INTRODUCTION

A stem cell is a special kind of cell that has a unique capacity to renew itself and to give rise to specialized cell types. Although most cells of the body, such as heart cells or skin cells, are committed to conduct a specific function, a stem cell is uncommitted and remains uncommitted, until it receives a signal to develop into a specialized cell. Their proliferative capacity combined with the ability to become specialized makes stem cells unique. Researchers have for years looked for ways to use stem cells to replace cells and tissues that are damaged or diseased. Recently, stem cells have received much attention. What is “new” and what has brought stem cell biology to the forefront of science and public policy?

Scientists interested in human development have been studying animal development for many years. This research yielded our first glimpse at a class of stem cells that can develop into any cell type in the body. This class of stem cells is called pluripotent, meaning the cells have the potential to develop almost all of the more than 200 different known cell types. Stem cells with this unique property come from embryos and fetal tissue.

In 1998, for the first time, investigators were able to isolate this class of pluripotent stem cell from early human embryos and grow them in culture. In the few years since this discovery, evidence has emerged that these stem cells are, indeed, capable of becoming almost all of the specialized cells of the body and, thus, may have the potential to generate replacement cells for a broad array of tissues and organs, such as the heart, the pancreas, and the nervous system. Thus, this class of human stem cell holds the promise of being able to repair or replace cells or tissues that are damaged or destroyed by many of our most devastating diseases and disabilities.

At about the same time as scientists were beginning to explore human pluripotent stem cells from embryos and fetal tissue, a flurry of new information was emerging about a class of stem cells that have been in clinical use for years—so-called adult stem cells. An adult stem cell is an undifferentiated cell that is found in a differentiated (specialized) tissue in the adult, such as blood. It can yield the specialized cell types of the tissue from which it originated. In the body, it too, can renew itself. During the past decade, scientists discovered adult stem cells in tissues that were previously not thought to contain them, such as the brain. More recently, they reported that adult stem cells from one tissue appear to be capable of developing into cell types that are characteristic of other tissues. For example, although adult hematopoietic stem cells from bone marrow have long been recognized as capable of developing into blood and immune cells, recently scientists reported that, under certain conditions, the same stem cells could also develop into cells that have many of the characteristics of neurons. So, a new concept and a new term emerged—adult stem cell plasticity.

Are human adult and embryonic stem cells equivalent in their potential for generating replacement cells and tissues? Current science indicates that, although both of these cell types hold enormous promise, adult and embryonic stem cells differ in important ways. What is not known is the extent to which these different cell types will be useful for the development of cell-based therapies to treat disease.

Some considerations are noteworthy regarding this report. First, in recent months, there have been many discussions in the lay press about the anticipated abilities of stem cells from various sources and projected benefits to be realized from them in replacing cells and tissues in patients with various diseases. The terminology used to describe stem cells in the lay
literature is often confusing or misapplied. Second, even among biomedical researchers, there is a lack of consistency in common terms to describe what stem cells are and how they behave in the research laboratory. Third, the field of stem cell biology is advancing at an incredible pace with new discoveries being reported in the scientific literature on a weekly basis.

This summary begins with common definitions and explanations of key concepts about stem cells. It ends with an assessment of how adult, embryonic and fetal stem cells are similar and how they are different. In between lie important details that describe what researchers have discovered about stem cells and how they are being used in the laboratory.

DEFINITIONS AND GENERAL CONCEPTS ABOUT STEM CELLS

In developing this report, some conventions were established to describe consistently what stem cells are, what characteristics they have, and how they are used in biomedical research. Here are some of the key definitions that are used throughout this report.

Stem cell. A stem cell is a cell from the embryo, fetus, or adult that has, under certain conditions, the ability to reproduce itself for long periods or, in the case of adult stem cells, throughout the life of the organism. It also can give rise to specialized cells that make up the tissues and organs of the body. Much basic understanding about embryonic stem cells has come from animal research. In the laboratory, this type of stem cell can proliferate indefinitely, a property that is not shared by adult stem cells.

Pluripotent stem cell. A single pluripotent stem cell has the ability to give rise to types of cells that develop from the three germ layers (mesoderm, endoderm, and ectoderm) from which all the cells of the body arise. The only known sources of human pluripotent stem cells are those isolated and cultured from early human embryos and from fetal tissue that was destined to be part of the gonads.

Embryonic stem cell. An embryonic stem cell is derived from a group of cells called the inner cell mass, which is part of the early (4- to 5-day) embryo called the blastocyst. Once removed from the blastocyst, the cells of the inner cell mass can be cultured into embryonic stem cells. These embryonic stem cells are not themselves embryos. In fact, evidence is emerging that these cells do not behave in the laboratory as they would in the developing embryo—that is, the conditions in which these cells develop in culture are likely to differ from those in the developing embryo.

Embryonic germ cell. An embryonic germ cell is derived from fetal tissue. Specifically, they are isolated from the primordial germ cells of the gonadal ridge of the 5- to 10-week fetus. Later in development, the gonadal ridge develops into the testes or ovaries and the primordial germ cells give rise to eggs or sperm. Embryonic stem cells and embryonic germ cells are pluripotent, but they are not identical in their properties and characteristics.

Differentiation. Differentiation is the process by which an unspecialized cell (such as a stem cell) becomes specialized into one of the many cells that make up the body. During differentiation, certain genes become activated and other genes become inactivated in an intricately regulated fashion. As a result, a differentiated cell develops specific structures and performs certain functions. For example, a mature, differentiated nerve cell has thin, fiber-like projections that send and receive the electrochemical signals that permit the nerve cell to communicate with other nerve cells. In the laboratory, a stem cell can be manipulated to become specialized or partially specialized cell types (e.g., heart muscle, nerve, or pancreatic cells) and this is known as directed differentiation.

Adult stem cell. An adult stem cell is an undifferentiated (unspecialized) cell that occurs in a differentiated (specialized) tissue, renews itself, and becomes specialized to yield all of the specialized cell types of the tissue from which it originated. Adult stem cells are capable of making identical copies of themselves for the lifetime of the organism. This property is referred to as “self-renewal.” Adult stem cells usually divide to generate progenitor or precursor cells, which then differentiate or develop into “mature” cell types that have characteristic shapes and specialized functions, e.g., muscle cell contraction or nerve cell signaling. Sources of adult stem cells include bone marrow, blood, the cornea and the retina of the eye, brain, skeletal muscle, dental pulp, liver, skin, the lining of the gastrointestinal tract, and pancreas. The most abundant information about adult human
stem cells comes from studies of hematopoietic (blood-forming) stem cells isolated from the bone marrow and blood. These adult stem cells have been extensively studied and applied therapeutically for various diseases. At this point, there is no isolated population of adult stem cells that is capable of forming all the kinds of cells of the body. Adult stem cells are rare. Often they are difficult to identify, isolate, and purify. There are insufficient numbers of cells available for transplantation and adult stem cells do not replicate indefinitely in culture.

**Plasticity.** Plasticity is the ability of an adult stem cell from one tissue to generate the specialized cell type(s) of another tissue. A recently reported example of plasticity is that, under specific experimental conditions, adult stem cells from bone marrow generated cells that resemble neurons and other cell types that are commonly found in the brain. The concept of adult stem cell plasticity is new, and the phenomenon is not thoroughly understood. Evidence suggests that, given the right environment, some adult stem cells are capable of being “genetically reprogrammed” to generate specialized cells that are characteristic of different tissues.

**Clonality or clonally derived stem cell.** A cell is said to be clonally derived or to exhibit clonality if it was generated by the division of a single cell and is genetically identical to that cell. In stem cell research, the concept of clonality is important for several reasons. For researchers to fully understand and harness the ability of stem cells to generate replacement cells and tissues, the exact identity of those cells’ genetic capabilities and functional qualities must be known. Human pluripotent stem cells from embryos and fetal tissue are by their nature clonally derived. However, very few studies have shown clonal properties of the cells that are developed from adult stem cells. It is crucial to know whether a single cell is capable of developing an array of cell types, or whether multiple stem cell types, that when grown together, are capable of forming multiple cell types. For instance, recent research has shown that a mixture of cells removed from fat tissue or umbilical cord blood are capable of developing into blood cells, bone cells, and perhaps others. Researchers have not shown that a single cell is responsible for giving rise to other cell types or, if so, what kind of cell it is. These results may well be attributable to multiple types of precursor cells in the starting tissue; such results from fat cells may, in fact, be due to the presence of hematopoietic stem cells in the fat tissue. The importance of showing that one cell type can reproducibly become another and self-replicate cannot be overemphasized.

**Progenitor or precursor cell.** A progenitor or precursor cell occurs in fetal or adult tissues and is partially specialized; it divides and gives rise to differentiated cells. Researchers often distinguish precursor/progenitor cells from adult stem cells in the following way: when a stem cell divides, one of the two new cells is often a stem cell capable of replicating itself again. In contrast, when a progenitor/precursor cell divides, it can form more progenitor/precursor cells or it can form two specialized cells, neither of which is capable of replicating itself. Progenitor/precursor cells can replace cells that are damaged or dead, thus maintaining the integrity and functions of a tissue such as liver or brain. Progenitor/precursor cells give rise to related types of cells—lymphocytes such as T cells, B cells, and natural killer cells, for example—but in their normal state do not generate a wide variety of cell types.

**CHALLENGES IN STEM CELL RESEARCH**

It is important to understand some of the difficulties that researchers have had in isolating various types of stem cells, working with the cells in the laboratory, and proving experimentally that the cells are true stem cells. Most of the basic research discoveries on embryonic and adult stem cells come from research using animal models, particularly mice.

In 1981, researchers reported methods for growing mouse embryonic stem cells in the laboratory, and it took nearly 20 years before similar achievements could be made with human embryonic stem cells. Much of the knowledge about embryonic stem cells has emerged from two fields of research: applied reproductive biology, i.e., *in vitro* fertilization technologies, and basic research on mouse embryology.

There have been many technical challenges that have been overcome in adult stem cell research as well. Some of the barriers include: the rare occurrence of adult stem cells among other, differentiated cells, difficulties in isolating and identifying the cells (researchers often use molecular “markers” to identify
adult stem cells), and in many cases, difficulties in growing adult stem cells in tissue culture. Much of the research demonstrating the plasticity of adult stem cells comes from studies of animal models in which a mixture of adult stem cells from a donor animal is injected into another animal, and the development of new, specialized cells is traced.

In 1998, James Thomson at the University of Wisconsin-Madison isolated cells from the inner cell mass of the early embryo, called the blastocyst, and developed the first human embryonic stem cell lines. At the same time, John Gearhart at Johns Hopkins University reported the first derivation of human embryonic germ cells from an isolated population of cells in fetal gonadal tissue, known as the primordial germ cells, which are destined to become the eggs and sperm. From both of these sources, the researchers developed pluripotent stem cell "lines," which are capable of renewing themselves for long periods and giving rise to many types of human cells or tissues. Human embryonic stem cells and embryonic germ cells differ in some characteristics, however, and do not appear to be equivalent.

Why are the long-term proliferation ability and pluripotency of embryonic stem cells and embryonic germ cells so important? First, for basic research purposes, it is important to understand the genetic and molecular basis by which these cells continue to make many copies of themselves over long periods of time. Second, if the cells are to be manipulated and used for transplantation, it is important to have sufficient quantities of cells that can be directed to differentiate into the desired cell type(s) and used to treat the many patients that may be suffering from a particular disease.

In recent months, other investigators have been successful in using somewhat different approaches to deriving human pluripotent stem cells. At least 5 other laboratories have been successful in deriving pluripotent stem cells from human embryos and one additional laboratory has created cell lines from fetal tissue. In each case, the methods for deriving pluripotent stem cells from human embryos and embryonic germ cells from fetal tissue are similar, yet they differ in the isolation and culture conditions as initially described by Thomson and Gearhart, respectively. It is not known to what extent U.S.-based researchers are using these additional sources of embryonic stem and germ cells.

At present, there have been multiple human adult stem cell lines that have been created through a combination of public and private resources (e.g., hematopoietic stem cells). Substantial adult stem cell research has been underway for many years, and in recent years this has included basic studies on the "plasticity" of such cells.

**WHAT KINDS OF RESEARCH MIGHT BE CONDUCTED WITH STEM CELLS?**

There has been much written about the new discoveries of various stem cell types and their properties. Importantly, these cells are research tools and they open many doors of opportunity for biomedical research.

**Transplantation Research—Restoring Vital Body Functions**

Stem cells may hold the key to replacing cells lost in many devastating diseases. There is little doubt that this potential benefit underpins the vast interest about stem cell research. What are some of these diseases? Parkinson's disease, diabetes, chronic heart disease, end-stage kidney disease, liver failure, and cancer are just a few for which stem cells have therapeutic potential. For many diseases that shorten lives, there are no effective treatments but the goal is to find a way to replace what natural processes have taken away. For example, today, science has brought us to a point where the immune response can be subdued, so that organs from one person can be used to replace the diseased organs and tissues of another. But, despite recent advances in transplantation sciences, there is a shortage of donor organs that makes it unlikely that the growing demand for lifesaving organ replacements will be fully met through organ donation strategies.

The use of stem cells to generate replacement tissues for treating neurological diseases is a major focus of research. Spinal cord injury, multiple sclerosis, Parkinson's disease, and Alzheimer's disease are among those diseases for which the concept of replacing destroyed or dysfunctional cells in the brain or spinal cord is a practical goal. This report features several recent advances that demonstrate the regenerative properties of adult and embryonic stem cells.

Another major discovery frontier for research on adult and embryonic stem cells is the development of
transplantable pancreatic tissues that can be used to
treat diabetes. Scientists in academic and industrial
research are vigorously pursuing all possible avenues
of research, including ways to direct the specializa-
tion of adult and embryonic stem cells to become
pancreatic islet-like cells that produce insulin and can
be used to control blood glucose levels. Researchers
have recently shown that human embryonic stem
cells to be directly differentiated into cells that pro-
duce insulin.

There are common misconceptions about both adult
and human embryonic stem cells. First, the lines of
unaltered human embryonic stem cells that exist will
not be suitable for direct use in patients. These cells
will need to be differentiated or otherwise modified
before they can be used clinically. Current chal-
lenges are to direct the differentiation of embryonic
stem cells into specialized cell populations, and also
to devise ways to control their development or prolif-
eration once placed in patients.

A second misconception is that adult stem cells are
ready to use as therapies. With the exception of the
clinical application of hematopoietic stem cells to
restore the blood and immune system, this is not the
case. The therapeutic use of this mixture of cells has
proven safe because the mixture is place back into
the environment from which it was taken, e.g., the
bone marrow. In fact, many of the adult stem cell
preparations currently being developed in the labora-
tory represent multiple cell types that are not fully
characterized. In order to safely use stem cells or cells
differentiated from them in tissues other than the tissue
from which they were isolated, researchers will need
purified populations (clonal lines) of adult stem cells.

In addition, the potential for the recipient of a stem
cell transplant to reject these tissues as foreign is very
high. Modifications to the cells, to the immune sys-
tem, or both will be a major requirement for their use.
In sum, with the exception of the current practice of
hematopoietic stem cell transplantation, much basic
research lies ahead before direct patient application
of stem cell therapies is realized.

Basic Research Applications
Embryonic stem cells will undoubtedly be key
research tools for understanding fundamental events
in embryonic development that one day may
explain the causes of birth defects and approaches
to correct or prevent them. Another important area of
research that links developmental biology and stem
cell biology is understanding the genes and mole-
cules, such as growth factors and nutrients, that
function during the development of the embryo so
that they can be used to grow stem cells in the
laboratory and direct their development into
specialized cell types.

Therapeutic Delivery Systems
Stem cells are already being explored as a vehicle
for delivering genes to specific tissues in the body.

Other Applications of Stem Cells
Future uses of human pluripotent cell lines might
include the exploration of the effects of chromoso-
mal abnormalities in early development. This might
include the ability to monitor the development of
early childhood tumors, many of which are embryon-
ic in origin. Another future use of human stem cells
and their derivatives include the testing of candidate
therapeutic drugs. Although animal model testing is a
mainstay of pharmaceutical research, it cannot
always predict the effects that a developmental drug
may have on human cells. Stem cells will likely be
used to develop specialized liver cells to evaluate
drug detoxifying capabilities and represents a new
type of early warning system to prevent adverse reac-
tions in patients. The coupling of stem cells with the
information learned from the human genome project
will also likely have many unanticipated benefits in
the future.

Critical Evidence and Questions about Stem
Cell Research

Executive Summary
transplantation—for example, neurons, heart muscle cells, or pancreatic islet cells—comes from experiments with stem cells from mice. And although more is known about mouse stem cells, not all of that information can be translated to the understanding of human stem cells. Mouse and human cells differ in significant ways, such as the laboratory conditions that favor the growth and specialization of specific cell types.

Another important aspect of developing therapies based on stem cells will be devising ways to prevent the immune system of recipients from rejecting the donated cells and tissues that are derived from human pluripotent stem cells. Modifying or evading the immune rejection of cells or tissues developed from embryonic stem cells will not be able to be done exclusively using mouse models and human adult stem cells.

As with any new research tool, it will also be important to compare the techniques and approaches that various laboratories are using to differentiate and use human embryonic stem cells. Such research will provide a more complete understanding of the cells’ characteristics. One key finding about the directed differentiation of pluripotent stem cells learned thus far is that relatively subtle changes in culture conditions can have dramatic influences on the types of cells that develop.

**What Is Known About Adult Stem Cells?**

- To date, published scientific papers indicate that adult stem cells have been identified in brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, epithelia of the skin and digestive system, cornea, dental pulp of the tooth, retina, liver, and pancreas. Thus, adult stem cells have been found in tissues that develop from all three embryonic germ layers.

- There is no evidence of an adult stem cell that is pluripotent. It has not been demonstrated that one adult stem cell can be directed to develop into any cell type of the body. That is, no adult stem cell has been shown to be capable of developing into cells from all three embryonic germ layers.

- In the body, adult stem cells can proliferate without differentiating for a long period (the characteristic referred to as long-term self-renewal), and they can give rise to mature cell types that have characteristic shapes and specialized functions of a particular tissue.

- Adult stem cells are rare. Often they are difficult to identify, isolate, and purify.

- One important, limiting factor for the use of adult stem cells in future cell-replacement strategies is that there are insufficient numbers of cells available for transplantation. This is because most adult stem cell lines when grown in a culture dish are unable to proliferate in an unspecialized state for long periods of time. In cases where they can be grown under these conditions, researchers have not been able to direct them to become specialized as functionally useful cells.

- Stem cells from the bone marrow are the most-studied type of adult stem cells. Currently, they are used clinically to restore various blood and immune components to the bone marrow via transplantation. There are two major types of stem cells found in bone: hematopoietic stem cells which form blood and immune cells, and stromal (mesenchymal) stem cells that normally form bone, cartilage, and fat. The restricted capacity of hematopoietic stem cells to grow in large numbers and remain undifferentiated in the culture dish is a major limitation to their broader use for research and transplantation studies. Researchers have reported that at least two other populations of adult stem cells occur in bone marrow and blood, but these cells are not well characterized.

- Evidence to date indicates that umbilical cord blood is an abundant source of hematopoietic stem cells. There do not appear to be any qualitative differences between the stem cells obtained from umbilical cord blood and those obtained from bone marrow or peripheral blood.

- Several populations of adult stem cells have been identified in the brain, particularly in a region important in memory, known as the hippocampus. Their function in the brain is unknown. When the cells are removed from the brain of mice and grown in tissue culture, their proliferation and differentiation can be influenced by various growth factors.
• Current methods for characterizing adult stem cells depend on determining cell-surface markers and making observations about their differentiation patterns in culture dishes.

• Some adult stem cells appear to have the capability to differentiate into tissues other than the ones from which they originated; this is referred to as plasticity. Reports of human or mouse adult stem cells that demonstrate plasticity and the cells they differentiate or specialize into include: 1) blood and bone marrow (unpurified hematopoietic) stem cells differentiate into the 3 major types of brain cells (neurons, oligodendrocytes, and astrocytes), skeletal muscle cells, cardiac muscle cells, and liver cells; 2) bone marrow (stromal) cells differentiates into cardiac muscle cells, skeletal muscle cells, fat, bone, and cartilage; and 3) brain stem cells differentiate into blood cells and skeletal muscle cells.

• Very few published research reports on the plasticity of adult stem cells shown that a single, identified adult stem cell can give rise to a differentiated cell type of another tissue. That is, there is limited evidence that a single adult stem cell or genetically identical line of adult stem cells demonstrates plasticity. Researchers believe that it is most likely that a variety of populations of stem cells may be responsible for the phenomena of developing multiple cell types.

• A few experiments have shown plasticity of adult stem cells by demonstrating the development of mature, fully functional cells in tissues other than which they were derived and the restoration of lost or diminished function in an animal model.

What is Known About Human Pluripotent Stem Cells?

• Since 1998, research teams have refined the techniques for growing human pluripotent cells in culture systems. Collectively, the studies indicate that it is now possible to grow these cells for up to two years in a chemically defined medium.

• The cell lines have been shown to have a normal number of chromosomes and they generate cell types that originate from all three primary germ layers.

• Cultures of human pluripotent stem cells have active telomerase, which is an enzyme that maintains the length of telomeres and is important for cells to maintain their capacity to replicate. Human pluripotent stem cells appear to maintain relatively long telomeres, indicating that they have the ability to replicate for many, many generations.

• Evidence of structural, genetic, and functional cells characteristic of specialized cells developed from cultured human and mouse embryonic stem cells has been shown for: 1) Pancreatic islet-cell like cells that secrete insulin (mouse and human); 2) cardiac muscle cells with contractile activity (mouse and human); 3) blood cells (human and mouse); 4) nerve cells that produce certain brain chemicals (mouse).

• At the time of this report, there are approximately 30 cell lines of human pluripotent stem cells that have been derived from human blastocysts or fetal tissue.

• Overall, it appears human embryonic cells and embryonic germ cells are not equivalent in their potential to proliferate or differentiate.

What are Some of the Questions that Need to be Answered about Stem Cells?

• What are the mechanisms that allow human embryonic stem cells and embryonic germ cells to proliferate in vitro without differentiating?

• What are the intrinsic controls that keep stem cells from differentiating?

• Is there a universal stem cell? That is, could a kind of stem cell exist (possibly circulating in the blood) that can generate the cells of any organ or tissue?

• Do adult stem cells exhibit plasticity as a normal event in the body or is it an artifact of the culture conditions? If plasticity occurs normally, is it a characteristic of all adult stem cells? What are the signals that regulate the proliferation and differentiation of stem cells that demonstrate plasticity?

• What are the factors responsible for stem cells to "home" to sites of injury or damage?

• What are the intrinsic controls that direct stem cells along a particular differentiation pathway to form one specialized cell over another? How are such intrinsic regulators, in turn, influenced by the
microenvironment, or niche, where stem cells normally reside?

• Will the knowledge about the genetic mechanisms regulating the specialization of embryonic cells into cells from all embryonic germ layers during development enable the scientists to engineer adult stem cells to do the same?

• What are the sources of adult stem cells in the body? Are they "leftover" embryonic stem cells, or do they arise in some other way? And if the latter is true—which seems to be the case—exactly how do adult stem cells arise, and why do they remain in an undifferentiated state when all the cells around them have differentiated?

• How many kinds of adult stem cells exist, and in which tissues do they exist?

• Is it possible to manipulate adult stem cells to increase their ability to proliferate in a culture dish so that adult stem cells can be used as a sufficient source of tissue for transplants?

• Does the genetic programming status of stem cells play a significant role in maintaining the cells, directing their differentiation, or determining their suitability for transplant?

• Are the human embryonic stem and germ cells that appear to be homogeneous and undifferentiated in culture, in fact, homogeneous and undifferentiated? Or are they heterogeneous and/or "partially" differentiated?

• What are the cellular and molecular signals that are important in activating a human pluripotent stem cell to begin differentiating into a specialized cell type?

• Will analysis of genes from human pluripotent stem cells reveal a common mechanism that maintains cells in an undifferentiated state?

• Do all pluripotent stem cells pass through a progenitor/precursor cell stage while becoming specialized? If so, can a precursor or progenitor cell stage be maintained as optimal cells for therapeutic transplantation?

• What stage of differentiation of stem cells will be best for transplantation? Would the same stage be optimal for all transplantation applications, or will it differ on a case-by-case basis?

• What differentiation stages of stem cells would be best for screening drugs or toxins, or for delivering potentially therapeutic drugs?

COMPARISONS OF ADULT STEM CELLS AND EMBRYONIC STEM CELLS

Biomedical research on stem cells is at an early stage, but is advancing rapidly. After many years of isolating and characterizing these cells, researchers are just now beginning to employ stem cells as discovery tools and a basis for potential therapies. This new era of research affords an opportunity to use what has already been learned to explore the similarities and differences of adult and embryonic stem cells. (In this discussion, comments about embryonic stem cells derived from human embryos, and embryonic germ cells derived from fetal tissue, will be referred to equally as embryonic stem cells, unless otherwise distinguished.)

How are Adult and Embryonic Stem Cells Similar?

By definition, stem cells have in common the ability to self-replicate and to give rise to specialized cells and tissues (such as cells of the heart, brain, bone, etc.) that have specific functions. In most cases, stem cells can be isolated and maintained in an unspecialized state. Scientists use similar techniques (i.e., cell-surface markers and monitoring the expression of certain genes) to identify or characterize stem cells as being unspecialized. Scientists then use different genetic or molecular markers to determine that the cells have differentiated—a process that might be compared to distinguishing a particular cell type by reading its cellular barcode.

Stem cells from both adult and embryonic sources can proliferate and specialize when transplanted into an animal with a compromised immune system. (Immune-deficient animals are less likely to reject the transplanted tissue). Scientists also have evidence that differentiated cells generated from either stem cell type, when injected or transplanted into an animal model of disease or injury, undergo “homing,” a process whereby the transplanted cells are attracted by and travel to the injured site. Similarly, researchers are finding that the cellular and non-cellular “environment” into which stem cell-derived tissues are placed (e.g., whether they are grown in a culture dish or transplanted into an animal) prominently influences how the cells differentiate.

Another important area that requires substantially more research concerns the immunologic characteristics of
human adult and embryonic stem cells. If any of these stem cells are to be used as the basis for therapy, it is critical understand how the body’s immune system will respond to the transplantation of tissue derived from these cells. At this time, there is no clear advantage of one stem cell source over the other in this regard.

How are Adult and Embryonic Stem Cells Different?

Perhaps the most distinguishing feature of embryonic stem cells and adult stem cells is their source. Most scientists now agree that adult stem cells exist in many tissues of the human body (in vivo), although the cells are quite rare. In contrast, it is less certain that embryonic stem cells exist as such in the embryo. Instead, embryonic stem cells and embryonic germ cells develop in tissue culture after they are derived from the inner cell mass of the early embryo or from the gonadal ridge tissue of the fetus, respectively.

Depending on the culture conditions, embryonic stem cells may form clumps of cells that can differentiate spontaneously to generate many cell types. This property has not been observed in cultures of adult stem cells. Also, if undifferentiated embryonic stem cells are removed from the culture dish and injected into a mouse with a compromised immune system, a benign tumor called a teratoma can develop. A teratoma typically contains a mixture of partially differentiated cell types. For this reason, scientists do not anticipate that undifferentiated embryonic stem cells will be used for transplants or other therapeutic applications. It is not known whether similar results are observed with adult stem cells.

Stem cells in adult tissues do not appear to have the same capacity to differentiate as do embryonic stem cells or embryonic germ cells. Embryonic stem and germ cells are clearly pluripotent; they can differentiate into any tissues derived from all three germ layers of the embryo (ectoderm, mesoderm, and endoderm). But are adult stem cells also pluripotent? When they reside in their normal tissue compartments—the brain, the bone marrow, the epithelial lining of the gut, etc.—they produce the cells that are specific to that kind of tissue and they have been found in tissues derived from all three embryonic layers. But can adult stem cells be taken out of their normal environment and be manipulated or otherwise induced to have the same differentiation potential as embryonic stem and germ cells? To date, there are no definitive answers to these questions, and the answers that do exist are sometimes conflicting.

These sources of stem cells do not seem to have the same ability to proliferate in culture and at the same time retain the capacity to differentiate into functionally useful cells. Human embryonic stem cells can be generated in abundant quantities in the laboratory and can be grown (allowed to proliferate) in their undifferentiated (or unspecialized) state for many, many generations. From a practical perspective in basic research or eventual clinical application, it is significant that millions of cells can be generated from one embryonic stem cell in the laboratory. In many cases, however, researchers have had difficulty finding laboratory conditions under which some adult stem cells can proliferate without becoming specialized. This problem is most pronounced with hematopoietic stem cells isolated from blood or bone marrow. These cells when cultured in the laboratory either fail to proliferate or do so to a limited extent, although they do proliferate if transplanted into an animal or human. This technical barrier to proliferation has limited the ability of researchers to explore the capacity of certain types of adult stem cells to generate sufficient numbers of specialized cells for transplantation purposes.

These differences in culturing conditions contribute to the contrasts in the experimental systems used to evaluate the ability to become specialized under particular laboratory conditions. Much of the information on the directed differentiation of embryonic stem cells into cells with specialized function comes from studying mouse or human embryonic cell lines grown in laboratory culture dishes. In contrast, most knowledge about the differentiation of adult stem cells differentiation are from observations of cells and tissues in animal models in which mixtures of cells have been implanted.

Stem cells also differ in their capacity to specialize into various cell and tissue types. Current evidence indicates that the capability of adult stem cells to give rise to many different specialized cell types is more limited than that of embryonic stem cells. A single embryonic stem cell has been shown to give rise to specialized cells from all three embryonic layers. However, it has not yet been shown that a
single adult stem cell can give rise to specialized cells derived from all three embryonic germ cell layers. Therefore, a single adult stem cell has not been shown to have the same degree of pluripotency as embryonic stem cells.

CONCLUSIONS

Two important points about embryonic and adult stem cells have emerged so far: the cells are different and present immense research opportunities for potential therapy. As research goes forward, scientists will undoubtedly find other similarities and differences between adult and embryonic stem cells. During the next several years, it will be important to compare embryonic stem cells and adult stem cells in terms of their ability to proliferate, differentiate, survive and function after transplant, and avoid immune rejection. Investigators have shown that differentiated cells generated from both adult and embryonic stem cells can repair or replace damaged cells and tissues in animal studies.

Scientists upon making new discoveries often verify reported results in different laboratories and under different conditions. Similarly, they will often conduct experiments with different animal models or, in this case, different cell lines. However, there have been very few studies that compare various stem cell lines with each other. It may be that one source proves better for certain applications, and a different cell source proves better for others.

For researchers and patients, there are many practical questions about stem cells that cannot yet be answered. How long will it take to develop therapies for Parkinson’s Disease and diabetes with and without human pluripotent stem cells? Can the full range of new therapeutic approaches be developed using only adult stem cells? How many different sources of stem cells will be needed to generate the best treatments in the shortest period of time?

Predicting the future of stem cell applications is impossible, particularly given the very early stage of the science of stem cell biology. To date, it is impossible to predict which stem cells—those derived from the embryo, the fetus, or the adult—or which methods for manipulating the cells, will best meet the needs of basic research and clinical applications. The answers clearly lie in conducting more research.