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Gene Therapy in Biomedicine:Ethical Dilemmas

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GENE THERAPY IN BIOMEDICINE: ETHICAL DILEMMAS

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INTRODUCTION

Biomedical research is moving so rapidly its progress is breathtaking. Yet despite its promise, it carries a host of ethical problems that have never before been faced in human history. Should we patent human genes? Should we study human embryos to learn the roots of gene defects? Should we alter genes to make our offspring healthier, prettier, smarter, or longer lived? Would Quaker perspectives cast unique insight into these questions? These ethical quandaries are complex and strain the limits of human wisdom. In this article we first offer scientific historical underpinnings of many of the most acute ethical dilemmas in biomedicine and then we raise several key queries on which we particularly seek divine instruction.

To many people, World War II is the key event marker of the mid-twentieth century. Those who personally recall World War II will also remember how different health care was some 50 years ago. Antibiotics were discovered just before the war began. Until then, it was common for apparently healthy people to become ill and die from infectious diseases like scarlet fever, tuberculosis, poliomyelitis, and "simple" infections, often within days or weeks of becoming infected. During the post-war economic boom, experts began to talk of sparing the human race from the ravages of infectious disease as new antibiotics and vaccines were being discovered and life expectancy increased. Scientific discovery has brought anesthetics, antibiotics, cardiac catheterization and bypass technologies, organ transplantation, and the comforting proton inhibitors (that prevent overacidification of the stomach). In 50 years we have come to expect to be cured of bacterial infections without missing work. Yet, while public expectations are high, many people may not realize that medical care is likely to change more in substance and scope in the upcoming few decades than in all of human history. Beyond the traditional discoveries, a new type of medical treatment is about to irreversibly alter the

nature of clinical medicine as the embryonic stages of a great molecular biology revolution emerge with the turn of the millennium.

Over the last two decades, the term *molecular biology* has come to have a specific meaning. It now refers, not to the study of biological molecules in general (as it once did), but to the molecules that carry the genetic code of living organisms, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Molecular biology is the study and use of genetic molecules and it is the use of these molecules that will alter, most profoundly, the way medicine will be practiced in the future. A historical overview is necessary to appreciate the scope of the ethical dilemmas raised by the molecular biology revolution.

The Nature of the Gene

At about the turn of the last century, the monk-scientist Gregor Mendel carried out experiments on the determination of pea color and other traits that laid the foundation for modern genetics. He showed that peas have heritable color traits that appear in the next generation as either dominant or recessive. He showed that these traits are carried by reproductive cells from one generation to the next via heritable units, now called "genes." Soon after World War II, Watson & Crick (1953) reported the double helix structure of the DNA molecule and explained how it might replicate. From there, it did not take long for scientists to make the connection between the chemical message encoded in every DNA molecule to the true meaning of a gene.

It is now known that virtually every cell in the body contains complete copies of all 46 human chromosomes. Chromosomes are composed of long twisted strands of DNA that encode all the genetic information that makes human beings unique as individuals. Since the discovery of the DNA code, the gene has been carefully defined as a region on a chromosomal DNA strand that carries the code for a single protein. When properly signaled, a cell can manufacture that protein by reading the gene's DNA code. To fathom how genes, which simply carry codes for proteins, can be the basis for fashioning a complex living, breathing, emotion-laden human being, it helps to know that biological creatures are formed on a complex, but central, protein master plan.

There are several classes of coded proteins that are essential features of living organisms. These include: 1) Structural proteins. These proteins are manufactured for use as structural building blocks. For example, hair and fingernails are made of a structural protein called keratin. 2) Enzymes. Proteins in this class regulate all the chemical reactions of the body. Enzyme names are easily recognizable because they usually end with an "-ase" suffix. Thus, for example, a lipase is an enzyme that promotes the breakdown of lipid (fat). 3) Gene switches. Gene switches are proteins with the sole purpose of binding DNA to either turn a gene "on" (cause it to begin the process of making a protein) or to switch the gene "off." Such switch proteins are known to scientists as transcription factors.

A technological tool that makes molecular biology research go faster is the DNA synthesizer. When a scientist wants to study a piece of DNA with a known code sequence, she or he can order it from any laboratory that has a synthesizer. Therefore, once a gene code is known, the gene itself could be manufactured artificially. Thus it is theoretically possible (while being wholly impractical) to manufacture all known genes "from scratch."

Gene Cloning

The word *clone* has several different but related meanings. In the gene world, to clone a gene means to remove the gene-DNA from an organism's chromosome and insert it into foreign DNA. Gene cloning has been possible since 1973 when Cohen and Boyer received the Nobel Prize for splicing a common bacterial gene. This became possible because of the discovery of special enzymes in bacteria (restriction enzymes) that are able to cut DNA at specific sites. These enzymes are used on DNA as a paring knife is used on a long sausage—you can cut out the piece you want and glue the cut ends back together. A piece of gene-coding DNA can be excised from an animal's DNA and inserted into bacterial or viral DNA (using another set of enzymes) and the original piece of DNA can then be reproduced at will by growing and harvesting the bacteria. This is called gene cloning. A cloned gene can be easily studied and/or re-inserted into the DNA strand of another organism. Such experiments are now so easily done and are so commonplace that most high school science classes include simple cloning experiments as part of their standard curriculum.

With this brief background we can address several difficult ethical issues that have arisen as biotechnology has given us new capabilities in gene manipulation.

Should We Alter the Human Gene Expression to Extend Life-Span?

Upon the discovery of gene switches, it was immediately apparent to developmental biologists that such switches could help explain the nature of the biological "clock." It appears that from the moment of conception, a chain of chemical events is set into motion that leads to the division of the fertilized egg, the development of the embryo, fetus, child, and adult over time. The biological clock, then, determines the timing of life's biological events, birth, puberty, maturity, aging, and death. The clock has its own inherent rate, though environmental factors may affect rate also. This chain of developmental events begins when a few master gene switches turn on and touch off a complex chain reaction where each successive set of genes turns on its own new set. As this highly regulated cascade begins, the biological clock starts "ticking." Studies on lower invertebrate organisms indicate that a few select genes are able to alter the rate of the clock. Changing the expression of these genes may severely affect life span—in the case of a roundworm, by more than doubling it. The intricate details of the human clock will eventually become understood and clock-rate (determines rate of aging) will then become alterable should we choose to do so.

Should We Patent Normal and Manufactured Human Genes?

The DNA code for a protein is determined by the spatial order in which chemical groups called nucleotides (sometimes called bases) occur on a DNA molecule. These groups come in four varieties, A, T, C, G. Within a gene, every three nucleotides code for one amino acid. For example, AAA is the DNA code for the amino acid called lysine. A protein is merely a string of different amino acids. When a gene is "turned on" to make a protein, the code on the DNA for that protein is sent to the cell's "protein factory" via another molecule known as messenger RNA. Thus the code for any gene that is turned on can

be found by chemically determining the sequence of nucleotides of its DNA or messenger RNA. Through incredible technological advances it is now possible for scientists to determine the coding sequence for long pieces of DNA using a DNA sequencing apparatus. Thus, it is now possible to rapidly determine the sequence of new genes as they are discovered. In fact, it is the goal of the scientific community to find the code for all human genes within the next year or so as part of the "Human Genome Project." Because it is estimated that there are some 150,000 genes in the human genome (the sum total of all human genes) and each gene may contain thousands of nucleotides, the human genome project is an enormous undertaking.

The Human Genome Project is largely funded by the National Institutes of Health (NIH) with great financial and labor assistance from many countries. The Project is coding many important research mammals. Similar projects are under way for some plants as well because of the obvious agricultural application. Because gene sequences are patentable, there is great financial reward for a discovered gene. Nowadays, virtually all research institutions get property rights on new genes and many private and public institutions depend on income from these patents to fuel further research and development. For NIH supported gene discoveries, the code must be put into a master computer database (a "gene bank") so that all scientists have access to the code information. Recently, private companies have indicated great interest in sequencing large numbers of human gene fragments for the purpose of claiming rights to those sequences, should the gene become commercially important. A couple of companies have expressed claims that they can determine code more quickly than is commonly done in most NIH laboratories and they plan to win the "race" to control the patents on the many yet undiscovered genes. This raises questions about private companies holding large quantities of genetic information that would not necessarily be made public. This might make research more expensive for all scientists because companies could require royalties on DNA sequences needed for research products. Proponents of patenting genes argue that patenting brings energy and capital to the research that is required to move the field rapidly forward. Without it, decades will pass before we find cures for common genetic disease.

Should Personal DNA Sequences Be Private Information?

An important technology that rarely hits the popular press is the "DNA Chip." The DNA chip is like a tiny computer chip that binds specific pieces of DNA. With special probes that turn color, the chips can be used to screen human or animal DNA and indicate identity. The technology has a powerful future because it allows rapid DNA screening for research and medical purposes. It will soon be possible to do mass screening of human DNA samples to check for virtually all known gene defects. It may be possible someday to use this technology to detect propensities for alcoholism, mental disease, and certain forms of cancer, to name a few uses. However, people carrying genes that predispose to disease may be at risk for losing their insurance coverage or worse, new types of group discrimination based on certain genetic typing could arise.

Should We Study Living Human Embryos?

Artificial reproduction technology (ART) has grown enormously in the past two decades and continues to be an area of intense research that is fraught with ethical difficulties. In vitro (in the dish) fertilization is a commonly used technique in human medicine, in animal research, and in animal husbandry. Sperm from any donor can be placed in a dish with mature eggs and the eggs fertilized. Human fertilized eggs (zygotes) can then be allowed to grow to early embryo stages whereupon the healthy-looking embryos can be placed back into the uterus of the donor or into a surrogate mother after manipulating the hormonal environment to ensure that the uterus (womb) is receptive. One of the early obstacles to the success of this technique was the acquisition of human eggs from the ovary. Most problems with egg harvesting have now been solved and it is possible to obtain several eggs, using fiber-optic endoscopy, from ovaries that have been hormonally primed. Test tube babies were once front page news but are now commonplace. In fact, countless thousands of women have been able to overcome reproductive failure through the use of these techniques. The treatment of reproductive problems is a lucrative medical business even though the pregnancy success rate at some centers remains quite low.

In addition to egg harvesting, there are several crucial advances that have led to improved success in artificial reproduction. Cryopreservation, one of the most important, is the "ultra-cold" storage of sperm, eggs, and embryos in liquid nitrogen. This technique allows the storage of semen, eggs, and embryos for extended periods of time, some argue, indefinitely. This technology has led to many new ways of thinking about reproduction. People have chosen to store their reproductive cells for later use. It has been argued that women, whose eggs are most fit during their twenties, should preserve their eggs in their prime and then become sterile. This would allow complete separation of reproductive and sexual activities. The technology also provides opportunity for men to store semen for the same purpose or in the case of the Nobel Laureate Sperm Bank, for preserving highly sought after semen for commercial purposes.

The study of living human embryos is illegal in the United States. In some countries, human embryos can be studied for a week or so after fertilization. The embryos must then be destroyed. In the U.S. alone there are thousands of frozen human embryos in storage waiting to be implanted. In many clinical cases, more embryos are fertilized than are needed to ensure a pregnancy, but the number is not known in advance.

The issue of studying human embryos in culture is controversial. Undoubtedly, if human embryos were to be used for experimentation, they would die in the process. This raises the question of whether a human life has been extinguished.

A recent finding complicates matters further. Scientists have found that embryonic cells in a later (bastocyst) stage are also important because they can be used as "stem cells." These embryonic stem cells (ESC) are the cells that segregate in the early embryo to make the fetal body (as opposed to the placenta). Animal and human ESC have been grown in artificial media this year. The culture of human ESC was funded by a private company (Geron Inc).

This breakthrough is scientifically important because ESCs can be simulated to become virtually any type of cell in the body and they can replicate in a dish. This gives hope that new brain, heart, and pancreas cells can be made for injection into individuals who are suffering for having too few functional cells in any such organ. However, the stem cells must come from a human embryo that will be destroyed in the process, thus it is not legal to use federal dollars for

such research. Because these cells can theoretically propagate indefinitely, it is possible that cells from a single human embryo could provide medical help for many people.

Should Humans Be Cloned?

Up to the time the human embryo has divided some three times to the eight cell stage, each embryo cell is able to be detached from the others and form a new independent individual. Thus, at the eight cell stage, it is theoretically possible for the cells to be separated and a mother could bear genetically identical octuplets from a single embryo—and each new embryo could be divided at the eight cell stage to repeat the process. This cell "potency" has been used to advantage in animal husbandry to glean a large number of genetically identical offspring from a prize breeding pair.

Any of these early embryonic cells (early blastomeres) could be used to clone a human being. If a nucleus, say, from a skin cell (which like other body cells contains all 46 chromosomes) were to be fused with a human egg to replace the normal egg nucleus and the new "egg" was stimulated to divide and grow when placed in the womb, a human clone would be formed. The clone would have the same genetic makeup as the donor, like an identical twin. Cloning has been accomplished in sheep ("Dolly") and in mice but not yet in humans. It is therefore theoretically possible for a woman to give birth to her or her father's (or anyone else's) "identical twin." While some argue that we have no problem with normal identical twins, so we should not object to making one, others argue that the unnatural circumstance would place a cloned "twin" at psychosocial risk. Recently, one scientist has announced his intention to produce the first human clone.

Should We Alter Human Genes to Cure Genetic Disease?

The use of DNA to "cure" medical problems is now a possibility and medical scientists around the globe are contemplating novel ways to alter genes as new forms of therapy. The most common way that is being attempted is called "gene therapy." Gene therapy is the delivery of gene products to increase or otherwise alter the manufacture

of a protein by cells that are involved in a disease process. For example, the disease cystic fibrosis (CF) is the most common lethal genetic disease in the United States. In this disease, a protein that moves chloride into or out of a cell is improperly made by the cell because its gene code has an error in it—a gene defect. Chloride is the major ingredient in table salt along with sodium and is important in a host of physiological processes including water balance. People who have cystic fibrosis cannot regulate chloride properly and one serious outcome is that they cannot make the lining of the lung wet enough. The lining of the lung requires a wet mucus layer to trap bacteria so that they can be moved out of the airways. Because of this deficiency, CF patients often die of lung infections before their 30s. Gene therapy is being tried in these patients by delivering normal copies of the CF gene to the lung cells via modified cold viruses and having patients inhale the virus so it can infect their lungs cells and insert the normal gene. This form of therapy has mixed reviews so far. Even in those for whom there is relief of symptoms, the effect is not long lasting because the cells lining the lungs are normally replaced every few weeks.

Nevertheless, gene therapy offers hope to a whole host of diseases. As new delivery viruses (vectors) are being engineered it is hoped that certain types can be made to infect only selected cells or to be turned on only in selected cells. Genes can then be delivered to cancer cells, heart cells, brain cells, or pancreas cells as needed to combat specific diseases. Some medical experts predict that delivering gene products to alter disease processes will be the predominant form of medical therapy in the future.

Should We Change Genes in the Germ Line?

This question carries the most serious consequences for the human race. Germ line therapy is different from "ordinary" gene therapy. Germ line therapy is the alteration of the "germ line," the DNA that will be sent to offspring for generations to come. With ordinary gene therapy, changing the gene expression of the cells lining the lung will not affect the offspring of the CF patient. However, if we were to "fix" the CF gene in the fertilized egg, the offspring would be born without the disease and the faulty gene would be eradicated from the germ line forever. Germ line therapy is not condoned anywhere in the Western world at present. However, it is within the power of present

technology. Once commonplace, could we not then alter other gene complexes, like those that code for intelligence, muscular strength, or life span?

Contemplating the Future

Now is the time to contemplate where rapid advances in technology will lead. For the first time in history, human beings will be able rapidly to alter the gene pool of the flora and fauna of the earth. The argument that selective breeding has been doing the same thing for centuries does not fairly represent the scale on which it is now possible to alter genes of plants and animals.

People who suffer from crippling disease may enjoy cures never before possible in human history. Evolutionists make the point that a manipulated genome prevents the laws of nature from protecting only those who are most biologically fit. Christians point to the dangers of mankind altering what God has created and losing respect for human life. We Quakers, who have provided conscience to the world on human issues for three centuries, now have opportunities to cast the light of Christ into the dark ethical corners of biomedicine.

Update Since Article Was Written

1. The magazine *Science* (Mar. 19, 1999) reports that the National Human Genome Research Institute plans to complete the "first draft" of the human genome project (coding human genes) by next spring. The NIH institute awarded some $80 million to finish the project within the year 2000.

2. There is recent evidence that the offspring of "Dolly" the sheep (the first cloned mammal) show signs of premature aging of their DNA. Thus, the clone's offspring may be more susceptible than normal to diseases of aging (like cancer and heart disease). This indicates another potential danger for human cloning.

3. The National Institutes of Health is reviewing its policy toward utilizing human stem cells for research. A Working Group has been established to advise the NIH Director, Harold Varmus, on the matter. Advice will be sought by the Group from the National Bioethics Advisory Commission, the public, and the Congress. A decision

could be forthcoming by late summer, 1999. If approved, products for human therapy may be available within a few years time.

RESPONSE

PHIL SMITH

I welcome the opportunity to comment on issues raised by Kent and Miles in their article on gene therapy. For reasons of space, my comments will be succinct, but I hope not superficial.

Medical science has always combined description and prescription. It's not just about discovering the facts, but about using knowledge to better human life, and wise use is at least as difficult a thing as discovery. The coming molecular biology revolution in medicine underscores our need for practical wisdom.

Some people will say all genetic therapy (or all germ line therapy) is wrong, since it's not natural. In practice some will endorse (though they may not say so explicitly) all genetic therapies, or at least all those for which people are willing to pay. Both of these answers are too simple. The division between natural and unnatural doesn't show the line between right and wrong, neither does consumer preference as registered in a free market.

We have to ask: What is the human good? What is God's intention for human beings? How can medicine serve the human good and God's intention? We can't just "read off" the answers to such questions from what we are or from what the geneticist is able to do. Our answers will be shaped by the story, God's story, in which we find ourselves.

God intends for people to be "good." (An Aristotelian would say "happy" and mean the same thing.) God intends that we be creative, loving, beautiful, healthy, generous, cooperative, intelligent, etc. The list of partial descriptors for "good" must be very long.

Medicine serves the human good in at least four ways, by: 1) promoting life, 2) reducing suffering, 3) removing impediments to other goods, and 4) enhancing quality of life. Medicine can frustrate God's

intention for human flourishing when it is used to a) destroy life, b) increase suffering, or c) increase invidious social inequality.

Medical interventions can have mixed results. A ventilator can be used to extend life, but sometimes that use increases suffering. Practical wisdom is needed to judge whether a particular intervention—genetic therapies included—serves some purposes of medicine without violating others. A genetic test may benefit a person greatly by allowing her to prepare ahead of time for some chronic disease, but that test information should not be used to create invidious inequality, by barring her from opportunity or from insurance, for example.

Germ line therapy will require special thoughtfulness. To a greater degree than past medical interventions, germ line therapy aspires to improve the quality of human life. But in seeking to make life better for some (our genetically improved descendants), germ line therapy also runs greater risks of creating invidious social inequality than past medical interventions. Germ line therapies must be judged not only by the promise they offer to the people thus created, but by the effects of the therapies on those whose parents can't afford to procure them.

God in Christ calls us into a kingdom where everyone is valued and where we share each other's burdens. Medicine is becoming an ever more powerful tool for these ends. We have to think, pray, and hold up to the light of Christ the practical questions Kent Thornburg and Miles Edwards have posed for us.