finally, in Massachusetts former Governor Mitt Romney vetoed several bills that proposed funding such research, but in May of 2009 Governor Patrick finally approved 1 billion in funding to establish the world’s largest stem cell depository on the campus of the University of Massachusetts Medical School.
Obama’s 2009 Stem Cell Policy

In January of 2009 Barack Obama, a proponent of ES cell research, was sworn in as the 44th president of the United States. Two months later, on March 9th of 2009, President Obama reversed George W. Bush’s 2001 executive ban. In Obama’s executive order there are a number of important points. The first was that due to the enormous successes and advances in stem cell research and an overall agreement within the scientific community, ES cell research should be federally funded. The Department of Health and Human Services had constantly advocated for ES cell research federal funding, however this has been hindered by earlier presidential actions. Therefore the overall purpose of Obama’s order would be to undo the actions of past presidents.

A second point is that in order to ensure that this research is handled responsibly, the National Institute of Health must review past guidelines, propose any necessary changes, and continually update the guidelines as needed in the future. The final point is simply the official removal of Bush’s 2001 policy from being active governmental policy (Stem Cell Tracker, 2009).

In April of 2009, the National Institute of Health drafted new guidelines for the research of ES cells. Under the proposed rules, the amount of lines eligible for federal funding will increase to approximately 700 cell lines. Although these rules are much more relaxed than President Bush’s 2001 executive order, there are still some limitations. Cell lines must still be obtained only through the donation and consent of couples that had been receiving fertility treatment. Lines derived through somatic cell nuclear transfer or cloning are considered ineligible for funding. Parthenotes are also still ineligible, as the Dickey-Wicker amendment still applies. Though the draft NIH guidelines were thought by many scientists to be a vast
improvement on the old guidelines, some aspects of the rules still need to be considered, so discussion continued until July 2009 (Stem Cell Tracker, 2009).

In July of 2009, the final guidelines were submitted by NIH. One such concern with the draft guidelines was concerning whether or not the cell lines approved by the Bush administration would be grandfathered in, or whether they would have to be reevaluated under the new guidelines. The answer in the final rules was that there would be no grandfathering in, and that each cell line would be dealt with in a case-by-case manner. It also outlined the requirements for cell lines created after the guidelines were published. Examples of such requirements were the need to review all informed consent requirements, protocols for evaluating the means by which stem cells were created in other countries if they are to be brought to the United States for research, and the continued ban of funding for research using somatic cell nuclear transfer, as well as cells derived from parthenogenesis (Stem Cell Tracker, 2009).

International Stem Cell Policies

Worldwide stem cell policies vary considerably. Figure-1 shows a map categorizing stem cell policies in various countries. Countries with permissive and flexible stem cell policies (dark brown) include England, Sweden, Finland, India, China, and Australia. These countries allow most forms of ES cell research, allow paid egg donors, and allow SCNT for therapeutic purposes. Countries with moderate stem cell policies (light brown) include the U.S., Brazil, Spain, France, Russia, Greece, Turkey, and Iraq. These countries allow some types of ES research, but with constraints on the source of embryos, such as the embryos must be provided
by IVF clinics, not paid egg donors. Countries with no stem cell policies include Mexico, Argentina, Chile, Greenland, Africa, Italy, Saudi Arabia, and Malasia.

**Figure 1: World Stem Cell Policy Map.** *Dark brown* denotes countries with permissive and flexible policies for embryo research, allowing most forms of ES cell research and SCNT, representing about 3.8 billion people, more than half of the world’s population. *Yellow* denotes countries with no stem cell policy. *Light brown* denotes countries with moderate policies, allowing IVF embryo donations for ES research, but not paid egg donations (University of Minnesota Medical School, 2009).

As updates to the map, although Ireland, Poland, and Lithuania are shown in the map as not having any stem cell policies, they have actually banned all forms of stem cell research. Germany and Italy banned any new extractions of ES cells from human embryos (Herman et al., 2008). The U.S., Denmark, Finland, France, Greece, Spain and the Netherlands restrict the derivation of ES cells to excess IVF embryos (Vestal, 2008). Japan, China, India, Singapore and South Korea all banned reproductive cloning, but permit therapeutic SCNT. China allows the performance of ES cell clinical trials on terminally ill patients, but has been criticized for their lack of oversight (Ralston, 2008).
Chapter-4 Conclusions

In the United States, the earlier 2001 ban on receiving federal money to fund ES research has now been lifted under the Obama administration, and as more discoveries are made, more countries have voted to allow ES cell use under certain circumstances. These countries that allow ES cell research now represent over half of the world’s population. As stem cell science becomes better studied, facts should emerge that will shed a more focused light on the ethical arguments, both for and against stem cell research. As new scientific information becomes available, the National Institute of Health will update their guidelines, and any necessary legislation can be put into place.

With respect to the author’s own personal conclusions, I view the evolution of U.S. stem cell laws as similar to laws involving human rights. In the United States slavery was allowed from 1619–1865. But it was so inflammatory to give slaves their rights that it was a major factor in one of the bloodiest wars our country has been involved in. It was a long and arduous process before the 13th amendment banning slavery was finally allowed. Similarly, giving women equal standing as men did not occur until the 1920s, and African American citizens were not given equal rights until the 1960s. The United States has a history of slowly recognizing laws necessary for acting in the people’s best interest. Since human ES cells were discovered in 1998, there has been an almost uninterrupted ban on federal funding of this research until very recently. With Obama’s new legislation and the National Institute of Health’s new guidelines, the United States has finally made the best decision for the country. States such as New Jersey, Florida, and California approved state funding in 2004 and 2005, and in 2009 Governor Patrick’s approval of one billion in funding for the world’s largest stem cell depository
in Worcester is a major boost in our state for this research. It has taken almost 30 years, but Obama’s legislative process came to the best decision.

Concerning the sources for embryos required to derive ES cells, I believe that in addition to IVF excess, additional lines should be created for the purposes of research. This means that sperm and egg donors would be paid for the purposes of research. However this would require that the women’s health be taken into account, as hormonal treatment is required. This would require litigation so that it is handled responsibly and with the donors consent. However while this is my opinion, it is not shared by those opposed to ES cell research. Therefore such law should be considered only if it is not shown that adult stem cells or iPS cells have the same potential as embryonic stem cells. As it stands now, ES cells are still the most useful and show the most promise, but to respect the wishes of those morally opposed to ES cell research I feel we should respect the guidelines set by the NIH and only use IVF embryos that had been created with the intent to reproduce.

Chapter 4 Works Cited


PROJECT CONCLUSIONS

The debate over the use of embryonic stem (ES) cells usually focuses on whether a 5-day-old fertilized egg (a blastocyst from which ES cells are obtained) has the same rights as a person. I feel that at this early stage of development, a blastocyst has potential life, and as such is not entitled to the same high moral value and rights as adult patients whose lives could be saved by its sacrifice. Therefore I believe that experimenting with such embryos is not morally wrong. However, there are strong religious and moral objections to using these cells, so scientists are working to find other means of creating induced pluripotent stem (iPS) cells that do not destroy an embryo. I agree that it would be prudent to explore these alternative options in deference to those individuals who are strongly against ES cell research, but only if these new iPS cells prove as potent as ES cells.

Concerning the sources for embryos to derive ES cells, I believe that in addition to using excess IVF embryos, the government should also support paying sperm and egg donors to create embryos for research purposes. As this latter position has strong opposition in the U.S., paid donors should only be considered if iPS cells are proven to lack pluripotency.

Countries with permissive and flexible stem cell policies include England, Sweden, Finland, India, China, and Australia. I agree with their legislations, as they all allow ES cell research, paid egg donors, and SCNT for therapeutic purposes. Though SCNT could potentially give rise to reproductive cloning, it is another method of creating ES cells genetically identical to a patient, and therefore could have strong medical applications. Hopefully with a worldwide effort, federal support, and continued scientific advancements in the field, stem cell research will show fewer hindrances, and the science of stem cell technology can move forward.