

ETHICAL CHOICES IN THE GENETIC AGE

Part 2: Embryonic Science

In less than three years, reproductive cloning has been eclipsed by stem-cell biology with its conceptual power and medical potential.

Reproductive cloning dominated the science news for several years after the announcement of Dolly the sheep's birth in 1997.¹ The extended debate has produced a broad consensus that cloning is too risky at present to apply the procedure to humans. The same conclusion was reached by the Christian View of Human Life Committee sponsored by the General Conference of Seventh-day Adventists.² Scientists' continuing inability to clone nonhuman primates and the report that multiple genes are inappropriately expressed in all cloned animals³ certainly reinforce those decisions. Furthermore, despite public fascination with the subject, there are relatively few practical uses for the technology. Even as a reproductive aid for infertile couples, reproductive cloning will likely find only limited use in human medicine.

In less than three years, reproductive cloning has been eclipsed by stem-cell biology with its conceptual power and medical potential. The spotlight of debate shifted dramatically to embryonic stem cells shortly after their discovery in 1998.⁴ Public discussion accelerated when President George W. Bush addressed the subject in a national speech, and the debate continues. On September 3, 2002, California

By Anthony J. Zuccarelli

Governor Gray Davis, in a press conference featuring paralyzed actor Christopher Reeve, signed state legislation that approved funding for embryonic stem-cell research in direct conflict with federal prohibitions.⁵ A few days later, former First Lady Nancy Reagan allowed her dissatisfaction with current stem-cell policy to become public.⁶ In June, Former President Gerald Ford spoke out in the *Washington Post*, calling a ban on embryonic stem-cell research the equivalent to "slamming the door to lifesaving cures and treatments."⁷ Though recent geopolitical events have pushed biomedical topics to the inside pages of newspapers, students (and probably their parents) are likely to be confused, or at least curious, why thoughtful scientists, respected politicians, and well-known personalities are butting heads with the U.S. Government over what seems to be a promising avenue of medical research. Furthermore, the stem-cell debate offers teachers an unrivaled opportunity to help their students examine and share their ideas about what makes human life valuable.

Adult Stem Cells

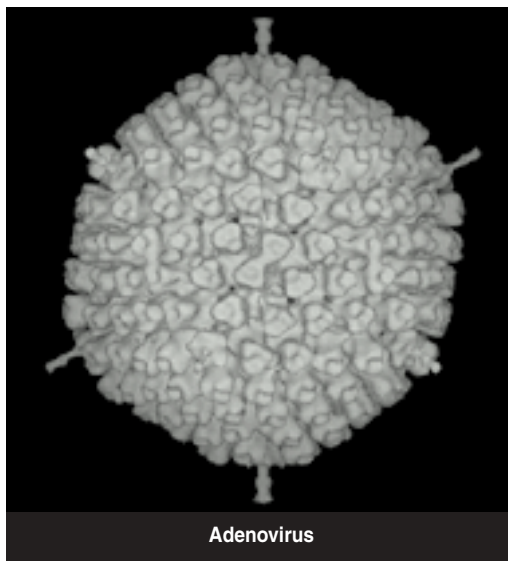
To understand the debate, we must first review a few concepts from human cell biology. Cytologists tell us that our bodies are mostly made up of “differentiated” cells that perform only the limited functions required for specific tissues. Scientists have identified more than 200 differentiated cell types—myocytes (muscle cells), neurons (nerve cells), erythrocytes (red blood cells), and so on. Highly specialized cell types, like the three just mentioned, cannot divide at all. Other differentiated cells may divide a few times and then stop. Consequently, differentiated cells cannot create more of themselves. Nor can they “change their spots”—a mature neuron cannot become a myocyte or any other type of cell. Under natural conditions, differentiation is a one-way street.

Fortunately, many tissues contain a few unspecialized stem cells.

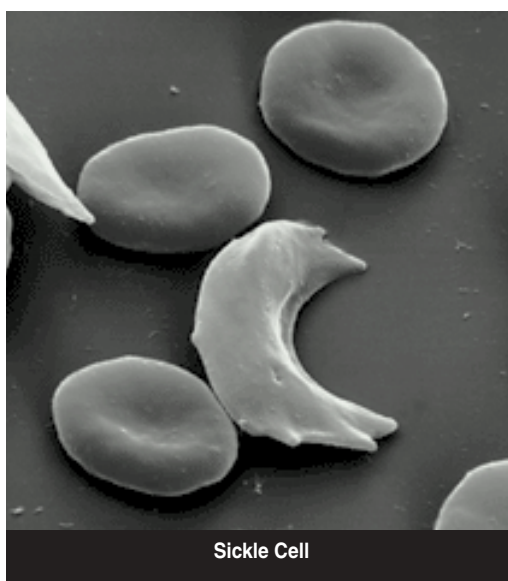
Whether they are obtained from a fetus, a newborn, or an adult, they are called “adult stem cells.” Given the proper environment, they divide repeatedly to make more stem cells, a property called “self-renewal.” Unlike differentiated cells, adult stem cells have not been trained to perform the specific tasks of specialized cells. The training program is called “differentiation”—an orderly process in which particular cellular genes are activated, while others are switched off permanently. Differentiation occurs most notably during the embryonic and fetal development, but it continues after birth to produce differentiated cells that have short lives or that must be replaced regularly (e.g., blood and epithelial cells).

Multipotency

In contrast to the fixed functions of differentiated cells, adult stem cells from a particular tissue are “multipotent,” which means they can mature into any one of several cell types found in that tissue. Hematopoietic stem cells from bone mar-



Picture Removed



row, for instance, can mature into erythrocytes or any of a dozen other cell types commonly found in the blood and immune system. This flexibility accounts for their alternative name, “multipotent stem cells.” The role of adult stem cells in the body is to generate replacements for cells that die as the result of damage, infection, or ageing. Without a means to replace those cells, human life would be quite short.

The enormous interest in stem cells results from their two distinctive traits—multipotency and self-renewal. If stem cells could be isolated and grown in the laboratory, they might be used therapeutically to replace human tissues that have been destroyed by disease or trauma. Such transplant tissue would be perfectly compatible with the donor’s immune system.

Unfortunately, several obstacles hinder that achievement. First, adult stem cells are scarce. Bone marrow, a well-known source of adult stem cells, contains only one per 10,000 cells. Other body tissues may contain more stem cells, but never exceeding one per several hundred differentiated cells, and their numbers decrease with age. The low numbers mean that one must have a large mass of normal tissue, a rare commodity, to obtain enough adult stem cells for most purposes. It seems unlikely that epileptics or Parkinson’s sufferers would have spare brain tissue from which neural stem cells could be isolated to treat their disease. For some tissues (like the heart and the insulin-producing cells of the pancreas), no stem cells have been identified. Also, separating adult stem cells from the large number of differentiated body cells is a difficult process. Furthermore, though they are self-renewing in the body, it is no simple matter to re-create their preferred growing conditions in laboratory cultures.

A further difficulty is that adult stem cells have limited flexibility. Typically, an adult stem cell can become one of the cell types found in

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the tissue from which it came. For example, a nerve stem cell may become a neuron, a glial cell, or an oligodendrocyte—all components of nerve tissues—but it cannot become a pancreatic cell or a bone cell. Some animal studies suggest that such cells' developmental flexibility sometimes exceeds expectations. Adult stem cells from one tissue have been reported to develop into cell types characteristic of other tissues, though recent studies dispute claims of broad flexibility.⁸ In any case, there is no evidence that an adult stem cell can produce all 200 specialized cell types.

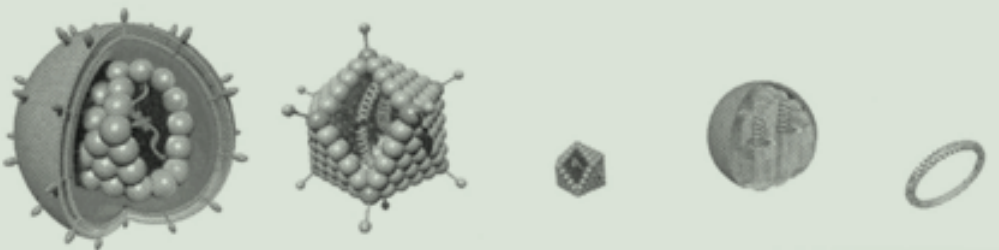
targets include Type I diabetes (loss of pancreatic islet cells), Parkinson's disease (loss of dopamine-producing neurons), rheumatoid arthritis (destruction of cartilage and chondrocytes), multiple sclerosis (loss of myelin and myelin-producing cells), macular degeneration (loss of retinal visual receptors), cirrhosis (loss of liver cells), osteoporosis (loss of bone and bone-forming cells), spinal cord injuries (loss of spinal neurons), heart failure (loss of myocardiocytes), leukemia (cancer of blood cells), and many other diseases. Significantly, there are few treatment options for many of these diseases.

Embryonic Stem Cells

The small numbers and limited capabilities of adult stem cells account for the enormous interest in their embryonic counterparts. In contrast to their more mature cousins, embryonic stem cells have unlimited flexibility and can become any cell type; they are often called "pluripotent stem cells." They are also self-renewing and tend

to be easier to propagate in the laboratory. One embryonic stem-cell line has been grown for more than two years through more than 300 doublings. The cells' ability to propagate indefinitely suggests that we can grow embryonic stem cells in culture until they increase to a mass large enough for transplantation. Their pluripotency suggests that once we learn how to mimic the signals that provoke them to differentiate, we may be able to make any type of differentiated cell needed by patients. Tantalizing reports show that embryonic stem cells can differentiate into dopamine-secreting neurons that will actually reverse the symptoms of Parkinson's disease—at least in rats and mice.⁹

The clinical potential of both types of stem cells has touched off an explosion of research, but our knowledge is still very limited. As a result, novel stem-cell therapies that go beyond the well-established use of bone-marrow cells are likely to be decades in the future. Nevertheless, the list of potential medical applications is impressive. Any condition that causes the death or depletion of a specific cell population may eventually benefit from stem-cell therapy. Some promising



	Retroviruses	Adenoviruses	Adeno-Associated Viruses	Liposomes	"Naked" DNA
Some Potential Advantages	Integrate genes into host chromosomes, offering chance for long-term stability	Most do not cause serious disease; large capacity for foreign genes	Integrate genes into host chromosomes; cause no known human diseases	Have no viral genes, so do not cause disease	Same as for liposomes; expected to be useful for vaccination
Some Drawbacks of Existing Vectors	Genes integrate randomly, so might disrupt host genes; many infect only dividing cells	Genes may function transiently, owing to lack of integration or to attack by the immune system	Small capacity for foreign genes	Less efficient than viruses at transferring genes to cells	Inefficient at gene transfer; unstable in most tissues of the body

By some estimates, more than 100 million Americans have conditions that may be treated with stem cells.

Source of Embryonic Stem Cells

No one disputes the potential value of stem-cell therapies. Bone marrow and its constituent stem cells have been used to treat blood disorders for 30 years. Rather, the debate converges on the source of embryonic stem cells—very early embryos.

After a human egg is fertilized, the resulting zygote divides repeatedly, typically arriving at the blastocyst stage about five days later. At this point, it is a pinhead mass of about a hundred cells that takes the form of a hollow, fluid-filled sphere. On the inside surface of the sphere is a small cluster of cells called the "inner cell mass." Embryonic stem cells are derived from the inner cell mass of blastocysts.

Most cell biologists agree that it is unnecessary to create embryos specifically to produce stem cells, since early embryos are available from other sources. In vitro fertilization is widely used to aid couples who are unable to conceive by nat-

ural means. In 1999, for example, more than 30,000 babies were born in the U.S. as the result of in vitro fertilization, about one million children worldwide since 1978.¹⁰ Doctors fertilize six to 14 eggs from each woman. Usually two to four are implanted in the patient's uterus to achieve a reasonable probability of pregnancy. The healthiest of the remaining embryos are frozen in case the first implantation attempt fails or the couple wants to enlarge its family at a later time. If we accept in vitro fertilization as a treatment for infertility, then excess embryos will exist.

By some estimates, more than 100,000 embryos are currently in frozen storage.¹¹ When patients decide not to use certain embryos, they can offer them to other couples, require that they be destroyed, or allow them to be used for research, provided that they do not develop beyond a specified stage. Almost all of the existing embryonic stem-cell lines were derived from such "extra" embryos. Many find it difficult to argue that it would be better for the embryos to be discarded as waste than for them to be used to save the lives of others.

When Is Life Human?

Because, under the proper conditions, blastocysts might develop into human beings, we must consider carefully how they should be treated. What degree of protection do they deserve? The debate centers around a knotty question: When does human life begin? Or more precisely, when does morally relevant personhood begin? The answer depends upon the moral doctrine one uses to assign human value.

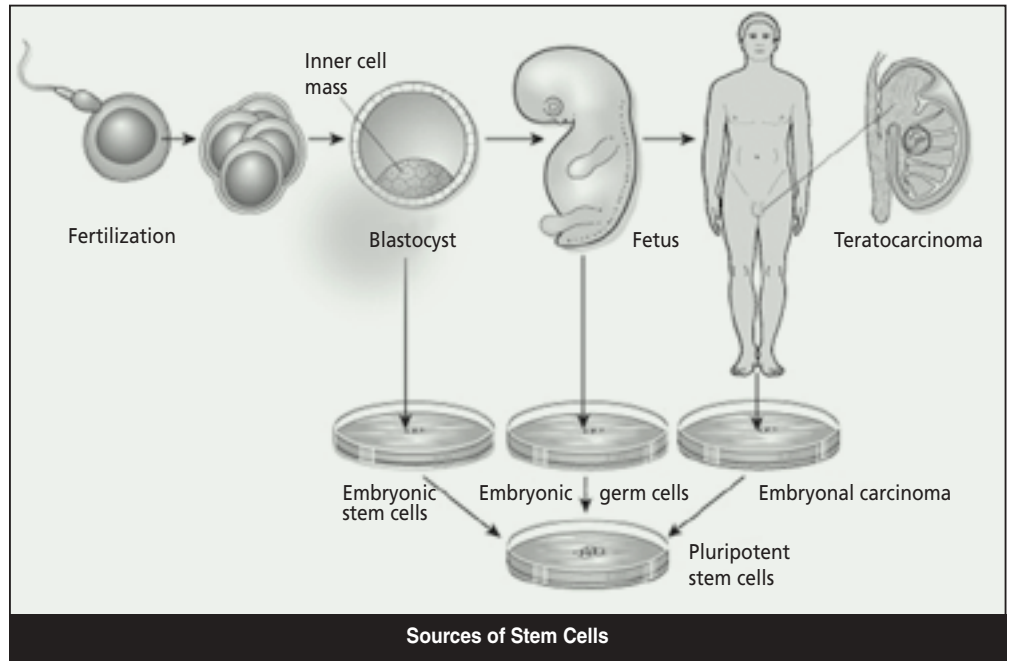
Some Christians find biblical support for the belief that human life begins at birth. Others subscribe to the concept that a new and unique person comes into existence at the moment of fertilization. This second doctrine leads to the conclusion that no benefit to others can justify the purposeful destruction of embryos.

Still other committed Christians hold that the moral value of an embryo develops gradually, like the brightening of a predawn sky, up to the moment of birth. There are many vital stages in this process. Certainly, implantation in the uterus is essential because without it, no further development can occur. Somewhat later, the earliest elements of the nervous system appear, which eventually support organized neurological activity. Human life could not exist without a functioning brain, so that is a key frame in the moving picture of prenatal development. At another point, the fetal heart begins to beat. Much later, at quickening, the fetus makes its first detectible movements, and still later, it is capable of sustained life outside of the womb. These are all critical steps in the progress

toward birth. A developmental view suggests that the embryo gradually attains human potential and increasing symbolic moral value. It also allows the possibility of embryo research after taking into account the stage of development and the objective of the research.

Embryo Status

The blastocysts from which embryonic stem cells are ob-



tained have no human features, no organs, no nerve cells, no differentiated tissues of any kind. Under natural conditions, a human embryo would implant in the uterine wall six to nine days after fertilization. Blastocysts used to establish embryonic stem-cell lines have not yet reached that stage. For some, the matter is decided by the fact that a five-day-old embryo lacks one essential quality of personhood. Until the 14th day, it is possible for an embryo to split into two or more parts that may become monozygotic offspring (i.e., identical twins). Consequently, before that time, the embryo does not correspond to one and only one individual; its identity is not established. Consequently, it is difficult to assert that the embryo is a person at this stage.¹¹

An understanding of the ruthlessness of natural reproduction informs the thinking of many people on this issue. The union of sperm and egg through natural conception fails more often than it succeeds in producing a new human being. Between 50 and 75 percent of embryos formed by sexual intercourse do not survive long enough to become newborns—and the failure rate is higher still with in vitro embryos. That leads some to argue that it is difficult to attribute great moral value to an entity that often fails under natural circumstances.¹²

Personhood

Adventists do not believe that the soul is an immaterial entity that, at a particular moment, takes up temporary resi-

dence in a physical body, but that it represents the whole person energized by life. It follows logically that the basis for human dignity includes the capacity for higher functions such as consciousness, autonomous reason, and ability to establish interpersonal relationships—attributes that Adventists have identified as elements of the image of God. An essay by Adventist ethicist James Walters explored the basis for decision-making in neonatal intensive care. In it, he outlined the concept of “proximal personhood” as a means for assigning moral value based upon a reasonable potential to achieve a personal life with self-awareness.¹³

Therapeutic Cloning

Concern about using early embryos is the first ethical obstacle to the use of embryonic stem cells. Biologists admit, however, that simply having a few embryonic stem-cell cultures and the knowledge to convert them into differentiated cells won't be enough to achieve broadly applicable cell therapies. Stem cells are marked with surface features that make them incompatible with the immune systems of some recipients. The only way to prevent rejection of stem-cell implants is lifelong treatment with immune-suppressing drugs. Such drugs have serious toxic effects and make recipients more susceptible to infections, but they would be essential in the absence of other options.

The most discussed alternative to immune-suppression therapy links stem-cell therapy with human cloning. It may be possible to create patient-specific embryonic stem cells using a technique originally named “therapeutic cloning” but now frequently called “nuclear transplantation therapy.” In this process, the nucleus from the patient's cell is transplanted into an enucleated egg. The egg is incubated in vitro to the blastocyst stage, when embryonic stem cells can be extracted. Tissue transplants derived from such stem cells would, in principle, be perfectly compatible with the patient who provided the nucleus.

The principle of therapeutic cloning has already been successfully demonstrated in cows, mice, and rats.¹⁴ But there are likely to be difficulties in adapting it for use in humans because the procedure consumes valuable resources. One estimate suggested that it would take more than 280 human eggs transplanted with patient nuclei to create one “custom” embryonic stem-cell line.¹⁵ In addition to the \$4,000 price tag for each human egg, the time and technical effort to derive an embryonic stem-cell culture for each patient would be incredibly cumbersome and expensive. Furthermore, therapeutic cloning is ethically distasteful to those who believe that a zygote is fully human.

Beyond Therapeutic Cloning

Are there other ways to avoid the problem of transplant

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rejection without the use of human eggs and therapeutic cloning? The British have taken the most direct approach—a stem-cell bank. They plan to collect existing and newly created embryonic stem-cell lines in order to include all of the major variations in cell surface antigens. To cover all of the antigenic tissue types, at least 5,000 different cell lines will be required. With a sufficiently diverse collection, it should be possible to select a cell line that matches any patient and to stimulate its differentiation into the specialized cells that the patient needs.

A second, more distant possibility would be the creation of “universal donor” embryonic stem-cell lines. Genes that encode major cell surface antigens

in existing stem cells could be modified to create derivatives that are not recognized as foreign in most or all patients. Some technical steps required for such genetic alterations have already been accomplished.

Researchers are also trying to understand how the internal environment of an egg “reprograms” nuclei. The egg cytoplasm somehow erases the nuclear memory of the differentiated state and resets it to the embryonic condition. Some chemical factors involved in reprogramming have been identified and isolated. If all of the conditions for reprogramming can be identified, scientists might be able to apply the process directly to adult cells. Bathing cells from a patient in a reconstituted egg environment could transdifferentiate them directly into the cell type of choice or convert them into stem cells. Tissue replacements could then be designed without the use of human eggs. Though this approach is admittedly futuristic, it is no more improbable than many recent developments in biomedicine.

Stem Cells Summarized

Some observers have overstated the usefulness of adult stem cells at the expense of embryonic stem cells to favor their philosophical posture of zygotic personhood. However, almost all scientists in the field agree that, in light of their therapeutic potential, too little is known to judge the relative merits or to limit research to one or the other. Embryonic and adult stem cells will likely provide complementary tools. About 76 embryonic stem-cell lines derived before President Bush's address have been approved for study with federal support.¹⁶ The research community must now produce evidence that there is actual—as opposed to theoretical—benefit to be derived from embryonic stem cells. That evidence will be a persuasive argument for their continued use and development.

Gene Therapy

Gene therapy raises different questions. It does not create new persons by asexual means. It does not consume fertilized

eggs, nor does it force us to calculate the moral worth of embryonic life. However, it does ask us to judge the permissible limits of intentional human modification.

Gene therapy is the modification of the genetic material in human cells to prevent, cure, or ameliorate a disease or defect. The added genetic material may encode information that is entirely new to the cells or it may represent additional copies of genes the cells already possess. The

source of the introduced genetic material is typically human, but in some cases, it may come from other organisms, or it may be entirely synthetic. Genetic modifications may be intentionally temporary or lifelong.

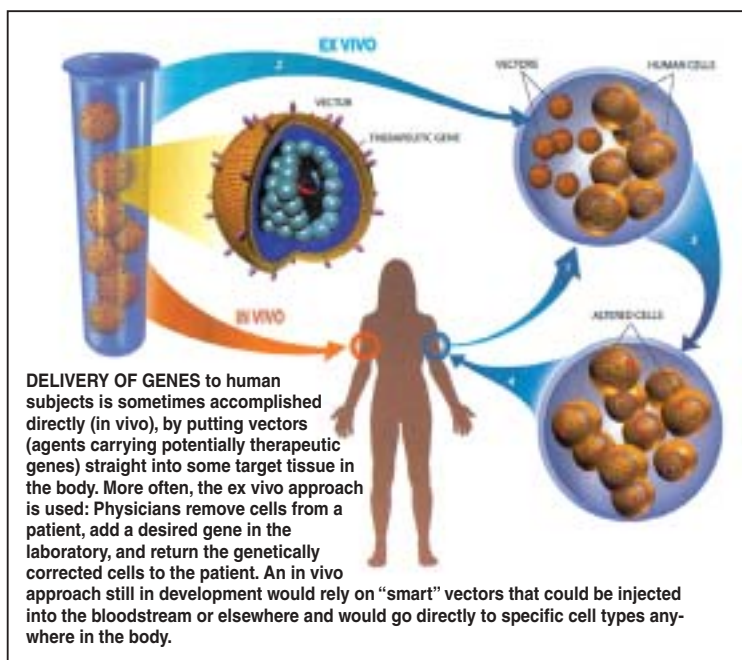
Somatic Gene Therapy

Gene therapy has two major subdivisions. Somatic gene therapy includes the genetic modification of cells that are not involved in reproduction. Many different organs and tissues have been targeted, including bone marrow, liver, muscle, skin, thyroid, intestines, lungs, vascular endothelium, heart, joints, brain, etc. If, for example, the gene for blood clotting factor VIII were introduced into liver cells of a patient with Type A hemophilia, its ability to supply a missing clotting protein would alleviate symptoms of the disease.

Somatic therapy's goal is the same as that of conventional medicine—to save the life or relieve the suffering of a particular patient. It does not attempt to achieve any therapeutic effects in the offspring that the patient may subsequently produce. In fact, it intentionally avoids making genetic changes in the germ (reproductive) cells of the patient.¹⁷

Techniques for accomplishing somatic gene therapy in humans are under intensive development. Since clinical trials began 12 years ago, nearly 4,000 patients have been treated in about 600 studies.¹⁸ There have been some promising results, but most tests of human gene therapy have been disappointing.¹⁹ This is not due to a shortage of genes that would have therapeutic effects, but to the difficulty of getting them into cells.

The “delivery problem” has been the major technological roadblock. The most common approach is to use viruses. Therapeutic genes are inserted into disabled virus particles to exploit the incredibly efficient mechanisms that viruses use to inject their own genes into cells during infection. Essential genes are removed from the viruses to prevent them from replicating, and they are replaced by therapeutic genes with the molecular signals to control them.²⁰ Some viruses used to



ferry therapeutic genes may be familiar: relatives of HIV, certain cold viruses, and the viral agent in smallpox vaccines. All viral vectors have inherent limitations and impose some risks.

The 1999 death of 18-year-old Jesse Gelsinger, a participant in a gene-therapy trial, though inadequately understood, has been attributed to an unusual inflammatory reaction initiated by the virus used in the study.²¹ Though easier to produce and less immuno-

genic than viruses, certain chemical or physical agents (e.g., liposomes, DNA-lipid complexes, and “gene guns”) have also been used to introduce genetic material into cells. Their lower efficiency has limited their use.²²

It is now generally accepted that the introduction of therapeutic genes into somatic cells is conceptually comparable to transplanting cells or organs for therapeutic purposes. Consequently, it raises no novel issues beyond safety and efficacy, as long as the intent is to treat clearly defined diseases.

Genetic Enhancement

Difficulties arise, however, when somatic gene therapy goes beyond the remedial. Once it becomes routinely successful in treating disease, we may expect proposals to use gene therapy to produce super-health. Current experience with cosmetic surgery suggests that the far side of this frontier is the exotic land of “enhancement,” a world beguiling in prospect but ethically treacherous. Who could resist a genetic treatment to reverse pattern baldness or to help lose a few pounds? How about increased resistance to cancer, infection, or heart disease? We already know several dozen alleles that reduce the incidence of cancer. An altered cell surface protein makes a few people resistant to HIV. Members of one fortunate community have an enzyme that protects them from heart disease no matter what they eat. Why not give everyone the genetic advantage now enjoyed by a few? But it doesn't stop there. There is little doubt that there are genes that influence height, intelligence, life expectancy, and every other human trait.

There are no simple prescriptions here. A proposal to limit gene therapy to treating disease suffers from the difficulty of defining “disease” unequivocally; it sometimes grades imperceptibly into the normal range of human variation. Also, the concept is influenced by culture. However, there is merit in the notion that gene therapy should be limited to conditions that are either demonstrably life-threatening or severely disabling.

Gene therapy is the modification of the genetic material in human cells to prevent, cure, or ameliorate a disease or defect.

I reject the “slippery slope” objection that seeks to forbid gene therapy because it will inevitably lead to enhancement. We do not prohibit every endeavor that, when pursued without restraint, might lead to undesirable consequences. Everything we do carries risk, which we attempt to balance against the benefits of our acts. Our deliberation implies that we can prescribe limits to our behavior. The reflection of God’s image that remains invites us to responsible action.

Germline Gene Therapy

Germline gene therapy is the second major category. It would purposely make genetic changes in all body tissues, including those that produce sperm and eggs. Such genetic alterations would be transmissible to the offspring of the original patient. In fact, the goal of germline therapy would be to affect all the descendants of a treated patient. Its justification would be the cost-effectiveness of permanently eliminating a genetic defect in a lineage rather than treating each affected individual separately. In this respect, it represents a fundamentally new objective for medicine. Germline modification in animals requires manipulation of fertilized eggs or very early embryos and several generations of controlled matings. Such techniques are inherently inefficient and unsuitable for use on humans.

Beyond the technical issues, germline alterations raise many unique ethical issues. God places enormous value on human freedom, but how does one get informed consent from persons who do not yet exist? Thoughtful individuals may make different choices regarding changes in their genes. The therapeutic choices of one generation may not be the preferences of the next. Furthermore, though we can assess the safety and efficacy of somatic therapies using animals and carefully controlled human tests, prospective evaluation of germline gene therapy is difficult, perhaps impossible. The “catch-22” is that we cannot foresee all the long-term consequences, but once changes are made, they will be permanent. Will the eradication of an undesirable feature also eliminate a secondary, but highly valued, trait? Animal tests cannot predict the subtle effects that gene changes may have on cognitive functions, yet these are the very capabilities that must be carefully guarded. Because of the multiple unknown risks and unresolved ethical issues, there is currently a moratorium on attempting germline gene therapy in humans.

Christian Motivation

Some might ask why we should concern ourselves with these arcane matters of genetic medicine. God has charged Christian health-care personnel with the responsibility of preserving life and alleviating suffering. The Scriptures portray God as endlessly concerned with the moral and physical restoration of His creatures. “And he sent them to preach the kingdom of God, and to heal the sick” (Luke 9:2, NIV).

Christ gave explicit instructions to continue His healing

ministry. Christian health professionals therefore have a moral obligation to use the most effective methods to prevent or treat disease. Adventists in particular appreciate the ministry of healing as part of God’s work on Earth.

We are powerfully driven to control disease, conditions that disrupt the order and harmony that God intended. Genetic medicine need not be an expression of human pride or arrogance. To the extent that it can prevent disease and restore health, we are obliged to investigate its potential.

When the aim is to alleviate suffering and when we use our creativity with courage,

caution, compassion, and prayer, genetic medicine has the same moral justification as traditional medicine. On the other hand, an attempt to redesign ourselves into creatures with new and superlative powers would be perilous. A balanced view of our God-likeness reminds us that we tamper with fundamental human attributes at great risk. However, we dare not neglect the opportunities and resources He provides. Ultimately, we are accountable to the Maker of the universe who holds us responsible for the care of each other and of the Earth. ✍



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spare time, he enjoys reading and thinking about the impact of biotechnology on individuals and society, as well as the ethical issues raised by advances in medicine. Part 1 of this article, “Reproductive Cloning,” appeared in the Summer 2002 Journal of Adventist Education.

NOTES AND REFERENCES

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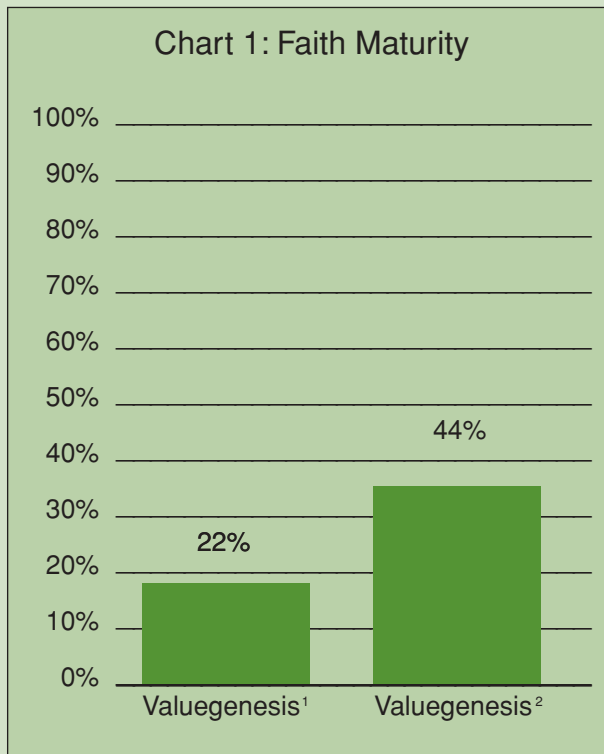
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22. See Endnote 20.

Corrections

Chart 1 on page 13 of the October/November 2002 issue included an incorrect element in the key. It should have appeared as follows:



The JOURNAL OF ADVENTIST EDUCATION Web site address was listed incorrectly in the Of Interest to Teachers page in the October/November 2002 and December 2002/January 2003 issues. It should be: <http://education.gc.adventist.org/jae/>.

The caption on page 3 of the December 2002/January 2003 issue omitted two names. The list of North American Division college/university presidents in the back row should have read as follows: Left to right: Gordon Bietz, Southern Adventist University; Charles Scriven, Kettering College of Medical Arts; Randal Wisbey, Columbia Union College; David Greenlaw, Florida Hospital College of Health Sciences; Delbert Baker, Oakwood College; Richard Hart, Loma Linda University; Sylvan Lashley, Atlantic Union College; N. C. Sorensen, Walla Walla College; and Fred Thomas, Southwestern Adventist University.

The name of the president of Southwestern Adventist University, Fred Thomas, was printed incorrectly in the December 2002/January 2003 issue. We apologize for this inadvertent error.

Claims for Missing Issues

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