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"IS IT TIME TO CHANGE OUR GENES?"

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Good Evening:

In February of 2003, Dr. Stephen Stephenson presented a paper to The Academy, titled "Designer Children". In this paper he offered an historical look at genetic engineering. My goal for this evening is to present at least part of the debate within our society of the pros and cons of genetic therapies in humans. One interesting part of the debate is whether we should allow science to determine how society makes decisions on the future of research, or whether we need input from voices outside the scientific arena such as history, philosophy, and religion to assist us in this process. While this question is not limited to genetic engineering, these therapies provide a current forum for such a discussion.

As I began my reading for this paper, I was shocked at how researchers in the area of human genetic engineering were arguing that their primary function was to perform "good science" and the application of their "good science" was outside their domain. I was reminded of classroom lectures I had heard 40 years earlier. As an undergraduate and graduate student during the 1960s I listened as my mentors described the differences between science and technology. Obviously, time has passed with inevitable memory loss. But, as I recall, science was described as a body of literature built using a specific methodology. This methodology was based on observation, description, and manipulation of our natural universe. Science was neither moral nor immoral. It was simply a compilation of information of

our natural world. By contrast, technology was described as the development of applications for the results of science. Technology could be for the benefit OR the detriment of society and by inference moral or immoral.

The classic example used during that period of time was the splitting of the atom. The scientific endeavor of splitting the atom was a manipulation of our natural universe and was neither moral nor immoral. However, technological results from splitting the atom ranged from nuclear medicine, to nuclear sources of energy, to nuclear bombs. Thus, the debate was set. Atoms were just atoms that could be split or not split. What we did with the split atom brought us both great hope and great fear, great joy and great sorrow.

To me the distinctions in this example have always seemed a bit forced. Certainly the scientists engaged in the original splitting of the atom had some ideas of what the results of their work would bring. Their "pure" science certainly was not divorced from technology. At the same time, the technological developments using the split atom led to a continuation of the science which allowed others to reach additional technological goals.

To me, science and technology formed a continuous loop; with technology dependent on science and science on technology. For the development of one to continue, there had to be development in the other.

Recently, Nobel laureate James Watson referred to this classic example as he reviewed his own research with DNA. He noted that prior to unraveling the DNA helix, Biology was at the bottom of the totem pole of the sciences. Physics was at the top as physicists in the late 1940s were revered for making atoms relevant to society and feared for what might happen if weapons they made possible would destroy civilization. Now, a half century later, Biology, with the rapid advances in sorting our genetic codes is at the top of the scientific pyramid and society is debating the pros and cons of genetic therapies. It appears Watson supports a separation of science from technology with Watson as the scientist.

For me this separation is more difficult to comprehend today than it was 40 years ago. To be more specific, the application of moral overtones to the applications of science and not to the scientific body of literature seems absurd. Science is a human enterprise and scientists work within the framework of the society in which they live. Too often it seems that current scientists view their own work as enlightened while viewing the work of past generations as naive.

As scientific disciplines continue to divide and then recombine into new configurations such as bio-psychology, chemical engineering, geophysics, biochemistry, and on and on, major research endeavors are becoming an ever greater intertwining of both science and technology. The question should not be whether science is separate from technology but whether the scientific enterprise in general is separate from philosophy. This is especially true as we discuss genetic therapies and the possibility of these therapies changing the way we perceive ourselves and our world.

To expand this point I offer several examples. The first set are from **SOMATIC GENE THERAPIES**: therapies which alter genes in our soma, or body cells but do not affect the next generation (Henig, 1998). Consider a gene therapy now under investigation to treat atherosclerosis. In a small study at St. Elizabeth's Medical Center in Boston, researchers delivered "naked" DNA for the gene via a catheter into the legs of patients with leg arteries so narrowed by atherosclerosis that some patients faced amputation of their legs. The treatment improved the condition of nearly all the patients. A similar example is from researchers at New York Hospital-Cornell Medical Center. They have designed a similar procedure--called the bio-bypass– that may work for treating patients with blocked coronary arteries. By delivering genes through a catheter directly to the heart, they hope to prompt new blood vessels to form around the clogged ones.

These genetic therapies to increase the blood flow of leg and heart arteries are achievement most of us would welcome without qualification. In these examples the medical problems are striking, a solution is available. Should we proceed? Of course!

But, what happens when healthy people want to grow new blood vessels for reasons that have less to do with saving life? Perhaps they are cyclists, runners, or soccer players hoping to get more oxygen to their legs. Or, maybe they are individuals convinced that better blood flow to the brain will boost their intelligence. Should these "enhancement uses" of the bio-bypass technology be allowed (Henig, 1998)? Again, many of us would probably answer, "why not?" The medical procedures are available, why not use them?

According to bioethicist Eric Juengst, gene therapies for just about any "enhancement" purpose will begin as therapy for a medical condition. Of course, the research protocols before agencies such as the FDA will not be labeled as `genetic enhancements' but as scientific endeavors to improve a medical condition. Expanding this point, Juengst suggests that it is a short step from developing a gene therapy to treat baldness resulting from cancer chemotherapy to offering the same genetic alteration to a far greater market: normal middle-aged men with run-of-the-mill male-pattern baldness. And, there is nothing in our current regulatory climate which can stop such usages. (Note: according to Juengst, such a product is already envisioned by researchers at Columbia University College of Physicians and Surgeons, who recently reported identifying the first human gene linked with hair loss.)

If we look to the "medical miracles" in our past we can find support for Juengst's position. That is, other types of therapies began as focused endeavors designed to alleviate severe medical condition and then were expanded to elective procedures for enhancement purposes. For example; plastic surgery was developed to correct the gross facial deformities of war injuries, but was soon used to straighten noses and tighten older, sagging skin. Breast implants were developed to reconstruct breasts in women who lost theirs to mastectomy, but were soon inserted into healthy women who just wanted to change their B cups to D cups. Growth hormone therapy was developed to add a few inches to hormone-deficient children who would always be abnormally short, but was soon sought after by parents who wanted to make their shortish kids less short or, in at least one instance, to make their tall daughter taller in hopes of snagging a college basketball scholarship.

As research in a specific area changes from being a medical miracle to an elective procedure, is our

philosophy moving in step with our science or is our science dictating our philosophy?

This question moves to the forefront with my next set of examples. Within the history of genetic therapies it is important to recognize the impact of the research on human infertility, specifically research on in-vitro fertilization. Briefly, over the past several decades in-vitro fertilization has been developed to assist couples who desire children but are unable to conceive. Multiple embryos are created in the laboratory, two or three embryos are transferred to the mother with the hope that at least one will make it to birth, and the other embryos are discarded. The research has been based on solid science and the body of data has been developed cautiously. As success followed success the practice expanded, and now is widely available, accepted and used. For many couples in-vitro fertilization has resulted in a medical miracle.

But that is just the start of the story. If in-vitro fertilization techniques are available, should we expand this area to include genetic diagnostics and concurrently embryo selection? Consider the situation of two couples. Both couples faced the same medical condition, both had the same goal, and both had the same result, one used genetic diagnostics the other did not. First Example: "Lee Ann Currie and her husband learned that their newborn first child, Natalie, had Fanconi anemia, an inherited disorder that usually brings cancer and death long before the child reaches adulthood. Natalie's best hope was a transplant of cells from a genetically matched donor. Thus, Lee Ann (the mother) decided to conceive more children in the hope that one of the succeeding children might have the right gene. Four years, three pregnancies, and two daughters later, she was successful with the birth of a new daughter. Their

first child, Natalie had a new lease on life.

..... Fast-forward fifteen years to August 2000. Linda and Jack Nash's six-year-old daughter, Molly suffered from the same deadly anemia, and the Nashes, like the Curries, were hoping to bear a healthy child who could donate umbilical cord blood to Molly." What brought the Nashes international attention was they used pre-screening genetic devices to select among healthy embryos to be sure that the one they selected would have the umbilical cord blood that would match Molly. That is, the Nashes delivered one baby with a perfect genetic match for Molly's condition. There was public outcry against the Nashes. They had aborted numerous embryos in search of the perfect match. But the writer who offered these case studies asks the questions: are there any real differences between the two families? If one child has such a need, but the parents do not want additional children, why not follow the example of the Nashes? If the science is available, what is the problem? Why shouldn't the Nashes use a genetic therapy technique to select an embryo that is the perfect match for Molly? Of course it is an extension of the original intent of the research, but why not use it?

According to the writer (Stock), prospective parents currently use: 1) amniocentesis to look for the telltale extra chromosome 21 of Down syndrome; 2) pre-implantation genetic diagnostics to select an embryo free of cystic fibrosis; and 3) ultrasound to determine the gender of a fetus so they can abort a baby girl. Perhaps the international attention received by the Nashes was the result of science moving faster than the ability of society to comprehend and incorporate these actions within its current philosophy. But again I want you to hold this thought a bit longer.

In-vitro fertilization is also associated with research on stem cells. To review, with in-vitro fertilization, multiple embryos are created in the laboratory, two or three of these are transferred to the mother with the hope that at least one will make it to birth, and the others are discarded. Questions are raised: why discard the extra embryos? Why not use them for research? Only embryos harbor stem cells with the genetic potential to become every part of the human body. Even though the embryo must be destroyed to harvest the stem cells, it isn't a question of destroying or saving the embryo. The question is only whether to use these "extra" embryos before they are discarded. We must note that this set of questions is not limited to stem cells from in-vitro fertilization. Such embryos and stem cells, are also available following elective abortions.

Currently our society is in strong support of this research, yet the debate is expanding. For example, many are questioning whether embryos should be created via in-vitro fertilizations exclusively for stem cell research. That is, with this research paradigm, the question is not whether to destroy the embryo now or later, but whether to create it for the express purpose of destroying it. One recent example of such research was reported in The Fresno Bee (September 29, 2004).

> "The creator of Dolly the sheep, the world's first mammal cloned from an adult, applied for a human cloning license .... to study how nerve cells go awry to cause motor neuron disease. "Ian Wilmut, who led the team that created Dolly at Scotland's Roslin Institute in 1996, said he plans to clone cells from patients with the incurable muscle-wasting disease, derive stem cells from the cloned embryo, make them develop into nerve cells and compare their development with nerve cells derived from healthy embryos. "Such work ..... which does not result in a

baby, is opposed by abortion foes and other biological conservatives because researchers must destroy human embryos to harvest the cells.

A second example is from the Boston Globe, October 13, 2004. Harvard Scientists have applied to the university's ethical review board for permission to clone human cells in the U.S. "This is exactly the kind of work that we envisioned for the Harvard Stem Cell Institute .... We want new ways to study and hopefully cure diseases."

Note: In neither of the above examples is the intent of the scientists to carry the embryo past several days. In both, the scientific goal is to insert the nucleus from a donor cell into an egg cell that has had its own nucleus removed. The egg will then be prompted to grow for several days forming a few hundred cells from which the embryonic stem cells will be removed.

If we agree that we can create and destroy embryos for the good of research, can we extend the therapies to create genetically engineered humans?

GERM-LINE THERAPIES: Therapies that alter genes of successive generations are referred to as germ-line therapies. This is a more difficult type of research intervention, but the topic is easier to discuss because the applications are still in the future. I will mention two types of germ-line therapies: children with specific genes chosen by their parents ("Designer Children") and clones. Both types of research can be viewed as extensions of stem cell research.

Research in this area will be extremely complicated and expensive. It will proceed slowly at first with experiments on organisms that are more simple than humans. The focus will begin with traits associated with single genes that we already understand. Complications will arise as we cross species and as we learn of the many traits that are the result of complex gene interactions.

One example from my past may demonstrate this point. It has been over a decade since the first report by Jeff Friedman at the Rockefeller University of his dramatic work in coding the gene responsible for obesity in mice. He and others had great hopes that his work would translate rapidly to humans and that a cure for genetic obesity in humans would be announced. As far as I know, cross species generalizations have yet to materialize. His results still apply only to mice and morbid obesity remains a chronic problem in our society.

The basic scenario of germ-line research is straight forward (Sullivan, McEwan, 1999): A disease carrying gene or a gene that enhances physical and behavioral characteristics is identified. A test to identify such a gene is then developed. Next, researchers develop gene transfer techniques. Clinical trials begin, are modified and refined. As development proceeds, the scope is widened to encompass a larger body of diseases and physical and behavioral characteristics. The procedure then moves from the experimental to the applied.

Some place germ-line therapies into the realm of science fiction. Others as the new frontier of science. One author even made the bold prediction that with germ-line therapies we are in the process of

viewing a shift from the study of "outer space" to "inner space". Distinguished organizations such as The American Association for the Advancement of Science and a group named The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health have begun to sponsor colloquia on this very topic. And the National Institute of Health is receiving grant applications.

Predictions for the future? ---- medical miracles as genetic illnesses are eliminated. Enhancement procedures beyond our dreams -----. Imagine that your grandchildren will be able to pick exactly how their babies will look, think, and act. The family curse of breast cancer or cystic fibrosis or early heart attack--not to mention dyslexia, fat thighs, or shyness --will be vanquished in a single stroke. According to one author, your great-grandchildren may be as lean, literate, loquacious, and long-lived as their parents want them to be (Henig, 1998).

Of course the science for such experiments is not yet available. But each year, maybe each month, such research becomes closer to reality. What about our Philosophy of Science? Is society going to have the tools to deal with these questions?

One of the primary sources for my paper was the book "Redesigning Humans Our Inevitable Genetic Future" by Gregory Stock (2002). This is perhaps the most shocking book I have ever read. Both for his conclusions and because I realize that Stock represents a substantial opinion on the subject. And he might be correct. His conclusions are simple. My synopsis ....

Hey folks, get over your concerns about this research. When the science is available, it will in-fact be used. It has been that way for the last century and it will continue in the future. We can block progress temporarily, but not forever, so why block it at all? We have used non-genetic biological interventions for years. Prescription glasses and hearing aids are biological interventions as are insulin pumps and heart monitors. If genetic interventions help us we will use them, and if they don't we won't. If genetic research can be afforded it will proceed, if it is too expensive it will stop. If the side effects outweigh the direct effects, we will stop, if side effects are minimal we won't. The scientific revolution is all about gaining information and using it. Scientists will make the discoveries, and society will make the decisions on their use. Over time our questions about these techniques will answer themselves. Our focus should be on where the research will be conducted and who will fund it.

The "marketplace" will adjudicate our future. If research cannot be conducted in the United States, it will be conducted in a foreign country. If it is not supported by public funds, it will be supported privately. If it works, it will be replicated, if it is cost effective, it will be used.

Stock's frightening conclusions are that science will lead and the marketplace will dictate our philosophy. As I mentioned previously, Stock does not have an isolated position. A Reuters news release on California's Proposition 71 (Sunday, October 3, 2004) is a great example of "marketplace" philosophy: "A proposal to spend $3 billion in California state funds on stem-cell research is likely to attract scientists and create jobs, but some critics question whether the investment will pay off."

Bio-ethicist, Glenn McGee (1997) argues that research on human "cloning must be banned, at least in the short-term, not because it is bad in principle, or sinful, or dangerous, but because there is no collective wisdom yet in our common conversations about cloning and reproductive genetics .... no consensus about what liberties people can take in altering their offspring."

Of course parents should have a right to make decisions about their children. They are currently making choices on which characteristic should or should not be part of society in the offspring they propagate. But in the area of genetic therapies, how can they make decisions? How can we? The science is complex, and until recently, public debate has been practically nonexistent. Individuals are being asked to make decisions without information. Thus, McGee concludes that temporary bans should be put in place to allow us time to think, to study, to learn, to develop a view for the future of our society.

What topics would we discuss? Firstly, in germ-line therapies, I believe we need to discuss how we feel about "clinical failures"? The term "clinical failures" sounds antiseptic but we must remember that when we refer to "designer children" and cloning clinical failures refer to:

-miscarriages and abortions.

-infants born with gross deformities and severe mental incapacitations.

-severe genetic defects that may not be apparent at birth but may appear later in life.

Secondly, if we can handle "clinical failures", what about multiple clinical failures? That is, how many clinical failures will we allow: one or two? A dozen? A hundred? Thirdly, we might want to focus on

exactly what are the boundaries of parenthood? What are the boundaries of families? (McGee 2001). If these are valid concerns, who should address them? Should we leave the discussion to our government? The National Science Foundation? The National Institute of Health? Of course all of these institutions will be involved. At the same time these issues must be debated publically.

We must also debate how genetic therapies, both somatic and germ-line, will impact us as a society. Many worry about the decline of the middle class. The separation of the "Haves" from the "Have Nots" continues to become more prevalent. Although articles are being written arguing vehemently that society, of necessity, must insure equal opportunity for genetic therapies for all individuals. I do not see how this will happen. In my opinion, complex medical procedures will continue to be more and more expensive and available only to the "Haves". If those who predict that new and innovative therapies will begin as medical miracles and lead rapidly to elective, enhancement procedures, the "Haves" will be the only ones able to afford the treatments. If public money is not available, the "Haves" will receive services from private labs. If banned in the US, the "Haves" will seek elective medical services from foreign labs. If services are available in the US the "Haves" will wiggle up the list just as they do the donor transplant list today. Our society doesn't distribute anything else equally, why would we expect genetic medicine to be any different. The future could see a gene-rich elite and gene-poor underclass.

Ironically, the topic of the "Haves" becoming more separated from the "Have Nots", includes the issues of allowing insurance companies to use genetic information. An article this past January in Lancet

suggested that, for the insurance industry, current genetic tests may be novel, but such tests do not involve ethical issues. For example, private insurance companies work on a mutuality basis, whereby individuals contribute to a pool of funds, and premiums are based on specific risks at the time of insurance. Individuals with risks, such as high cholesterol, smoking, family histories of diabetes, obesity, and/or heart disease, age, sex, all contribute to the premium. Such individuals are placed into specific groups, called "Risk Groupings" and share premiums with others within the group. This makes a lot of sense. Why should a lean nonsmoker with normal blood pressure, and low blood cholesterol levels, and no family history of heart disease pay the same insurance rate as an obese chain smoker with high blood pressure, high blood cholesterol levels, and a history of heart disease?

If genetic screening would further define such risk groupings, why deny the screening? For example: consider two individuals at increased risk of coronary heart disease. Individual A has the higher risk based on a blood cholesterol test. Individual B has the same risk identified by a hypothetical genetic test. Individual A has to declare this information to the insurance company, while individual B does not. Perhaps the genetic test is simply a refinement and elaboration of currently used tests to predict the future and estimate risk.

Others argue the issue may be more complex than it appears. As more and more genetic tests are made available and medical procedures continue to improve, the "veil of ignorance" (Sullivan, 2000) of our genetic past and future will become increasingly thin. Insurance companies will be able to divide large groups in the population into ever smaller and more precise risk groups. The result of such

knowledge on the viable future of health and life insurance is questionable. For example: with all the information, will any of us qualify for affordable rates? Put another way, with the removal of the "veil of ignorance" will rates become so high that only the "Haves" will be able to afford private insurance? If so, will those able to afford such services lobby for further reductions in support of social services for the diseases in question? And finally with limited and unequal access to health care and social services, will parents who learn they are at risk for bearing a child with a genetic disease or disability feel forced to use "genetic solutions"?

In discussions of genetic testing and insurance coverage we must also focus on the differences between genetics and heritability. Assume a gene is discovered that carries a specific disease. Further, assume a test is created to determine whether or not a particular individual carries the gene. If an individual is given the test and the results are positive, is it inevitable that the individual will contract the disease? If the environment of the individual has absolutely no effect, the answer is yes, it is inevitable. But, as we all know, the environment has an effect.

Heritability refers to genes interacting in the environment. The classic example that highlights heritability is from the studies of identical twins raised apart. The similarities between the two twins is attributed to their identical genetic makeup. The differences between these twins is attributed to the environment. The behavior patterns of the identical twins are closer than those of nonidentical siblings raised apart, but the behavioral patterns certainly are not identical.

Likewise, some of us as adults may be prone to high levels of cholesterol or heart disease, but with a lot of work on our diet and our exercise programs, plus our daily 10mg of lipitor we are doing quite well, thank you very much. We have used factors in our environment to lessen the odds we were given by our genetic endowment There is no way a genetic test can sort, in an apriori manner, those of us who will and those who will not reduce their odds of being stricken with disease. Because of this lack of ability to discriminate, it can be argued that such genetic information should not even be allowed to be taken for fear that it will be misused.

I will mention three additional philosophical issues before closing. All are valid with the arena of a discussion on genetic therapies. At the same time all are valid over a wide range of issues. The first is the role of genetic research on the extension of life. Our society already has great concerns on how to deal with the current projections of the increase in the percentage of aged individuals (a topic becoming more near and dear to most of us every day). Should society consider gene therapies with the intended target to extend life? What are the financial costs to society of dramatically increasing the population of elderly people? What are the social costs?

Second, the direct costs of funding genetic research and genetic therapies must be placed on a priority list with the costs of other social programs. Considering the overall needs of society in the areas of health, education, and social services where should we place genetic research? How do we calculate the value of research in a particular area?

Finally, allowing the government (federal or state) to control the funding of genetic research raises the history of all of the negative images regarding genetic manipulations from the past.

CONCLUSION: So, where do we go from here? We often hear that we should allow "good science" to lead us. And that is certainly the conclusion of Stock. If we listen to Stock, we better get in, buckle up, shut up, and get ready for the ride. Because research at this level with its sophistication and complexity is all "good science". As I implied earlier, Stock's conclusions seem overly simplistic and really quite frightening. At the same time, I realize we cannot stop this research. The chance to cure diseases and the medical miracles that await us are just too great for us to quit.

To me models where science dictates philosophy or the obverse where philosophy dictates science are both too rigid and dangerous. We need a model where both components of the puzzle work in tandem. If our science is moving ahead of our philosophy, perhaps we need a time to reflect on:

-where we are going?

-who will have access to these medical miracles?

-what enhancement procedures should be funded?

-what is the human cost of our rush to unravel our genetic heritage?

"IS IT TIME TO CHANGE OUR GENES?" I'll end my talk in the 60s where I began. Our generation thought it had some wonderful solutions to the problems created by our parents. As the new century unfolds it looks as if we have created a huge set of new problems, and will have to rely on our children for the solutions.