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Position Paper on Human Germ Line Manipulation Presented by Council for Responsible Genetics, Human Genetics Committee Fall, 1992

THE POSITION OF THE COUNCIL FOR RESPONSIBLE GENETICS

The Council for Responsible Genetics (CRG) strongly opposes the use of germ line gene modification in humans. This position is based on scientific, ethical, and social concerns.

Proponents of germ line manipulation assume that once a gene implicated in a particular condition is identified, it might be appropriate and relatively easy to change, supplement or otherwise modify the gene by some form of therapy. However, biological characteristics or traits usually depend on interactions among many genes, and these genes are themselves affected by processes that occur both inside the organism and in its surroundings. This means that scientists cannot predict the full effect that any gene modification will have on the traits of people or other organisms. In purely biological terms, the relationship between genes and traits is not well enough understood to guarantee that by eliminating or changing genes associated with traits one might want to avoid, we may not simultaneously alter or eliminate traits we would like to preserve. Even genes that are associated with diseases that may cause problems in one context can be beneficial in another context.

Two frequently destructive aspects of contemporary culture are linked together in an unprecedented fashion in germ line gene modification. The first is the notion that the value of a human being is dependent on the degree to which he or she approximates some ideal of biological perfection. The second is the ideology that all limitations imposed by nature can and should be overcome by technology. To make intentional changes in the genes that people will pass on to their descendants would require that we, as a society, agree on how to identify 'good' and 'bad' genes. We do not have such criteria, nor are there mechanisms for establishing them. Any formulation of such criteria would necessarily reflect current social baises.

Moreover, the definition of the standards and the technological means for implementing them would largely be determined by the economically and socially privileged. By implementing a program of germ line manipulation these groups would exercise unwarranted influence over the common biological heritage of humanity.

WHAT IS "GERM LINE MANIPULATION"?

The undifferentiated cells of an early embryo develop into either germ cells or somatic cells. *Germ* cells, or reproductive cells, are those that develop into the egg or sperm of a developing organism and transmit all its heritable characteristics. *Somatic* cells, or body cells, refer to all other cells of the body. While both types of cells contain chromosomes, only the chromosomes of germ cells are passed on to future generations.

Techniques are now available to change chromosomes of animal cells by inserting new segments of DNA into them. If this insertion is performed on specialized or *differentiated* body tissues, such as liver, muscle, or blood cells, it is referred to as *somatic cell* gene modification, and the changes do not go beyond the individual organism. If it is performed on sperm or eggs before fertilization, or on the undifferentiated cells of an early embryo, it is called *germ cell* or *germ line* gene modification, and the changes are not limited to the individual organism. For when DNA is incorporated into an embryo's germ cells, or undifferentiated cells that give rise to germ cells, the introduced gene or genes will be passed on to future generations and may become a permanent part of the gene pool.

Deliberate gene alterations in humans are often referred to as 'gene therapy'. The Council for Responsible Genetics (CRG) prefers to use the terms 'gene modification' and 'gene manipulation' because the word 'therapy' promises health benefits, and it is not yet clear that gene manipulations are beneficial.

WHY MIGHT GERMLINE MODIFICATION BE ATTEMPTED IN HUMANS?

If one or both partners carry a version of a gene that could predispose their offspring to inherit a condition they want to avoid, genetic manipulation may appear to be a potential way to prevent the undesired outcome. The earlier during embryonic development the targeted gene or genes are replaced, the less likely is the resulting individual to be affected by the unwanted gene. But while the immediate goal of such a modification might be to alter the genetic constitution of a single individual, modifications made at the early embryonic stages would

incidentally result in germ line modification, and so all the offspring of this person would have and pass on the modification.

Alternatively, germ line modification may be the intended consequence of the procedure. One goal might be to 'cleanse' the gene pool of 'deleterious' genes. For example, Daniel E. Koshland, Jr., a molecular biologist, and the editor-in-chief of *Science*, has written, "keeping diabetics alive with insulin, which increases the propagation of an inherited disease, seems justified only if one ultimately is willing to do genetic engineering to remove diabetes from the germ line and thus save the anguish and cost to millions of diabetics." (1) Another goal of germ line manipulation may be to avoid multiple treatments of somatic gene modification that would be required under proposed treatment protocols for certain conditions such as cystic fibrosis.

Some people may also look forward to the possibility of introducing genes into the germ line that can 'enhance' certain characteristics desired by parents or other custodians of the resulting offspring. In the article referred to above, Koshland raises the possibility that germ line alterations could be perceived to meet future 'needs' to design individuals "better at computers, better as musicians, better physically."

The attempt to improve the human species biologically is known as *eugenics*, and was the basis of a popular movement in Europe and North America during the first half of this century. Eugenics was advocated by prominent scientists across the entire political spectrum, who represented it as the logical consequence of the most advanced biological thinking of the period. In the U.S., eugenic thinking resulted in social policies that called for forced sterilization of individuals regarded as inferior because they were 'feeble minded or paupers.' In Europe, the Nazis took up these ideas, and their attempts at implementation led to widespread revulsion against the concept of eugenics. Today public discussion in favor of influencing the genetic constitution of future generations has gained new respectability with the increased possibility for intervention presented by in-vitro fertilization and embryo implantation technologies. Although it is once again espoused by individuals with a variety of political perspectives, the doctrine of social advancement through biological perfectibility underlying the new eugenics is almost indistinguishable from the older version so avidly embraced by the Nazis.

It is important to recognize that the dream of eliminating 'harmful' genes (such as those associated with cystic fibrosis or Duchenne muscular dystrophy) from the entire human gene pool could be realized only over time scales of thousands of years, and then only with massive, coercive programs of germ line manipulation. Such a program would be neither feasible nor morally acceptable. As a practical matter then, any presumed beneficial effects of germ line modification would pertain to individual families, not to the human population as a whole. This is in contrast to harmful effects, which would be widely disseminated.

Furthermore, parents who carry a gene which they would not want a child of theirs to inherit could arrange to have unaffected, biologically-related offspring *without* germ line modification. If a gene is well enough characterized to consider gene manipulation, there will always be a diagnostic test available to identify a fetus that carries that gene and parents, if they choose, may then terminate the pregnancy. Given that there are alternatives for avoiding the inheritance of unwanted genes, the main selling point of germ line modification techniques over the long term would appear to be the prospect of enhancement of desired traits.

WHAT IS THE FEASIBILITY OF MODIFYING THE GERMLINE OF HUMANS?

Both somatic and germ line modification are widely performed on laboratory animals for research purposes. Somatic gene modifications have already been performed on humans and additional experimental protocols are being approved by the National Institutes of Health in increasing numbers.

No published reports have yet appeared on germ line modification in humans, but there appear to be no technical obstacles to such experiments, and articles proposing these procedures are becoming more and more common in the literature (2,3,4). Germ line gene modification has actually proved technically easier than somatic modification in mice and other vertebrate animals which have been employed as 'models' for human biology in the past, because the cells of early embryos incorporate foreign DNA and synthesize corresponding functional proteins more readily than most differentiated somatic cells. A widely-reported example of the successful experimental use of the germ line technique was the introduction of an extra gene that specified growth hormone into fertilized mouse eggs. In the presence of the high levels of growth hormone produced, the mice grew to double their normal size. Germ line techniques are also being used in attempts to modify farm animals, with stated goals of increasing yields or enhancing nutritional quality of meat and other animal products.

Given what has been accomplished in animals, the only remaining technical requirements for germ line gene modification in humans are procedures for collecting a woman's eggs, fertilizing them outside her body, and implanting them in the uterus of the same or another woman, where they can be brought to term. These are already well established procedures for humans and are widely used in in-vitro fertilization clinics.

WHAT ARE THE TECHNICAL PITFALLS?

Current methods for germ line gene modification of mammals are inefficient, requiring the microinjection of numerous eggs with foreign DNA before an egg is successfully modified. Moreover, introduction of a foreign gene (even if there is a copy of one already present) into an inappropriate location in an embryo's chromosomes can have unexpected consequences. For example, the offspring of a mouse that received an extra copy of the normally present *myc* gene developed cancer at 40 times the rate of the unmodified strain of mice. (5)

Techniques to introduce foreign DNA into eggs, however, are constantly being improved and eventually will be portrayed as efficient and reliable enough for human applications. It may soon be possible to place a gene into a specified location on a chromosome while simultaneously removing the unwanted gene. This will increase the accuracy of the procedures, but does not eliminate the possibility that gene combinations will be created that will be harmful to the modified embryo, and its

descendants in future generations. Such inadvertent damage could be caused by technical error, or more importantly, by biologists' inability to predict how genes or their products interact with one another and with the organism's environment to give rise to biological traits. It would have been impossible to predict, *a priori*, for example, that someone who has even *one* copy of the gene for a blood protein known as hemoglobin-S would be protected against malaria, whereas a person who has *two* copies of this gene would have sickle cell disease.

This unpredictability applies with equal force to genetic modifications introduced to 'correct' presumed disorders and to those introduced to enhance characteristics. Inserting new segments of DNA into the germ line could have major, unpredictable consequences for both the individual and the future of the species that include the introduction of susceptibilities to cancer and other diseases into the human gene pool.

WHAT ARE THE SOCIAL AND ETHICAL IMPLICATIONS OF GERM LINE MODIFICATION?

Clinical trials in humans to treat Adenosine Deaminase Deficiency—a life threatening immune disorder—and terminal cancer with somatic gene modification are already in progress and experiments to treat diabetes and hypertension are under development. It is important to distinguish the ethical problems raised by these protocols from the additional, and more profound questions raised by germ line modification. While the biological effects of somatic manipulations reside entirely in the individual in which they are attempted, such treatments are not strictly analogous to other therapies with individual risk. Radiation, chemical or drug treatment can be withdrawn if they prove harmful to the patient, while some forms of somatic modification cannot. Thus, somatic gene modification requires a person to forfeit his/her rights to withdraw from a research study because the intervention cannot be stopped, whether harmful or not. Valid objections have also been raised to the fact that the first somatic gene modification experiments, involving Adenosine Deaminase Deficiency, were carried out on young children who were not themselves in a position to give informed consent. While it appears that somatic gene modification techniques will be used increasingly in the future, the CRG urges that they be used with greatest caution, and only for clearly life-threatening conditions.

Germ line modification, in contrast, has not yet been attempted in humans. The Council for Responsible Genetics opposes it unconditionally. Ethical arguments against germ line modification include many of those that pertain to somatic cell modification, as well as the following:

- Germ line modification is not needed in order to save the lives or alleviate suffering of existing people. Its target population are 'future people' who have not yet even been conceived.
- The cultural impact of treating humans as biologically perfectible artifacts would be entirely negative. People who fall short of some technically achievable ideal would increasingly be seen as 'damaged goods.' And it is clear that the standards for what is genetically desirable will be those of the society's economically and politically dominant groups. This will only reinforce prejudices and discrimination in a society where they already exist.
- Accountability to individuals of future generations who are harmed or stigmatized by wrongful or unsuccessful germ line modifications of their ancestors is unlilely.

In conclusion, the Council calls for a ban on germ line modification.

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This document was written by the Human Genetics Committee of the Council for Responsible Genetics (CRG). The Council is a Cambridge-based national organization of scientists, public health advocates, trade unionists, women's health activists and others who want to see biotechnology developed safely and in the public interest. The Council believes that an informed public can and should play a leadership role in setting the direction for emerging technologies. A fundamental goal of the CRG is to prevent genetic discrimination.

The Human Genetics Committee has 14 members with backgrounds in the biological sciences, public health, law, disability rights, occupational health and safety, and women's health. Members include: Abby Lippman, Professor of Epidemiology, McGill University, Chairperson; Philip Bereano, Professor of Engineering and Public Policy, University of Washington; Paul Billings, Chief of Genetic Medicine, Pacific Presbyterian Medical Center; Colin Gracey, Head of the Religious Life Office, Northeastern University; Mary Sue Henifin, Deputy Attorney General, State of New Jersey; Ruth Hubbard, Professor Emerita of Biology at Harvard University; Sheldon Krimsky, Associate Professor of Urban and Environmental Policy, Tufts University; Richard Lewontin, Alexander Agassiz Professor of Zoology, Harvard University; Karen Messing, Professor of Biology, University of Quebec in Montreal; Stuart Newman, Professor of Cell Biology and Anatomy, New York Medical College; Judy Norsigian, Co-Director, Boston Women's Healthbook Collective; Marsha Saxton, Director, Project on Women and Disability; Doreen Stabinsky, California Biotechnology Action Council and University of California at Davis; and Nachama L. Wilker, Executive Director, Council for Responsible Genetics.

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