DISCUSSED | human embryonic stem cells (HESC), adult stem cells, in vitro fertilization (IVF), Catholics, Evangelicals, George W. Bush, General Conference of SDAs, core principles, ethical guidelines, stem cell based therapies

The Promise of Stem Cell Research | BY E. ALBERT REECE

Editor's note: An unedited version of this presentation was delivered on January 10, 2008, as part of the Jack Provansha Lecture Series, which is sponsored by the Center for Christian Bioethiccs at Loma Linda University. The lecturer, E. Albert Reece, is vice president for Medical Affairs at the University of Maryland, John R. and Akiko K. Bowers Distinguished Professor, and dean of the School of Medicine.

Tonight I will try to address the lecture topic that was posed to me, which is human embryonic stem cell research. Can medicine live without it? Can we? I would like to cover some stem cell basics. I'm going to assume that the audience is varied and that people are here from different backgrounds and have different levels of appreciation, understanding, or expertise. So we'll do some stem cell basics, Stem Cell 101. Then I'll take an in-depth look at the human embryonic stem cell controversy, what's happening on both sides of the issues, in the press and elsewhere. I will address what the current state of the science is. Then I'll answer the issue that you've asked me to address, which is whether we can we live without it. Hopefully, we'll be able to end on some common ground.

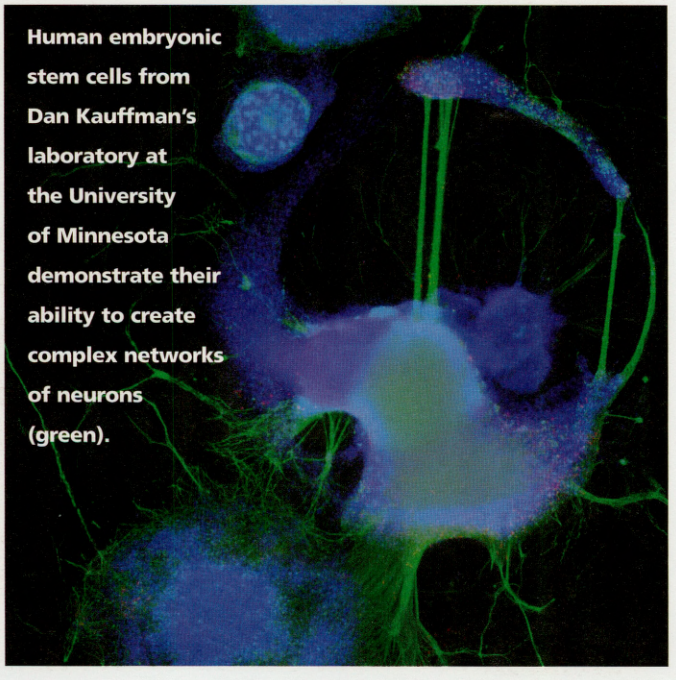
Stem Cells 101

Let's start with stem cell lab basics. Stem cells are the primary original fundamental undifferentiated cells that eventually give rise to a host of other cells. They serve to replenish, restore, or renew other cells over time.

Stem cells are pluripotent; they can differentiate into a number of cell lines. As a result, bone marrow cells could be used to address leukemia, Parkinson's, or potentially Alzheimer's, or to repair heart muscle because of injury from microinfarctions. Potentially, stem cells could also be used with pancreatic cells to address diabetes. We could even study the differentiation to prevent birth defects. These are just some of the potential applications of stem cells in terms of differentiation.

There are two main types of stem cells. One is obviously the human embryonic stem cell. This type is the one that creates a lot of controversy and discussion. The second is adult stem cells. Let's talk about the human embryonic stem cells first. These obviously are derived from human embryos, and they come primarily from leftover IVF embryos. These come into existence when couples who are infertile use reproductive technologies that result in extra embryos being created and stored.

After successful pregnancies, such couples are given three options. First, they have the option of saving the leftover embryos for use by themselves in the future.



Human embryonic stem cells from Dan Kauffman's laboratory at the University of Minnesota demonstrate their ability to create complex networks of neurons (green).

TERRY BURNS

Second, they can store them for research purposes. Finally, they have the option of discarding them. This is the typical source for human embryonic stem cells.

The second major type of stem cell is the adult type. Cells of this kind are derived from adult tissues; they could come from the brain, heart, blood, or skin, for instance.

Now let's talk about different potential applications, their advantages and disadvantages. To begin, I have three terms to share with you, terms that we need to understand: totipotent, pluripotent, multipotent. The term *totipotent* basically describes the condition after the sperm and egg come together. This creates a zygote, which will go through two, four, or eight multiple stages of development or divisions. These cells are totipotent because after the zygote is formed and starts going through multiple divisions, it will eventually create a ball of cells—about sixteen—which is called the morula.

After several more stages, the morula starts to separate out to a ball of cells called the inner cell mass, which is separated from a rim of cells and is basically the remainder. The inner cell mass goes on to form the embryo, and the non-inner cell mass goes on to form the yolk sac or the placenta, the primitive placenta. So essentially those two sets of cells create either the embryo or the extra-embryonic component. Those are totipotent cells capable of going in either direction to form the embryo or the placenta.

The next word is *pluripotent*. Pluripotent cells are basically offspring, descendents of the totipotent cells that can differentiate into cell lines, endoderm, mesoderm, and ectoderm. The third term is *multipotent*. This is important because multipotent cells are basically progenitor cells, cells that can differentiate into other cells. Some examples include early progenitor blood cells that can differentiate into a variety of blood cells but can't differentiate into muscle cells, or early progenitor muscle cells that can differentiate into a variety of muscle cells, but can't differentiate into blood cells or anything else.

Imagine starting with a single cell that divides then forms the morula. By about day six in humans, we have the blastocyst. At that point, the inner cell mass is separated from the rim of cells. This is the stage when the embryo would be implanted in the uterine cavity. If you take the inner cell mass and put it in a Petri dish, it would expand and potentially form various cell lines.

So what are the advantages of using human embryonic stem cells? Why don't we use adult stem cells? Here are some advantages. Not only are embryonic stem cells easy to grow in cell culture, they're also very flexible and can go into a lot of different cell lines. Also, the likelihood of them being rejected immunologically is very low because they're rather naïve in their immunogenicity.

Keep in mind that the antigens are laid down around fifteen weeks in the human embryo. Hence, the likelihood of rejection is very low. Furthermore, they can be maintained for long periods in cell culture, they are a potentially unlimited source of all types of clinically relevant cells, and they're abundant. Right now, there are probably half a billion embryos stored in freezers throughout the United States. So potentially a lot are available.

What are the disadvantages of using human embryonic stem cells? If the cells are made by IVF, there's a low potential for something called graft versus host rejection, in which the recipient and the donor have basically different antigenic profiles. This is basically a mismatch in the antigen profiles of recipient and donor. It is also difficult sometimes to control differentiation in such cells. Differentiation may occur in certain cell lines, but not in others, which requires the use of certain growth factors added to the culture medium to force differentiation in one area. For example, some may be forced to become cardiac cells instead of muscle cells. Another disadvantage is the controversy that surrounds such research.

Controversy

In 2002, the Pew Foundation did a survey that asked the question, Do you support federal research funding being used for human embryonic stem cell research? At that time, 25 percent of the population in the United States said we should fund such research using federal dollars. About 75 percent thought we should not.

The survey also asked another question: What is more important, should we research human embryonic stem cells potentially to save lives, or should we not tamper with human embryos, despite the fact that doing so might result in helping other lives? The foundation directed this question to secular Americans, mainline Protestants, Catholics, and Evangelicals.

Well, about 25 percent of the Evangelicals said that research was more important, and the percentage has increased over time. Catholics started at 45 percent in

2002, then went up to about 65 percent, and more recently have come down a bit. Percentages for secular Americans and Mainline Protestants are also going up.

What I take from this survey is that education and exposure to more information appears to produce greater acceptance of research with human embryonic stem cells; it becomes more acceptable. However, the controversy continues in various areas—in the media, in the bioethics community, in the religious community, in the scientific community. So let's look at some controversy.

In 2001, President George W. Bush decided that the federal government should restrict federal funding for human embryonic stem cell research. He essentially said that funding could be used only for stem cells that existed at that time. These have been dubbed the so-called Presidential Lines. Essentially, this decision permits any kind of stem cell research, but only on these particular lines. Since 2001, many attempts have been made to bypass or circumvent this decision.

For example, in order for me to do stem cell research in my institution we've had to create a separate set of laboratories renovated with our own internal funds—every pipette, centrifuge, and reagent must be bought with local university funds; they cannot be bought with federal dollars. Everything and everybody needs to be totally sterile of federal dollars. It becomes very cumbersome to do that, provided one can work with non-presidential lines.

Since President Bush's edict, attempts have been made to find other sources of funding. California has led this effort, and it plans to invest three billion dollars over ten years in nonfederal funds to support stem cell research. New York has followed and plans to spend two billion dollars over ten years.

Current Status of the Science

While we wait for the controversy to settle down, go away, or maybe heat up, most of the stem cell research in the United States is currently focused on adult stem cell work. The major tools that we have in our arsenals are in the newly emerging field of what we call regenerative medicine.

For those who may not be familiar with how this works, within bone marrow for example, there are the progenitor red cells that can be harvested. Progenitor red cells can go on to form multipotent, so they become other cells in that red cell line. Then we have adult stem cells, which tend to become the same cells I mentioned before. They can be coaxed into becoming other types of cells, too. Sometimes you need to add a growth factor to have them go in the right direction. These cells typically start out and generate a series of red cells or muscle cells, as the case might be.

We can use these cells therapeutically. We harvest the stem cells and put them in a petri expander, which enables us to use them in a variety of transplants. They might be used for a transplant with a leukemia patient or with patients who have multiple myeloma, which is a bone marrow cancer. These cells then generate other cells, which are passed back into the individual. This is clearly an effective way to use adult stem cells therapeutically.

What are some of the advantages of using adult stem cells? Well, organ tissue rejection is unlikely if a patient receives their own stem cells. Also, these kinds of cells are easy to find, as with blood cells. These are partially specialized, and they require less coaxing because they are partially specialized, so they can generate their own offspring cells rather easily.

What are some of the disadvantages? Adult stem cells usually have a shorter life expectancy. Furthermore, they're difficult to isolate and extract, and sometimes there is limited flexibility in the types of cells they can produce. In addition, they may not be so common; they may become scarce as people get older. There are fewer stem cells in our bodies as we age and they are harder to harvest, which makes it difficult to generate multiple cell lines.

So here's a question: How far along are we? I don't think we're ready for you to donate two stem cells one day and use them for therapy the morning after. But we certainly are making significant progress using adult stem cells in certain cases. I think the news is actually getting better and we're almost there. Adult stem cells are already being used to cure certain illnesses.

Adult stem cells are being very effective in treating certain cancers. There are also some other future potential uses on the horizon, for example, with diabetes. In fact, at one of the stem cell meetings I recently attended, a presenter told us he was doing some work with ALS, Lou Gehrig's disease. That is very exciting because there's just no other therapy out there right now. This is new. It's not well-published or well-

researched, but we are pleased to know about folks out there who are beginning to do some work with a disease as devastating as ALS.

The most recent breakthrough, as of November last year, was news that scientists have used ordinary skin cells to take on what they describe as chameleon-like powers. These have been termed *induced pluripotent stem* (iPS) *cells*. Essentially, this is a way for the scientists to have cells potentially return to embryonic stem cell status in the laboratory. Two separate investigators on two separate continents have corroborated this discovery.

This is exciting, though, in fact, we're not sure whether these are truly identical human embryonic stem cells. They certainly have been restored and characterized as stem cells, but whether or not they are equivalent to embryonic stem cells remains to be worked out. Nevertheless this is very exciting. It's exciting that we can now produce at least two studies indicating that use of plain old skin cells would permit us to produce embryonic stem cells and circumvent the controversy that has swirled around us.

If the work is corroborated, such an approach would have great potential. The availability, accessibility, and the noncontroversial potential is extraordinary.

But the news gets better. In December 2007, the *Washington Times* and *Washington Post* reported that scientists can cure mice of sickle cell anemia using stem cell techniques. This is the first direct proof or report of an actual curing. This is an experimental study, but nevertheless it suggests great potential.

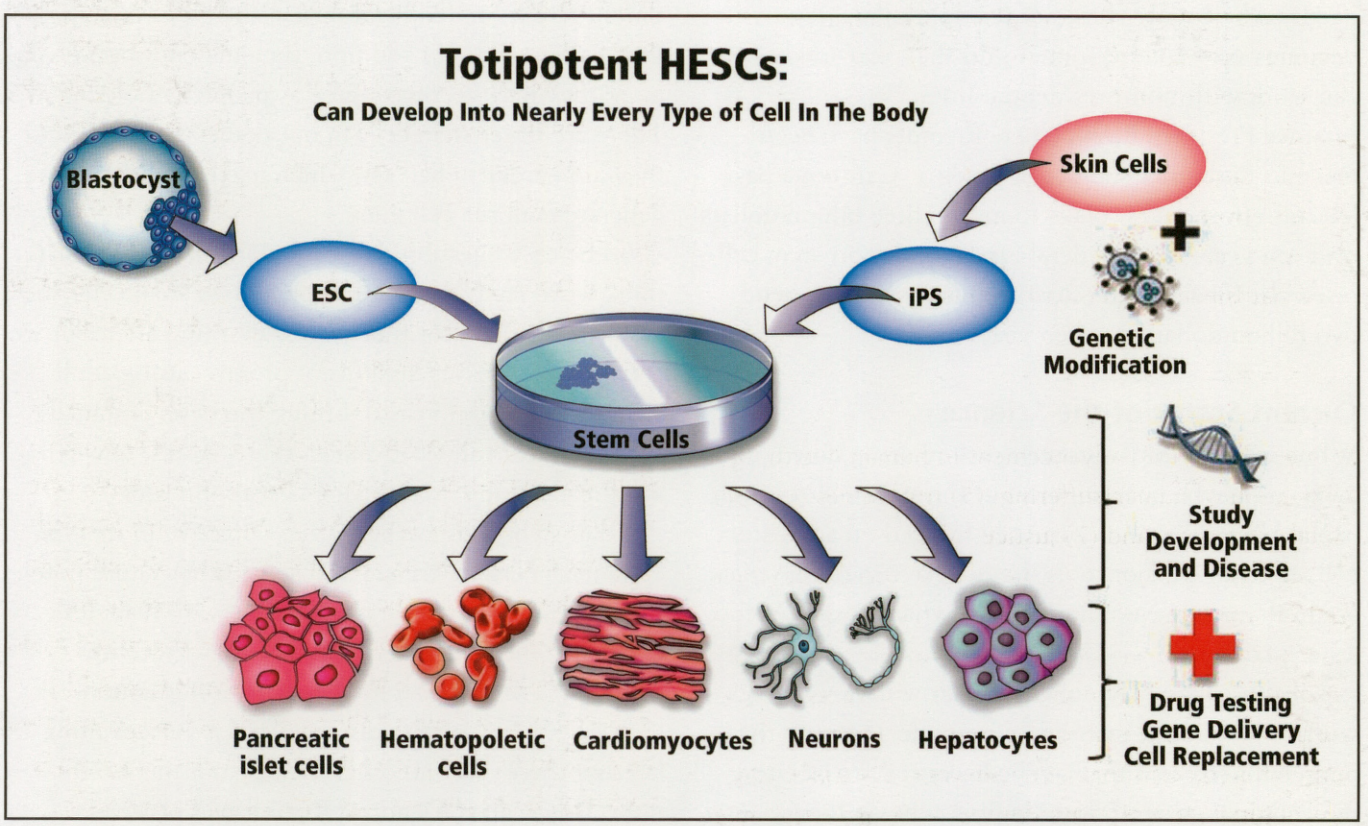
There are certain caveats you should consider before you run out and try to buy some stem cells from your own body and apply them personally. Skin cells are reprogrammed and the vectors being used are viruses. This sometimes has the potential of increasing risk of cancer.

Another consideration is that we're not certain whether these derived stem cells or stem cell lines are identical to genuine human embryonic stem cells.

However, these caveats should not dampen the excitement. Instead, it basically says that we need precise scientific definition, and we need to characterize these reprogrammed stem cells to ensure that they are not only equivalent, but also identical to the human embryonic stem cells.

The Promise

With these thoughts in mind, I can answer the question I was originally asked to address: Can we live without human embryonic stem cell research? My



answer would be possibly, but not yet. We won't know until we understand much more about human embryonic stem cells

So why do we study human embryonic stem cells? They are the gold standard right now. We still don't understand many aspects of what makes them so unique, but they're particularly valuable for studying some diseases, they offer a good animal model, and they provide a good cell model.

Something else is also important. If we postponed doing stem cell research or decided not to do it at all, there would be opportunity costs. Some people would be sick or even die that could have been helped; there would be increased suffering for patients and their families. There would also be an economic cost for caring for sick or dying people who could have been helped.

Since this is an Adventist institution, I want to ask what the Seventh-day Adventists say about this issue. They typically pride themselves for thinking independently, I made a similar statement once at Georgetown, which is a Catholic university. Most of the people there are not Catholics, but when I enter that campus I know I'm in a Catholic university. Adventists are a bit more subtle.

On April 2 and 3, 2008, the General Conference convened an ad hoc committee in which I joined with some of my colleagues to find out what Adventists should say on the subject of stem cell research. Some important principles emerged from this meeting but they never became an official statement of the Seventh-day Adventist Church, and thus were never published or distributed as such.

What the ad hoc committee proposed was very reasonable—that stem cell research and stem cell evaluation should be based on seven core principles: (1) respect for the gift of human life, (2) protection of human dignity, (3) advancement in human health, (4) alleviation of human suffering, (5) truthfulness, (6) personal autonomy, and (7) justice.

We then decided to operationalize these recommendations into practical guidelines that we hoped the Church would support. We proposed first that human embryos should not be created for the express or sole purpose of human embryonic stem cell research. Second, we suggested that stem cell research is ethically justifiable if stem cells are derived without compromising the well-being of the embryo or the fetus, Thirdly, we proposed that the destruction of embryos for the sole purpose of research not be encouraged or justified.

PHOTO BY JUSTIN IDE/HARVARD UNIVERSITY NEWS OFFICE/WWW.NCRR.NIH.GOV/CLINICAL_RESEARCH_RESOURCES/CLINICAL_AND_TRANSLATIONAL_SCIENCE_AWARDS/CONSORTIUM_DIRECTORY/

Scientists performing research on human embryonic stem cells derived after August 9, 2001, must frequently work in segregated laboratories with separate equipment and supplies to prove that no federal money is being spent on the new cells.

Last, we acknowledged that there are settings in which embryonic stem cell research is being conducted in secular places all over the world. We then proposed that under those circumstances—regardless of who the scientists are—research should be conducted under the strictest ethical guidelines and with oversight provided by an embryonic stem cell oversight committee. We felt that stem cell research is ethically justifiable if the cells are derived without compromising the well-being on the embryo.

Not long ago, a paper came out in *Science* by the Laser Group, a biotech company. Laser described a pregenetic diagnosis, in which the company basically removed one cell out of the multiple cell stage and used that cell to try to expand it and get stem cells from it. Basically, Laser showed that this could be done by

extracting one of the cells of the embryonic, the morula for example, to create a stem cell line.

Laser was criticized rather heavily because people took its work out of context. What the group tried to do was to show simply that the procedure could be done, not that it actually had been done. In any case, Laser was criticized for destroying the remainder of the cells.

The discoveries keep coming. On January 11, 2008, the *Washington Post* reported that scientists in Massachusetts have created several colonies of human embryonic stem cells without harming the human embryos from which they had been taken. This is the latest in a series of recent advances that could spread development of stem cell based therapies for a variety of diseases. I believe that the recommendations we offered the General Conference were right on target.

Conclusion

In summary, I hope I have shown that there clearly are benefits for human embryonic stem cells in medicine,

Guidelines for Stem Cell Research at Loma Linda University

Ethical Concerns

Current discussions about embryonic stem cells focus on a fundamental question: When does human life begin?

Some Christians, basing their views on the creation story (Gen. 2:7), believe that a human life begins with the first breath after birth. On this view, a new human life begins at the time of birth. Research with embryonic stem cells can obviously be accommodated within this position.

Other Christians believe that a new and unique person comes into existence at conception. They point to biblical evidence that prenatal life is valued (Ps. 139:13). This view often leads to the conclusion that, from the "moment" of conception, an embryo deserves the protection accorded to any other human being. From this perspective, no potential benefit to other humans could justify the destruction of a human embryo.

Still other Christians hold that the moral status of prenatal life develops gradually through many important stages, in a crescendo building to birth. Scripture speaks, for example, of having been "knit together" in the womb (Ps. 139:13), thus indicating an awareness of a developmental process. And the legal status assigned to prenatal life differed from that given to established personal life (Ex. 21:22–25). According to the developmental view, implantation is of crucial importance because further progress is impossible if an embryo does not become implanted in a uterus. Another important time is the onset of organized neurological activity. Viability, when the fetus is capable of sustained life outside the womb, is still another significant step in prenatal development. While the developmental view may include the belief that early embryos have human potential and possess symbolic moral value that is worthy of respect, it may also allow embryo research after taking into account both the stage of embryo development and the purpose of the research.

Principles

As an integral part of their distinctive mission of faith, Seventh-day Adventists seek to preserve human health and wholeness. When confronted with complex ethical questions, Adventists look for guidance from the Bible. The following ethical principles are drawn from Scripture and are intended to guide decisions regarding research involving embryonic stem cells.

1. **Respect for the gift of human life.** Our Creator is the Giver and Sustainer of human life (Gen. 1:30, 2:7; Ps. 36:9; Acts 17:24–28). The Bible prescribes protection of human beings, and God holds them accountable for taking the life of another (Gen. 9:5, 6; Ex. 20:13; Deut. 24:16; Prov. 6:16, 17; Rom. 13:8–10). Although we may disagree about the exact time when human life begins, Scripture portrays the Creator as involved in the development of human life during pregnancy (Ps. 139:13) and stipulates penalties for those who would negligently injure a developing fetus (Ex. 21:22-25).[1] This means that, once pregnancy has begun, the developing gift of prenatal life must be given serious moral consideration.
2. **Protection of human dignity.** Human beings were created in God's own image (Gen.1:26, 27) and thus were given personal dignity. Care must be exercised to avoid actions that would threaten or diminish the personal dignity of human beings. With reference to embryonic stem cell research, this means that embryos should not be created for purposes of research or for commercial gain.
3. **Advancing human health.** Human beings are multidimensional units comprised of physical, mental, and spiritual components. Humans can become host to the indwelling Holy Spirit (1 Cor. 6:19; 2 Cor. 6:16; Eph. 3:14–19; Eph. 5:30–32) which permits them to become reflectors of Gods character while remaining mortal. This indwelling follows the awareness of God and a conscious desire to yield to His influence. Independent life commences at birth, matures with aging and reaches the highest degree of wholeness when the Holy Spirit indwells the life. In light of this belief Adventists promote the health of all with the objec-

and this is extremely promising. There clearly are controversial areas both for moral and ethical reasons. I believe that we are making progress in this field and that the level of controversy will get less and less as we potentially derive stem cells from non-embryonic sources. If the report I just cited is correct, we will also be able to obtain stem cells without jeopardizing the well-being of other embryonic cells. Already, physicians are applying adult stem cell advances in treating illnesses or injury in the new field of regenerative medicine.

I believe that some day we will be able to reprogram adult cells to become pluripotent, and that these will potentially take the place of human embryonic stem cells. We also need to be realistic and acknowledge that at this time there may, in fact, be instances where research using human embryonic stem cells may be warranted so long as some of the recommendations we have made are taken seriously, adhered to, and applied appropriately. Whatever is done, it should be done under the strictest ethical guidelines and oversight. ■

tive of obtaining the highest degree of wholeness possible

4.1 **Preventing and alleviating human suffering.** God's plan for human beings includes a growing understanding and appreciation of the wonders of His creation (Ps. 8:3–9; 139:1–6; 13–16; Matt. 6:26–29). Efforts to understand the basic structures of life through careful research should be encouraged, especially when such investigation holds the promise of serving human health. Christians accept the responsibility to prevent suffering and preserve or restore human health whenever feasible (Luke 9:1, 2; Acts 10:38). Because it may be possible to use stem cells in the restoration of health, ethical research in this area is worthy of pursuit.

5. **Truthfulness.** Christians favor truthfulness and openness (Prov. 12:22; Eph. 4:15). Thus research with embryonic stem cells should be governed by clear presentations of the truth about the proposed research, without exaggeration of the potential benefits or research's success.

6. **Justice.** Scripture teaches that people should be treated fairly (Deut. 10:17–20; Amos; Micah 6:8; Matt. 5:43–48). If benefits result from stem cell research, these should be made available on the basis of medical needs and not on the basis of perceptions of social worth.

Specific Provisions

Investigators contemplating embryonic stem cell research or providing support services to such research are expected to abide by the following provisions which flow from the stated principles and the current (February, 2008) state of research technology:

1. Research will not be conducted for the purpose of producing human clones.
2. Human embryos will not be created for the purpose of producing embryonic stem cells.
3. Human embryonic stem cell research will be considered when the stem cells are derived by means that do not compromise the well-being of a viable embryo or fetus.
4. While the destruction of human embryos for the purpose of research is not encouraged, research with cells derived from embryos that would otherwise be destroyed will be considered.

Note: Currently, the embryonic stem cell preparations available for study were derived, with informed consent, from excess embryos remaining after infertility procedures. The donors elected not to use them or to allow others to use them for reproductive purposes. Consequently, their fate would have been indefinite storage or destruction. While intentional destruction of human embryos for research is not condoned, a decision not to use these "abandoned" embryos would have been equivalent to their destruction.

Their developmental stage corresponds to that of a naturally generated embryo two or three days before implantation in the uterus. They have no differentiated structures. About half of natural embryos at that stage do not survive to term. Indeed, many contraceptives act by preventing them from implanting in the uterus.

While adult (multipotent) stem cells are now available, their potential is currently much more restricted. Until cells with equivalent properties are available, we will consider research using embryonic stem cell preparations derived elsewhere from early embryos, after all other options have been exhausted.

Footnote

1. Seventh-day Adventists have set forth principles for the protection of prenatal life in the statement "Guidelines on Abortion" intended to provide guidance when termination of an established pregnancy is under consideration. The statement was approved at the Annual Council of the General Conference, October 12, 1992. ■

Excerpted from the LLU February 2008 Research Affairs Document Stem Cell Research.